

Ring Strain Energy in the Cyclooctyl System. The Effect of Strain Energy on [3 + 2] Cycloaddition Reactions with Azides

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Abstract: Ring strain energies (SEs) and enthalpies of hydrogenation (ΔH_{hyd}) of a series of *E*- and *Z*-alkenes, cyclic alkynes and allenes (C_5 – C_9) are computed at the G3 level of theory. The SE for cycloheptyne, cyclohexyne, and cyclopentyne are calculated to be 25.4, 40.1, and 48.4 kcal/mol, respectively. The SE for *E*-cycloheptene and *E*-cyclohexene are calculated to be 25.2 and 49.3 kcal/mol (G3). The SE of cyclooctyne is 2.0 kcal/mol greater than that of *E*-cyclooctene (17.9 kcal/mol) but only 7.7 kcal/mol greater than that of cyclooctane. The SE of 3,3-difluorocyclooctyne (DIFO) is predicted to be slightly reduced ($\Delta SE = 2.6$ kcal/mol) relative to the parent cyclooctyne to 17.3 kcal/mol. The SE and ΔH_{hyd} are correlated with activation barriers for the [3 + 2] cycloaddition of a series of azides to *E*- and *Z*-cycloalkenes and alkynes at the G3 level of theory. The energy barrier for the cycloaddition of methyl azide to cyclooctyne is 9.2 kcal/mol lower than addition to 4-octyne and 3.1 kcal/mol lower for reaction with *E*-cyclooctene. The activation energies for [3 + 2] cycloaddition of benzyl azide and acetamido azide (${}^2\text{HN}(\text{C}=\text{O})\text{CH}_2\text{-N}_3$) to DIFO are 2.3 and 5.3 kcal/mol lower in energy than cycloaddition to cyclooctyne [B3LYP/6-311+G(3df,2p)].

Introduction

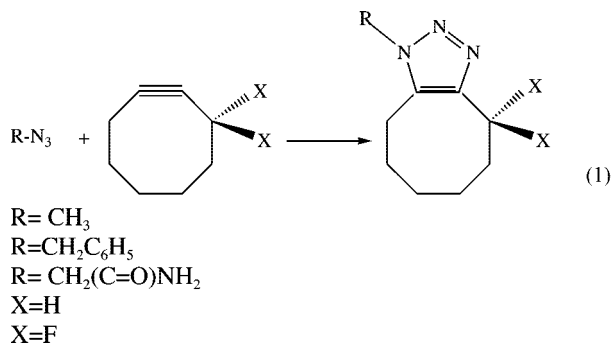
Medium ring hydrocarbons have played an important role in the development of mechanistic organic chemistry. The eight-member ring has been especially influential because of the series of transannular hydrogen shift reactions discovered by Cope in the 1950s.^{1a} Particular attention has also been given to the reactions of *E*-cyclooctene because it has generally been assumed to be a highly strained alkene and hence exhibited atypical rates for various types of addition reactions. This area of medium ring chemistry was also originally developed by Cope and his many collaborators.² More recently, cyclooctyne has come into prominence because it has been utilized in strain-promoted [3 + 2] dipolar cycloaddition reactions with azides as described initially by Huisgen.³ In a series of biological applications Bertozzi and co-workers⁴ have exploited the unusual reactivity of cyclooctyne in Cu-free click chemistry for

the purposes of labeling biomolecules rapidly and selectively in living systems. This technique has led to the imaging of carbohydrates as they are produced on cell surfaces of live animals. Fox and co-workers^{5a} have more recently described a bioorthogonal reaction based on the Diels–Alder reaction of (*E*)-cyclooctene and 3,6-diaryl-*s*-tetrazines. These inverse electron demand Diels–Alder reactions proceed with very fast reaction rates (up to k_2 2000 $\text{M}^{-1} \text{s}^{-1}$) enabling protein modification at low concentration. Hilderbrand and co-workers^{5b} have also recently applied tetrazine-based cycloadditions to pretargeted live cell imaging.

A cyclooctyne, bearing two electron withdrawing fluorine substituents, promotes a facile [3 + 2] cycloaddition reaction with benzyl azides installed metabolically into biomolecules. The origins of this rather fast cycloaddition to a cyclooctyne, to form a five-member ring triazole (eq 1) has been ascribed largely to the combined rate enhancing features of ring SE and the electron withdrawing capacity of the α -difluoromethylene moiety (CF_2). An eight-member ring alkyne is the smallest ring size that can tolerate this deformed geometry and still be isolated as a stable molecule. It has generally been stated that the C–C \equiv C bond angle in cyclooctyne deviates 17° from the idealized 180° angle of a triple C–C bond. Despite the considerable resurgence in the application of alkyne chemistry to this newly developed application, the SE of cyclooctyne has not been established with any degree of certainty. Bertozzi has assigned an SE of 18 kcal/mol apparently based upon some heats of hydrogenation of cyclooctyne reported by Turner and co-workers⁶ a number of years ago. In the present study we continue a systematic investigation of ring SEs in a variety of

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cyclic molecules.⁷ We now assign an SE to cyclooctane and *E*- and *Z*-cyclooctene in addition to cyclooctyne and its important α -difluoroalkyne (DIFO)⁴ on the basis of high-level ab initio calculations employing several proven comparative methodologies. Our rationale for the relative rates of cycloaddition with methyl azide correlates well with the suggested ring SEs.⁸

Results and Discussion

Any discussion of the ring SE in either cyclooctene or cyclooctyne should also address the strain associated with the repulsive transannular H–H interactions that occur in medium ring hydrocarbons. These destabilizing interactions in cyclooctane were obviously largely responsible for the multitude of transannular hydride transfer reactions observed initially by Cope and his co-workers.¹ Since this type of interaction is less well understood than more typical steric interactions, there have been a great variety of methods applied to conformational studies on medium ring compounds. The numerous attempts to assign relative SEs to C₈–C₁₂ cyclic hydrocarbon systems have established that the SE increases with each additional CH₂ group until about cyclododecane where the SE is about the same as that in cyclooctane.⁹

The cyclic molecules included in this study are generally large enough so that we prefer to apply two corroborating methods to provide a level of confidence in the results. To reliably assign SEs, in addition to the well-established homodesmotic reactions, we have applied at least two additional methods that compliment each other.⁷ For example, SEs have been by convention calculated relative to some strain-free reference compound that has traditionally been a linear all-anti hydrocarbon. The SE of a cyclic compound may also be calculated, relative to this reference compound, by using calculated energy terms balancing the difference in the number of atoms and bonds in the cyclic versus the acyclic reference compound.¹⁰ When this cyclization method was applied to cyclohexane, an SE of 2 kcal/mol was predicted relative to all-anti *n*-hexane.^{7a}

Our best argument for the nonzero SE of cyclohexane perhaps derives from the second methodology that we have employed in the present study. Since we now enjoy the luxury of carrying

out very accurate calculations such as G3,¹¹ at near experimental accuracy, on molecules with at least 10 heavy atoms we can provide an accurate energy correction for the addition or extrusion of a CH₂ fragment from a homologous series of molecules. In several recent reports,⁷ we have shown that this protocol can provide very accurate and reproducible SEs for a series of cyclic hydrocarbons including those that have heteroatoms. We maintain that these methods constitute a marked improvement over the more traditional use of isodesmic and homodesmotic reactions that have been utilized previously to estimate ring SEs.⁸ An isodesmic reaction maintains the same number and types on bonds in both reactants and products while a homodesmotic chemical equation attempts to preserve both the bond type and valance characteristics of each participant in the equation. In these same studies we have convincingly demonstrated that while well-balanced homodesmotic reactions continue to work reasonably well for hydrocarbons, this method fails miserably when heteroatoms are involved and this is especially true for compounds that contain the relatively weak O–O bond as in peroxides.^{7c,d}

The most accurate energy value for a CH₂ fragment is best derived as the energy differences between all-anti *n*-hexane and *n*-heptane or *n*-octane with an average value of -39.27105 au.^{7a} We have shown that the energy differences between homologous linear hydrocarbons level off at about C⁶–C⁸. On the basis of this analysis, we find that the corresponding energy equivalent for each CH₂ group in cyclohexane is -39.27048 au at the G3 level that corresponds to an SE for this C₆H₁₂ hydrocarbon of 2.15 kcal/mol. This SE assignment is based solely upon these CH₂ energy equivalents, garnered at a credible level of accuracy, and does not rely upon any system of equations and therefore should represent the best estimate of the strain in chair cyclohexane relative to a linear hydrocarbon reference compound. Most of our data on the SE of an entire series of compounds have been garnered at the G2 or G3 level of theory because recent studies by Schreiner^{13a} have made it increasingly evident that many versions of DFT theory do not give reliable energy differences between isomeric hydrocarbons. It should also be emphasized that earlier scholars in the area of ring strain, such as Wiberg¹² and Schleyer,^{9b} ascribed a nonzero value to the SE of cyclohexane as a consequence of its obligatory gauche interactions. However, this conclusion is somewhat complicated by the more recent suggestion by Schleyer and co-workers^{13b} that cyclohexane actually has a negative SE on the basis of the newly developed concept of stabilizing 1,3-alkyl–alkyl interactions due to hydrocarbon branching described as proto-branching.^{13b} They argue that “*n*-alkane, cyclohexane, and other hydrocarbons are seriously compromised as reference molecules

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Table 1. Calculated SEs of Alkenes, Alkynes, and Allenes at the G3 Level of Theory

	G3-CH ₂ Insertion	G3-cyclization	literature
cyclopropene			54.1 ^a
cyclobutene			29.5 ^b
cyclopentene			4.7 ^b
cyclopentene	48.4		59 ^c
cyclohexane		1.98	1.43 ^a 2.15 ^b
<i>E</i> -cyclohexene	49.3		
<i>Z</i> -cyclohexene			0.7 ^a
cyclohexyne	40.1		
cycloheptane	8.4, 8.5		
<i>E</i> -cycloheptene	25.2		
<i>Z</i> -cycloheptene	5.8, 5.4		
cycloheptyne	25.4		
cyclooctane	12.3 ^d	12.16	11.88 ^e 12.26
(<i>E</i>)-cyclooctene		17.9	16.4 ^f
(<i>Z</i>)-cyclooctene		6.8	
cyclooctyne		19.9	
3,3-difluorocyclooctyne		17.3	
1,2-cyclooctadiene		11.9	
cyclononane	15.49		15.47 ^e
(<i>E</i>)-cyclononene	16.4		
(<i>Z</i>)-cyclononene	11.4		
cyclononyne	13.4, 13.4		
1,2-cyclononadiene	10.9		

^a See ref 7b. ^b See ref 7a. ^c See ref 22. ^d Two CH₂ equivalents with an SE of cyclohexane = 2.15 kcal/mol. ^e Engler, E. M.; Androse, J. D.; Schleyer, P. von R. *J. Am. Chem. Soc.* **1973**, *95*, 8005. ^f Wiberg, K. B. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 312.

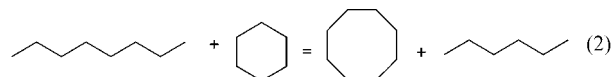
for the evaluation of energies associated with the concepts of ring strain". It is difficult to reconcile this argument with the present study because, based simply upon CH₂ energy equivalents, where the cyclic and acyclic structures both have a comparable number of 1,3-alkyl-alkyl interactions, we get essentially identical SE values for cyclohexane from both the cyclization and CH₂ energy equivalents protocols. In fact, many of the arguments presented in favor of stabilizing protobranching 1,3-interactions serve to corroborate our earlier suggestions that well balanced homodesmotic reactions must use larger linear hydrocarbons (C₆–C₈) as reference materials rather than CH₄ and CH₃–CH₃ in order to get reliable SEs. We prefer to reason that such simple unsubstituted molecules are poor reference molecules for branched hydrocarbons because their C–H bond dissociation energies^{7b} are vastly different from the molecules they are attempting to model. In our experience, using C₁–C₃ hydrocarbons to balance homodesmotic equations always gave poorer results than when we used the larger reference hydrocarbons that do in fact have such 1,3-interactions. The necessity to include such 1,3-interactions in protobranching has recently been criticized.^{13c,d}

Since we have traditionally measured SEs relative to an acyclic strain-free reference compound, our best estimate for the SE of cyclohexane remains at 2.2 kcal/mol.^{7a} This SE was reported as 2.2 kcal/mol^{7d} at the G2 level based upon the cyclization protocol and corroborated at a higher level of theory (CBS-APNO) as 2.18 kcal/mol, based upon the CH₂ energy equivalent method.^{7a}

SE in Cyclooctane

a. Cyclization Method. When *n*-octane is adjusted for the removal of two hydrogen atoms and the formation of the C–C bond attending cyclization to cyclooctane, an SE of 12.2 kcal/mol^{14a} (Table 1) was predicted for the lowest energy chair-boat conformation.¹⁵

The crown conformation of cyclooctane was found to be 1.75 kcal/mol higher in energy at this G3 level. Using a simple homodesmotic equation, cyclooctane + *n*-hexane = cyclohexane + *n*-octane (eq 2), we get a difference in SE of 10.2 kcal/mol and upon correction for the nonzero SE of cyclohexane, the SE of cyclooctane is predicted to be 12.4 kcal/mol in excellent agreement with the above methods.



b. Cycloalkane SE by the CH₂ Insertion Method. Employing a variation of this expansion protocol, insertion of a –CH₂– energy equivalent into cyclooctane, provides cyclononane that has a slightly higher predicted SE of 15.5 kcal/mol due to the increased transannular interactions in this medium ring. While we do not guarantee with certainty that we have isolated the global minimum in this case, the cyclononane molecule we report here is the so-called global TBC minimum conformer described in detail by De Almeida and co-workers in a very thorough conformational study where eight different conformers were located at the MP2 level of theory.¹⁵ The calculated SEs for cyclooctane and cyclononane, arrived at by both cyclization and CH₂ insertion, are in excellent accord with earlier SE assignments based upon molecular mechanics calculations.⁹

The SE of cycloheptane derived from extrusion of a CH₂ group from cyclooctane suggests an SE of 8.4 kcal/mol when the total energies are adjusted for the SE of cyclooctane (Table 1). Expansion of cyclohexane by a CH₂ group suggests an SE for cycloheptane of 8.5 kcal/mol when the SE of cyclohexane is assigned as 2.2 kcal/mol. The internal consistency of this series of reactions is gratifying and supports our long standing contention that this methodology has fewer internal errors and represents a substantial improvement over the use of homodesmotic reactions.⁷

c. SE in *E*- and *Z*-Cyclooctene. When this cyclization method was applied to *Z*-4-octene,^{14b} it came as no surprise that the SE of the resulting *Z*-cyclooctene was 5.4 kcal/mol lower than that of cyclooctane because the introduction of a C=C constitutes the loss of two transannular interactions resulting in a net

- (14) (a) For the cyclization method the equation $SE = E_{cyclic} - E_{acyclic} - E_{corr}$ was used to estimate the SE. The energy balancing terms required are the breaking two C–H bonds and forming one C–C bond. All energies reported are total energies from G3 calculations; $E_{corr} = 2E_{C-H} - E_{C-C} + 2E_H = 2(E_{CH_3CH_2CH_2CH_3} - E_{CH_3CH_2CH_2CH_2}) - (E_{n-octane} - 2E_{CH_3CH_2CH_2CH_2}) + 2(E_H) = -1.180743$ where $E_H = (-0.501003)$ au at the G3 level and E_{C-H} = the energy difference between *n*-butane and its terminal primary free radical and H atom (–0.158949 au); E_{C-C} = the energy difference between *n*-octane and two primary *n*-butane free radicals (–0.139161 au) with an $E_{corr} = -1.180743$ au. (b) For *Z*-4-octene $E_{C-H} = -0.159006$ au, the energy difference between *Z*-4-octene and its primary terminal free radical + H atom and $E_{C-C} = -0.139161$ au with an $E_{corr} = -1.180857$ au. (c) For *E*-4-octene $E_{C-H} = -0.159316$ au, the energy difference between *E*-4-octene and its primary terminal free radical + H atom and $E_{C-C} = -0.139161$ au with an $E_{corr} = -1.181477$ au. (d) For 4-octyne $E_{C-H} = -0.159484$ au, the energy difference between 4-octyne and its primary terminal free radical + H atom and $E_{C-C} = -0.139161$ au with an $E_{corr} = -1.181813$ au. (e) For 3,3-difluoro-4-octyne $E_{C-H} = -0.16054$ au, the energy difference between 3,3-difluoro-4-octyne and its primary terminal free radical + H atom and $E_{C-C} = -0.139161$ au with an $E_{corr} = -1.183925$ au.
- (15) For a thorough discussion of the various conformations of cyclooctane and cyclononane calculated at the MP2 level see: (a) Rocha, W. R.; Pliego, J. R., Jr.; Resende, S. M.; Dos Santos, H. F.; De Oliveira, M. A.; De Almeida, W. B. *J. Comput. Chem.* **1998**, *19*, 524. (b) Franco, M. L.; Ferreira, D. E. C.; Dos Santos, H. F.; De Almeida, W. B. *Int. J. Quantum Chem.* **2007**, *107*, 545.

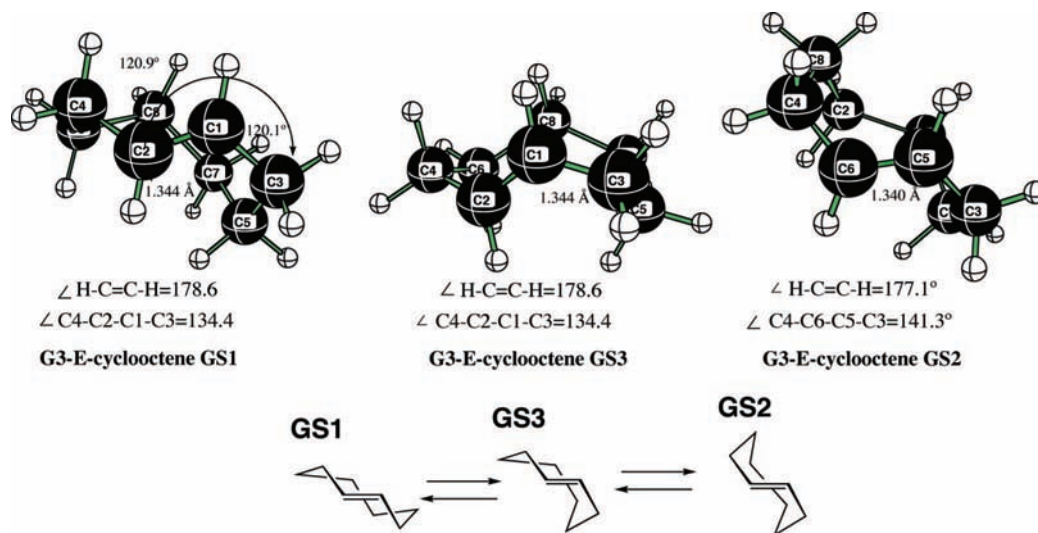


Figure 1. Three ground-state conformers of *E*-cyclooctene at the G3 level. It did surprise us when we recently reported^{7a} that the SE of cyclohexene was about 1.5 kcal/mol lower than that of cyclohexane because as noted above we have become accustomed over the years to assuming the SE of this “strain-free” cyclic C₆ saturated hydrocarbon to be zero.

One of the more intriguing molecules that have been used over the years in mechanistic probes is *E*-cyclooctene. This cyclic alkene has generally been described as having a “highly strained twisted C=C” that often exhibits enhanced reactivity relative to a simple disubstituted alkene. This optically active molecule is of particular interest because it does not have a chiral center, possesses only molecular asymmetry, and is void of the more classical functional groups. It demonstrates its molecular asymmetry as a result of restricted rotation of the C=C bond through its hexamethylene chain. This strained cyclic alkene was first resolved into its enantiomers by Cope in a classic experiment utilizing diastereomeric platinum complexes.^{2b,c} The levorotatory enantiomer was assigned the *R* configuration^{2d} and the Arrhenius activation energy for thermal racemization was shown to be relatively high at 35.6 kcal/mol. However, this oversimplified version of the conformational aspects of *E*-cyclooctene was immediately challenged by Roberts¹⁶ who suggested that in addition to the asymmetrical environment of the C=C, a second element of dissymmetry, the C⁵–C⁶ bond, also existed as a component of chirality. It was suggested that the alkene could potentially exist as two basic structures, a twist (or crown) and a chair conformation. It was further suggested that the twisting of this CH₂–CH₂ single bond through the ring appeared to be about as difficult as interconversion of the absolute configurations of the C=C bond.¹⁷

(16) Binsch, G. B.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 5157.

(17) This controversy preceded the introduction of diastereotopic hydrogens (Mislow and Raban In *Topics in Stereochemistry*; 1967; Vol. 1, p 2), and it was difficult at that time to comprehend how the NMR of two “enantiomers” could differ. *E*-Cyclooctene exhibits a multiplet in its proton NMR spectrum centered upfield at ≈ 0.5 ppm as a consequence of two hydrogens of the C⁵–C⁶ fragment buried in the π -cloud of the transannular C=C. Interconversion of the twist with the chair conformer of (+)-*E*-cyclooctene, by twisting the C⁵–C⁶ fragment through the ring, exchanges the environment of these two hydrogens in and out of the π -cloud while maintaining the same absolute configuration of the C=C. A stereospecific synthesis of *E*-cyclooctene, with stereospecific deuteration at C⁵–C⁶, could have provided a conformational assignment of this diastereomeric alkene. Unfortunately, the untimely death of Professor Cope on June 4, 1966, prevented completion of these experiments.

We reported an early X-ray analysis of the dibromocarbene adduct of *E*-cyclooctene¹⁸ that did support the assignment made by Cope that the twist form is indeed the ground state, but this question was not satisfactorily resolved until 30 years later when reliable theoretical studies on such eight-carbon systems became feasible.¹⁹ Indeed, the process of racemization and interconversion of these two basic conformations of *E*-cyclooctene, as suggested by Roberts,¹⁶ is not a simple manner as noted in an exemplary theoretical analysis reported by Olson.^{20a} Although the rate-limiting transition state for racemization involving twisting the C=C through the ring is formed directly, arriving at the actual mirror image GS enantiomer involves two consecutive ring inversion TSs and one intermediate in what Olson has termed the “jump rope” mechanism.^{20a}

The cyclization of *E*-4-octene to *E*-cyclooctene^{14c} suggests an SE of 17.9 kcal/mol; a value 11.1 kcal/mol higher than that of *Z*-cyclooctene but surprisingly only 5.7 kcal/mol greater than that of cyclooctane. At the G3 level the total energy of *E*-cyclooctene is 10.1 kcal/mol higher in energy than its *Z*-isomer. An earlier estimate of the SE in *E*-cyclooctene was quoted in a review as 16.4 kcal/mol¹² with no supporting data given. On the basis of the CH₂ insertion protocol, we suggest an SE for *E*- and *Z*-cyclononene of 16.4 and 11.4 kcal/mol. This represents an increase in SE for the homologous *Z*-alkene but a decrease in the *E*-alkene relative to the cyclooctene systems. We have also identified three conformations of *E*-cyclooctene at the G3 level of theory and as anticipated the twist conformer is 5.4 kcal/mol lower in energy than the more stable of two chair conformations. The latter two conformations (GS2 and GS3), as noted by Olson,^{20a} are separated by the TS required to complete the overall racemization process, and GS2 is only 0.5 kcal/mol lower in energy than GS3 due to the chair–boat relationship of the end CH₂ groups (Figure 1). The

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(19) (a) Nevens, N.; Chen, K.; Allinger, J. *Comput. Chem.* **1996**, *17*, 669. (b) Leong, M. K.; Mastryukov, V. S.; Boggs, J. E. *J. Mol. Struct.* **1998**, *445*, 149. (c) Barrows, S. E.; Eberlein, T. H. *J. Chem. Educ.* **2005**, *82*, 1334.

(20) (a) Olson, L. P. *Internet J. Chem.* **1999**, *2*. (b) For a study on the mechanism of the thermal isomerization of *E*-cyclooctene see: Andrews, U. H.; Baldwin, J. E.; Grayston, M. W. *J. Org. Chem.* **1982**, *47*, 287.

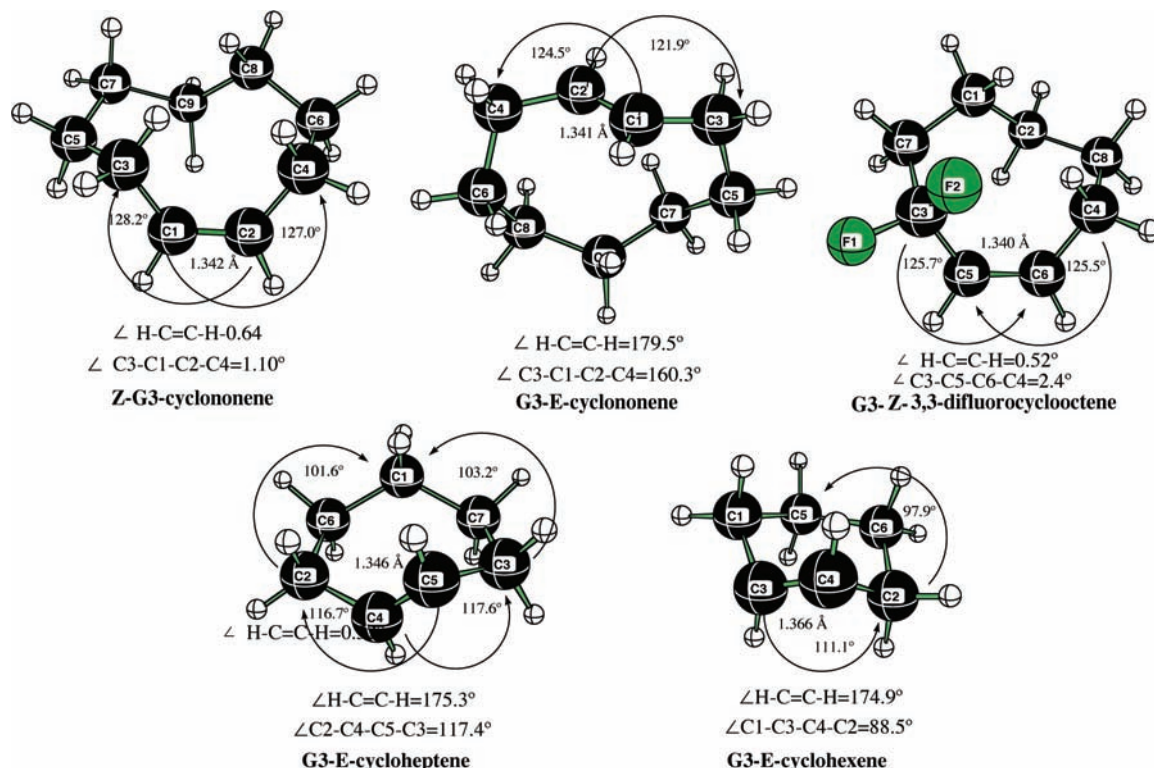


Figure 2. Selected *E*- and *Z*-cycloalkenes at the G3 level.

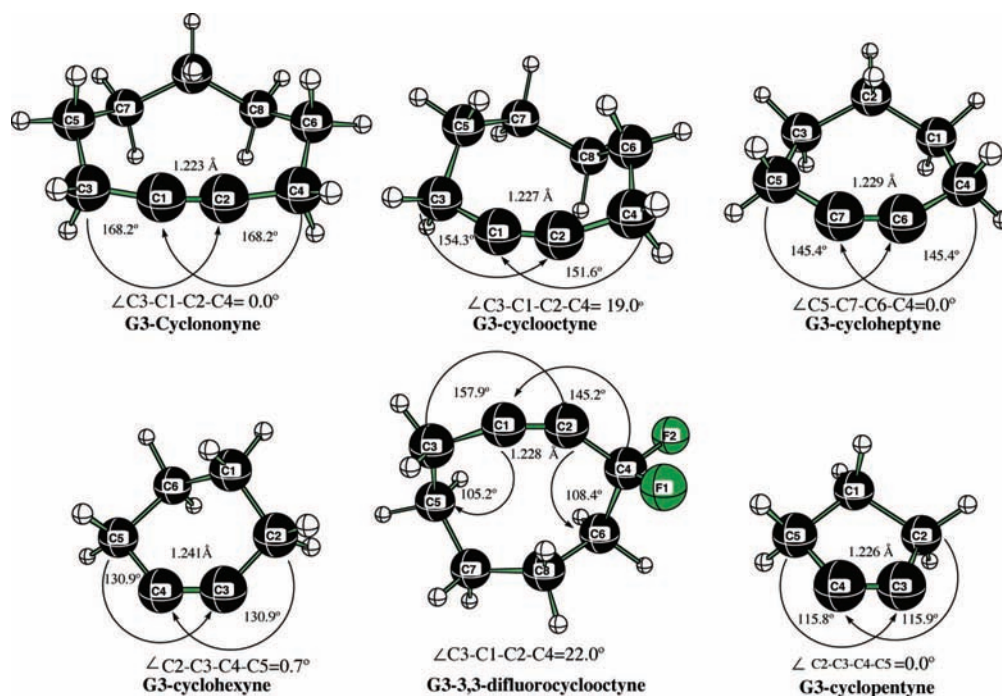


Figure 3. Cyclic alkynes ($\text{C}_5\text{--C}_9$) optimized at the MP2(Full)/6-31G(d) level (G3).

Cartesian coordinates for these and related molecules may be found in the Supporting Information.

The effect of the ring SE on chemical reactivity for smaller cyclic alkenes has been a point of interest for many years. The SE of *Z*-cycloheptene, based upon the extrusion of a CH_2 group from *Z*-cyclooctene, is predicted to be 5.8 kcal/mol. Ring expansion of cyclohexene suggests a comparable SE of 5.4 kcal/mol when the estimated SE of cyclohexene is 0.7 kcal/mol.^{7a} Although an SE for highly strained *E*-cycloheptene has not to

our knowledge been reliably assigned,²¹ we felt that the present study afforded an excellent opportunity to provide an internally consistent set of SEs for such highly strained cyclic alkenes with high accuracy. When the above exercise is repeated for

(21) For earlier ab initio studies on *E*-cycloheptene see: (a) Cain, D.; Pawar, D. M.; Noe, E. A. *J. Mol. Struct. (Theochem)* **2004**, 674, 251. (b) Squillacote, M. E.; DeFellipis, J.; Shu, Q. *J. Am. Chem. Soc.* **2005**, 127, 15983.

the highly strained *E*-isomer of cycloheptene, relative to *E*-cyclooctene, we get an SE of 25.2 kcal/mol.

The SE of *E*-cyclohexene is best arrived at by a simple comparison of the total energies (G3) of the *E*- and *Z*-isomers ($\Delta E = 50.0$ kcal/mol) because the SE of *Z*-cyclohexene is close to zero (0.7 kcal/mol).^{7a} The resulting SE of 49.3 kcal/mol provides ample explanation for the inability to isolate this highly strained cyclic alkene.

As expected, the geometry of *E*-cyclohexene alkene is very distorted (Figure 2). Although the H–C=C–H dihedral angle is close to the anticipated 180°, the corresponding C¹–C³–C⁴–C² dihedral is only 88.5°. The C=C–C and C²–C⁶–C⁵ angles are also contracted (111.1° and 97.9°).

d. SE in Cycloalkynes. Cyclization of 4-octyne to cyclooctyne, with the energy corrections for the cleavage of two C–H bonds and C–C bond formation attending ring closure,^{14d} suggests a SE of 19.9 kcal/mol which places its SE 2.0 kcal/mol above that of *E*-cyclooctene. While cyclooctyne can be isolated and characterized, the corresponding seven-, six-, and five-membered-ring alkyne analogues have but a fleeting existence and have only been observed in low-temperature experiments or as transient intermediates while cyclobutene remains elusive.

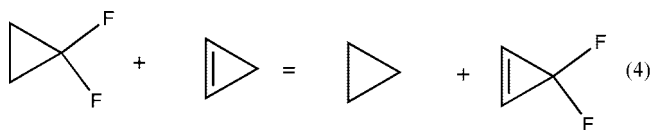
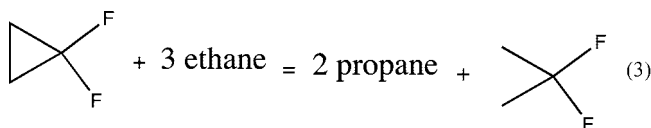
On the basis of the difference in G3 total energies, isomeric 1,2-cyclooctadiene has an SE (11.9 kcal/mol) that is 8.0 kcal/mol lower than cyclooctyne. Ring expansion of this cyclic allene to 1,2-cyclononadiene, by addition of a CH₂ energy equivalent, suggests a slight reduction in SE to 10.9 kcal/mol. The fact that 1,2-cyclooctadiene is not readily isolable may be due to the fact that it is both bent and twisted. The C=C=C angles of 161.6° vs 172.8° show some evidence of ring strain in both allenes. The relative positions of the terminal C–H bonds ideally should be 90° are 95.7° in the C⁸ allene but nearly perfect in the C⁹ case (89.9°). The H–C–C=C dihedral angles in the former are 127.3° and 146.2° but are both 136.6° in 1,2-cyclononadiene indicative of twisting in the more kinetically labile allene.

Ring contraction of cyclooctyne to cycloheptyne, based upon the CH₂ insertion/extrusion protocol, results in a dramatic increase in SE to 25.4 kcal/mol while ring expansion to cyclononyne reduces the SE by 6.5 kcal/mol (Table 1). Thus, the difference in SE for cycloheptyne versus cycloheptene ($\Delta SE = 19.8$ kcal/mol) is much greater than that for cyclooctyne compared to *Z*-cyclooctene ($\Delta SE = 13.1$ kcal/mol). As anticipated, the estimated SE for cyclohexyne based upon two CH₂ energy equivalents was 40.1 kcal/mol. A similar procedure for cyclopentyne (extruding 3 × CH₂) produces a highly strained cyclic alkyne with an SE = 48.4 kcal/mol, a value somewhat lower than an earlier estimate of 59 kcal/mol based upon experimental data.²²

The geometries of this series of cycloalkynes (Figure 3) have an obvious influence upon their SE. While the calculated C–C≡C–C dihedral angles for most of the cyclic alkynes approach zero (0.008–0.68°) this dihedral angle for cyclooctyne and DIFO deviates from zero by 19.0° and 22.0°, suggesting an enhanced reactivity due also to the twisting of the C=C in that plane. The C–C≡C bond angles for C₉ through C₅ show a progressive decline for the entire series with a slight asymmetry about the triple bond. This bond angle in cyclononyne was calculated to be an average of 168.2° and the angles in cyclooctyne deviated 27° from the ideal angle of 180°. These bond angles in the C₇, C₆, and C₅ cyclic alkynes were calculated to be 145.4°, 130.9°, and 115.9°, respectively.

This deviation from the ideal C–C≡C angle of 180° is largely responsible for the increased SE for these highly strained cyclic alkynes.

The above data provide considerable support for the suggestion that facile [3 + 2] dipolar cycloaddition reactions with azides are a consequence of not only the ring SE in cyclooctyne, but also the twist strain of the triple bond. First, we address the more fundamental question of the influence upon cycloaddition rate of a difluoro substituent adjacent to the triple bond. We know that in general, fluorine prefers to be bonded to carbon orbitals having high p character. In an earlier report on SE we showed that *gem*-difluoro substitution on a three-membered ring results in a marked increase in the SE of a cyclopropane.^{7c} The homodesmotic reaction (G3) involving 2,2-difluoropropane giving 1,1-difluorocyclopropane (eq 3) predicts an SE of 40.9 kcal/mol; an effective increase in SE over the parent cyclopropane of 14 kcal/mol. This finding is also supported by heats of



hydrogenation that indicated a thermodynamic increase in the energy of hydrogenation of the difluorocyclopropane relative to cyclopropane of 13.4 kcal/mol.^{7c} Equation 4, however, suggests that *gem*-difluoro substitution on cyclopropene results in a net stabilization of 9.0 kcal/mol. The question remains as to the effect of *gem*-difluoro substitution adjacent to the triple bond in an alkyne? A similar but smaller reduction in SE is noted for *gem*-difluoro substitution adjacent to a triple bond. The cyclization exercise for 3,3-difluoro-4-octyne^{14e} produces DIFO⁴ with a predicted SE slightly reduced ($\Delta SE = 2.6$ kcal/mol) relative to the parent cyclooctyne to 17.3 kcal/mol. Thus, difluorinated cyclooctyne has a ring SE comparable to that of *E*-cyclooctene and it remains an open question as to the relative reactivity of these two modestly strained cyclic hydrocarbons.

e. Relationship between SE and the Enthalpy of Hydrogenation. One of the established methods used in the past to estimate the chemical reactivity of an unsaturated hydrocarbon has been to examine the amount of heat released upon its hydrogenation. Although there has been a relationship established between the enthalpy of C=C hydrogenation and the ring SE of alkenes,^{7b} much less is known about this correlation with alkynes. For example, the enthalpy of hydrogenation (ΔH_{hyd}) of a disubstituted alkene is about 4 kcal/mol lower than that of ethylene (Table 2). In general, a linear *Z*-alkene has a ΔH_{hyd} that is about 1 kcal/mol higher than the corresponding *E*-alkene. A highly strained alkene such as cyclopropene (SE = 54.1 kcal/mol) has a correspondingly high $\Delta H_{\text{hyd}} = 54.6$ kcal/mol. By contrast, cyclobutene has a relatively high SE (29.5 kcal/mol)^{7b} but exhibits a more typical $\Delta H_{\text{hyd}} = 32.3$ kcal/mol. Although *E*-cyclooctene is not nearly as strained as cyclobutene, it has a comparable heat of hydrogenation ($\Delta H_{\text{hyd}} = 33.8$ kcal/mol) that is much higher than that of *Z*-cyclooctene ($\Delta H_{\text{hyd}} = 23.6$ kcal/mol). This decrease in the heat liberated upon the addition of H₂ across the C=C bond ($\Delta\Delta H_{\text{hyd}} = 10.2$ kcal/mol) is a reflection of the reduced SE of *Z*-cyclooctene (SE = 6.8 kcal/

Table 2. Heat of Hydrogenation (H_{hyd}) of Alkenes and Alkynes to their *Z*-Alkenes at the G2, G3, and CBS-Q Levels of Theory

	G2	G3	CBS-Q
acetylene		41.3	
ethylene	32.3		31.9
(<i>E</i>)-2-butene	27.5		
(<i>Z</i>)-2-butene	28.8		
(<i>E</i>)-3-hexene		27.8	27.2
(<i>Z</i>)-3-hexene		29.2	
cyclopropene	54.4	54.6	54.3
cyclobutene	32.2	32.3	31.4
cyclopentene	26.4	26.3	
cyclohexene		100.4	
<i>Z</i> -cyclohexene	28.3	28.1	27.9
		27.1 ^c	
<i>E</i> -cyclohexene		74.0	
cyclohexyne		76.3	
<i>Z</i> -cycloheptene	25.8	26.4	
		25.85 ^c	
<i>E</i> -cycloheptene		52.6	
cycloheptyne		56.6	
<i>E</i> -4-octene		27.6	
<i>Z</i> -4-octene		28.8	
		27.39 ^b	
(<i>E</i>)-cyclooctene		33.8	
		32.24 ^a , 34.41 ^a	
(<i>Z</i>)-cyclooctene		23.6, 22.98 ^a , 23.53 ^a , 23.04 ^a	
4-octyne		35.9	
		35.4 ^b	
<i>Z</i> -3,3-difluorocyclooctene		26.4	
cyclooctyne		50.1	
		45.5 ^b	
3,3-difluorocyclooctyne		53.6	
3,3-difluorooctyne		41.1	
1,2-cyclooctadiene		42.1	
(<i>Z</i>)-cyclononene		25.0	
		23.67 ^c	
(<i>E</i>)-cyclononene		29.1	
		26.62 ^c	
cyclononyne		38.2	
		38.3 ^b	
1,2-cyclononadiene		36.5	

^a Rogers, D. W.; von Voithenberg, H.; Allinger, N. L. *J. Org. Chem.* **1978**, *43*, 360. ^b Turner, R. B.; Jarrett, A. D.; Goebel, P.; Mallon, B. J. *J. Am. Chem. Soc.* **1973**, *95*, 790. ^c Turner, R. B.; Meador, W. R. *J. Am. Chem. Soc.* **1957**, *79*, 4133.

mol) relative to that of the fully saturated product of hydrogenation, cyclooctane. Since cyclooctane experiences an increase in transannular H–H interactions, as described above, its internal strain increases (SE = 12.2 kcal/mol). The ΔH_{hyd} of the linear alkene, *Z*-4-octene, is comparable to that of a typical disubstituted alkene or that of the essentially strain-free cyclohexene.

However, the enthalpy of hydrogenation (Table 2) of highly strained *E*-cycloheptene ($\Delta H_{\text{hyd}} = 52.6$ kcal/mol) and *E*-cyclohexene ($\Delta H_{\text{hyd}} = 74.0$ kcal/mol) clearly reflect the relief of twist strain upon saturation and the heat liberated is close to the sum of the heat of hydrogenation of the *Z*-alkene plus its SE.

The situation with both cyclic and acyclic alkynes is much more complex. First, the enthalpy of hydrogenation of a linear alkyne such as 4-octyne is considerably higher than that of the corresponding alkene ($\Delta H_{\text{hyd}} = 35.9$ kcal/mol). Even cyclononyne, which has a modest SE of 13.4 kcal/mol, exhibits a $\Delta H_{\text{hyd}} = 38.2$ kcal/mol. Thus, the reduction in the degree of unsaturation upon going from an alkyne to an alkene is accompanied by a rather large liberation of heat as a result of the addition of dihydrogen. Cyclooctyne has a calculated $\Delta H_{\text{hyd}} = 50.1$ kcal/mol, a value, however, that appears to be much greater than that based upon its SE of 19.9 kcal/mol. Recall,

Table 3. Calculated Activation Energy (ΔE^\ddagger) for Concerted [3 + 2] Cycloaddition Reactions with $\text{CH}_3\text{-N}_3$

alkyne/alkene	method	barrier kcal/mol
acetylene	G3	20.1
acetylene	B3LYP/6-311+G(d,p)	19.5
ethylene	G3	19.3
ethylene	B3LYP/6-311+G(d,p)	19.7
<i>Z</i> -4-octene	B3LYP/6-311+G(d,p)	23.9
4-octyne	G3	17.5
4-octyne	B3LYP/6-311+G(d,p)	23.6
cyclooctyne	G3	8.3
cyclooctyne	G3//B3LYP/6-311+G(3df,2p)	8.2
cyclooctyne	G3//MP2/6-311+G(d,p)	8.7
cyclooctyne	B3LYP/6-311+G(d,p)	11.5
cyclooctyne	B3LYP/6-311+G(3df,2p)	12.9
<i>E</i> -cyclooctene	G3	11.4
<i>E</i> -cyclooctene	B3LYP/6-311+G(d,p)	14.7
<i>E</i> -cyclooctene	B3LYP/6-311+G(3df,2p)	16.5
<i>Z</i> -cyclooctene	B3LYP/6-311+G(d,p)	21.7
<i>Z</i> -cyclooctene	B3LYP/6-311+G(3df,2p)	23.6
3,3-difluoro-cyclooctyne(syn)	B3LYP/6-311+G(d,p)	9.4
3,3-difluoro-cyclooctyne(anti)	B3LYP/6-311+G(d,p)	10.9

the SE of cyclopropene is 54.1 kcal/mol and its enthalpy of hydrogenation is 54.6 kcal/mol. However, we can now attribute this increase in ΔH_{hyd} , at least in part, to the out-of-plane twist noted above for cyclooctyne. So part of the overall relationship that exists between SE and reactivity relates to the degree of strain in the alkyne, as well as the amount of relief of ring strain or twist strain upon reduction to the corresponding alkene. Second, the ΔH_{hyd} of the more strained cycloalkynes increase at a rate even greater than that indicated by their SEs. The enthalpies of hydrogenation of cycloheptyne, cyclohexyne and cyclopentene are calculated (G3) to be 56.6, 76.3, and 100.4 kcal/mol, respectively. The hydrogenation of cyclic allenes, 1,2-cyclooctadiene and 1,2-cyclononadiene, to their corresponding *Z*-alkenes, also appear to have a quite high ΔH_{hyd} given their relatively modest SEs. More importantly, the hydrogenation enthalpy for DIFO has increased by 3.5 kcal/mol relative to the parent alkyne to $\Delta H_{\text{hyd}} = 53.6$, suggesting an increase in reactivity. These combined data for the series of cyclic alkynes clearly indicate that reduction by H_2 to a lower level of unsaturation is highly favored energetically and this in turn suggests that the rate of [3 + 2] cycloaddition of an azide with an alkyne should be quite high for a cyclic alkyne and especially rapid for DIFO.

f. Relative Rate of [3 + 2] Cycloaddition Reactions with Methyl Azide. A second primary goal of this study is to accurately measure the effect of ring SE on the rate of dipolar [3 + 2] cycloaddition of azides to alkynes. Recent DFT calculations by Houk and co-workers,²³ at the B3LYP/6-31G* level, showed a reduction in activation energy for the cycloaddition of phenyl azide to cyclooctyne of 8.2 kcal/mol relative to that of the parent acetylene ($\Delta G^\ddagger = 16.2$ kcal/mol). A further decrease in activation energy of 2 kcal/mol was attributed to the inductive effects of the 3,3-difluoro moiety in DIFO.

In order to place the calculated activation barriers for [3 + 2] cycloaddition to cyclooctyne, in perspective, we first compare the activation energy (ΔE^\ddagger) for [3 + 2] cycloaddition of methyl azide to a series of alkenes and related alkynes (Table 3). For comparison, the G3 activation barrier for [3 + 2] cycloaddition

(22) Broadus, K. M.; Kass, S. R. *J. Am. Chem. Soc.* **2001**, *123*, 4189.

(23) Ess, D. H.; Jones, G. O.; Houk, K. N. *Org. Lett.* **2008**, *10*, 1633.

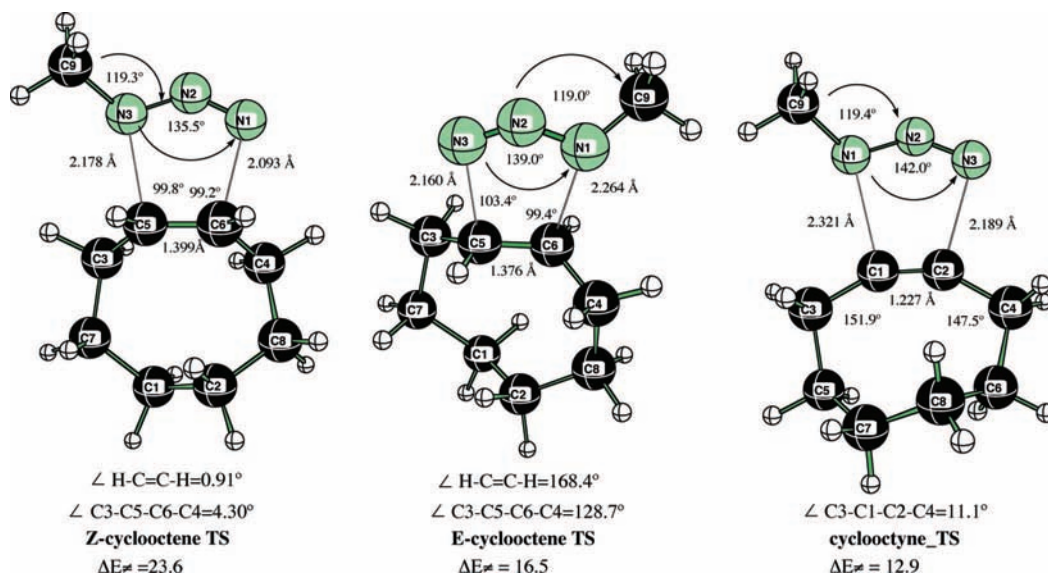


Figure 4. Transition structures for cycloaddition of methyl azide to *E*- and *Z*-cyclooctene and cyclooctyne at the B3LYP/6-311+G(3df,2p) level. Activation energies are in kcal/mol.

of methyl azide to acetylene is 0.8 kcal/mol greater than that for addition to ethylene. The rate of cycloaddition of methyl azide to 4-octyne is only slightly lower than that for cycloaddition to *Z*-4-octene ($\Delta\Delta E^\ddagger = 0.3$ kcal/mol). However, the G3 barrier for [3 + 2] cycloaddition of methyl azide to cyclooctyne ($\Delta E^\ddagger = 8.3$ kcal/mol) is 9.2 kcal/mol lower than that for the comparable addition to 4-octyne, reflecting the considerable difference in SE of the cyclic alkyne ($\Delta\Delta\text{SE} = 19.9$ kcal/mol). As noted above, the π -bond in cyclooctyne is twisted out of plane by some 19° and that also obviously contributes to the rate increase. The rather large discrepancy in calculated activation barriers ($\Delta\Delta E^\ddagger = 4.6$ kcal/mol) for cyclooctyne at the G3 level [optimized geometry at MP2/6-31G(d)] with that at the DFT level with a relatively flexible basis set [B3LYP/6-311+G(3df,2p)] raised the question as to whether this is a basis set or an electron correlation effect?

However, applying the G3 protocol to this TS, when the geometry is frozen at the MP2/6-311+G(d,p) or the B3LYP/6-311+G(3df,2p) afforded activation barriers in close agreement with the original G3 value (Table 3), suggesting that the effects of electron correlation is dominant in determining the magnitude of the barrier. This may well be a reflection of the numbers of lone-pairs of electrons in the azide moiety.

The above data suggest that the magnitude of the DFT barriers are somewhat inflated, and this fact should be taken into consideration with major emphasis being placed upon the relative activation barriers. For comparison, the calculated activation barrier for this cycloaddition reaction (Figure 4) with *E*-cyclooctene ($\Delta E^\ddagger = 16.5$ kcal/mol), where the π -bond is also twisted out of plane by 25.7° ($\angle \text{C}-\text{C}=\text{C}-\text{C} = 128.7^\circ$) is greater than that for cyclooctyne but considerably less than that of *Z*-cyclooctene ($\Delta E^\ddagger = 23.6$ kcal/mol) as a consequence of its considerable SE (17.9 kcal/mol).

Significantly, the barrier for [3 + 2] cycloaddition of methyl azide to DIFO is 2.1 kcal/mol lower than that for its parent alkyne as a consequence of the electron withdrawing effects of the α -difluoromethylene moiety (Figure 5). The syn regioisomer, with the methyl group of methyl azide adjacent to the CF_2 group, is slightly favored over the opposite anti orientation ($\Delta\Delta E^\ddagger = 1.2$ kcal/mol).

We also wish to identify the origin of the rate increase for [3 + 2] cycloaddition to a strained C–C triple bond. A comparison between reactions that produce highly strained products like epoxides and [3 + 2] cycloaddition reactions that form less-strained five-membered ring products is instructive. Alkenes strained by twist or π -bond torsion, such as *E*-cyclooctene, often exhibit lower barriers for electrophilic addition reactions such as peracid epoxidation. The decrease in the barrier is primarily due to relief of twist strain in the oxygen transfer step.²⁴

The calculated [B3LYP/6-311+G(3df,2p)]/B3LYP/6-31+G(d,p) barriers for peroxyformic acid epoxidation of *E*- and *Z*-cyclooctene, $\Delta E^\ddagger = 6.1$ and 9.6 kcal/mol, reflect the differences in SE (17.9 and 6.8 kcal/mol) between these two medium ring alkenes. However, the relatively small $\Delta\Delta E^\ddagger = 3.5$ kcal/mol also suggests that the epoxide product of *E*-cyclooctene still retains some of its transannular ring strain. The experimental activation energy difference between these isomeric alkenes for *m*-chloroperbenzoic acid epoxidation (a more reactive peracid) was reported to be 2.3 kcal/mol ($E_a = 7.6$ and 9.9 kcal/mol) in excellent agreement with the differences in our theoretical barriers. Although the increased rate for *E*-cyclooctene is mainly due to relief of twist-strain in the TS, the relatively small magnitude of the rate increase is a reflection of the fact that the epoxide product, a three-membered ring, is still a strained molecule (SE = 26.3 kcal/mol).^{7d}

By comparison, the activation energies for picryl azide cycloaddition to *E*- and *Z*-cyclooctene also differ by only 2.1 kcal/mol ($E_a = 11.2$ and 13.3 kcal/mol).^{25a} Likewise, the change in HOMO energy did not affect significantly the reactivity of picryl azide addition to a series of alkyl substituted alkenes. However, a good correlation was found in a plot of the log k_{rel} versus the relief of strain in the TS for a similar series of alkenes. The angle of approach of a peracid versus an azide is also a factor in determining the relative reactivities for these two classes of addition reaction. Moreover, the [3 + 2] cycloaddition product forms a five-membered ring triazole that is considerably less strained than an epoxide.

(24) Bach, R. D. In *The Chemistry of Peroxides*; Rappoport, Z., Ed.; Wiley: New York, 2006; Vol. 2, Part 1, pp 1–92.

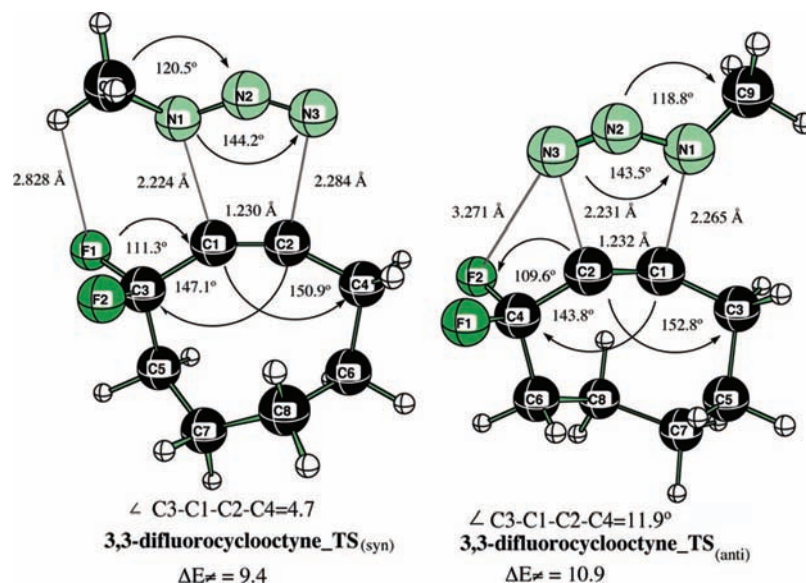


Figure 5. Transition structures for cycloaddition of methyl azide to 3,3-difluorocyclooctyne in syn and anti orientations at the B3LYP/6-311+G(d,p) level. Activation energies are in kcal/mol.

Table 4. Calculated Activation Energy (ΔE^\ddagger) for Concerted [3 + 2] Cycloaddition Reactions with Model Azides

alkyne/alkene	azide	theory	barrier kcal/mol
cyclooctyne	PhCH ₂ -N ₃	B3LYP/6-311+G(d,p)	11.4
cyclooctyne	PhCH ₂ -N ₃	B3LYP/6-311+G(3df,2p)	12.8
3,3-difluoro-cyclooctyne(syn)	PhCH ₂ -N ₃	B3LYP/6-311+G(d,p)	8.8
3,3-difluoro-cyclooctyne(syn)	PhCH ₂ -N ₃	B3LYP/6-311+G(3df,2p)	10.5
3,3-difluoro-cyclooctyne(anti)	PhCH ₂ -N ₃	B3LYP/6-311+G(3df,2p)	12.1
cyclooctyne	₂ HN(C=O)CH ₂ -N ₃	B3LYP/6-311+G(d,p)	15.3
cyclooctyne	₂ HN(C=O)CH ₂ -N ₃	B3LYP/6-311+G(3df,2p)	16.4
3,3-difluoro-cyclooctyne(anti)	₂ HN(C=O)CH ₂ -N ₃	B3LYP/6-311+G(d,p)	14.6
3,3-difluoro-cyclooctyne(anti)	₂ HN(C=O)CH ₂ -N ₃	B3LYP/6-311+G(3df,2p)	10.6
3,3-difluoro-cyclooctyne(syn)	₂ HN(C=O)CH ₂ -N ₃	B3LYP/6-311+G(d,p)	9.4
3,3-difluoro-cyclooctyne(syn)	₂ HN(C=O)CH ₂ -N ₃	B3LYP/6-311 +G(3df,2p)	11.1

The series of calculations on the relative activation barriers for the [3 + 2] cycloaddition of methyl azide demonstrate that the activation energies for addition to alkenes do not differ markedly from that for the corresponding reaction with alkynes unless the effects of ring strain are involved (Table 3). We have also clearly established a relationship between the rate of cycloaddition and the SE of the C=C double bond involved as noted for *E*-cyclooctene and cyclooctyne.

g. Cyclooctyne [3 + 2] Cycloaddition Reactions with Model Azides. The azides utilized by Bertozzi included benzyl azide and azide-labeled glycans (Ac₄GalNAz).⁴ We have carried out a series of calculations determining the activation energy for [3 + 2] cycloaddition of cyclooctyne with benzyl azide at several levels of theory. We have also modeled azide-labeled glycans with an azido-substituted acetamide [NH₂(C=O)CH₂N₃]. These results are summarized in Table 4.

The activation barriers for the [3 + 2] cycloaddition of methyl azide and benzyl azide are essentially the same while the barriers for DIFO differ by 1.1 kcal/mol (Table 4). The syn orientation of the azide group with respect to the CF₂ moiety again exhibits a slightly lower activation energy ($\Delta\Delta E^\ddagger = 1.6$ kcal/mol) and the CF₂ moiety in the syn TS does appear to affect the orientation of the benzyl group in the TS due to a relatively weak hydrogen bond of the benzyl C-H with a fluorine atom (Figure 6).

Cycloaddition of the acetamido azide [H₂N(C=O)CH₂-N₃] to cyclooctyne has a higher activation barrier than the benzyl

azide ($\Delta\Delta E^\ddagger = 3.6$ kcal/mol). The [3 + 2] cycloaddition of acetamido azide to DIFO gave a mixed result with the smaller DFT basis set favoring the syn orientation but the larger basis set favoring the anti juxtaposition of the amide group with respect to the azide functionality in the transition state. A relatively long-range (2.40 Å) hydrogen bond of the C=O to the C-H bond may be responsible for this reversion in regiochemistry.

Another aspect of this [3 + 2] cycloaddition chemistry that can influence the rate of reaction is the overall exothermicity of the reaction. While the total energy differences between isolate reactants and the cycloaddition product for *E*- and *Z*-cyclooctene with methyl azide is not very substantial (25.1 and 12.4 kcal/mol) the heats of reaction for cycloaddition to an alkyne are quite large. For example, [3 + 2] cycloaddition of methyl azide to cyclooctyne resulted in the liberation of -71.1 kcal/mol. Very similar ΔE values for the reaction of cyclooctyne with acetamido azide and benzyl azide (-70.9 and -71.4 kcal/mol) are sufficiently large to suggest a very early TS along the reaction pathway and a lowering of the activation energy consistent with general transition state theory. The Cartesian coordinates for these [3 + 2] cycloaddition reaction products are given in the Supporting Information (Table S2). Comparable ΔE values are given for [3 + 2] cycloaddition of benzyl azide (-74.7 kcal/mol) and acetamido azide (-69.8 kcal/mol) to DIFO. As can be seen for these final products of reaction (Figure 8) the NH₂ group of the acetamido group enjoys a hydrogen

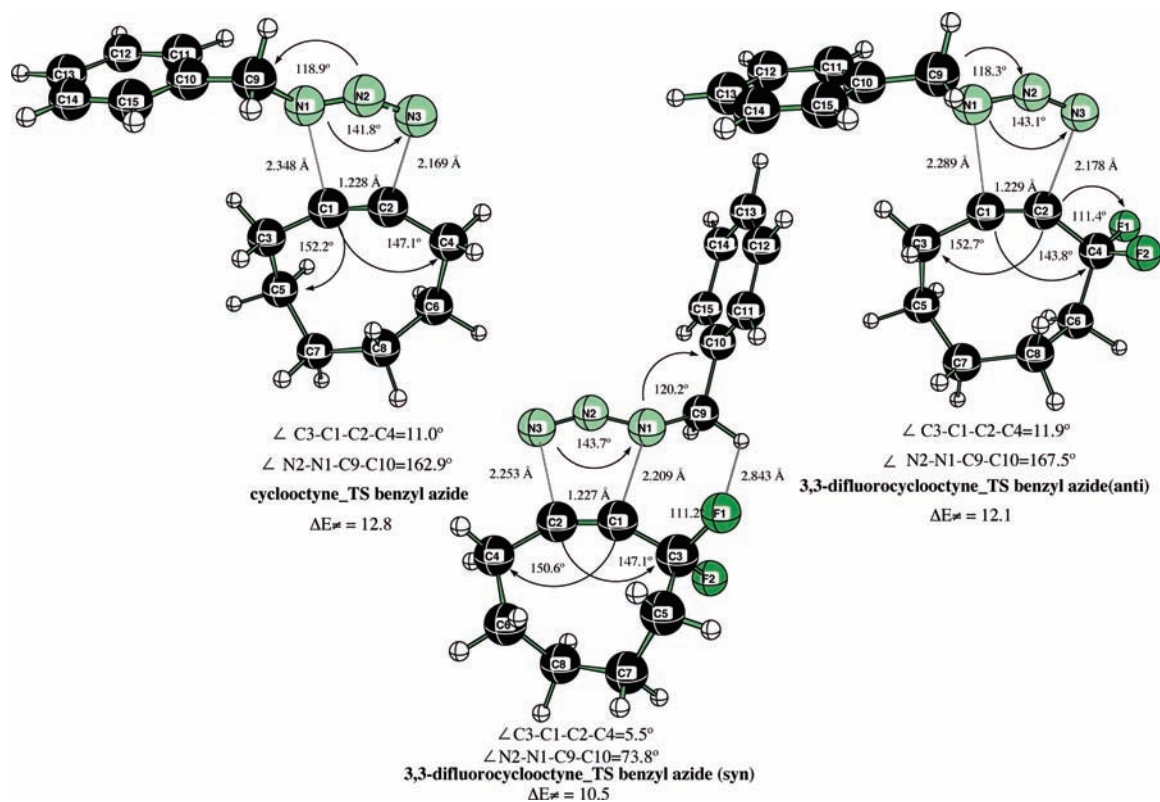


Figure 6. Transition structures for cycloaddition of benzyl azide to cyclooctyne and DIFO in the syn and anti orientations at the B3LYP/6-311+G(3df,2p) level. Activation energies are in kcal/mol.

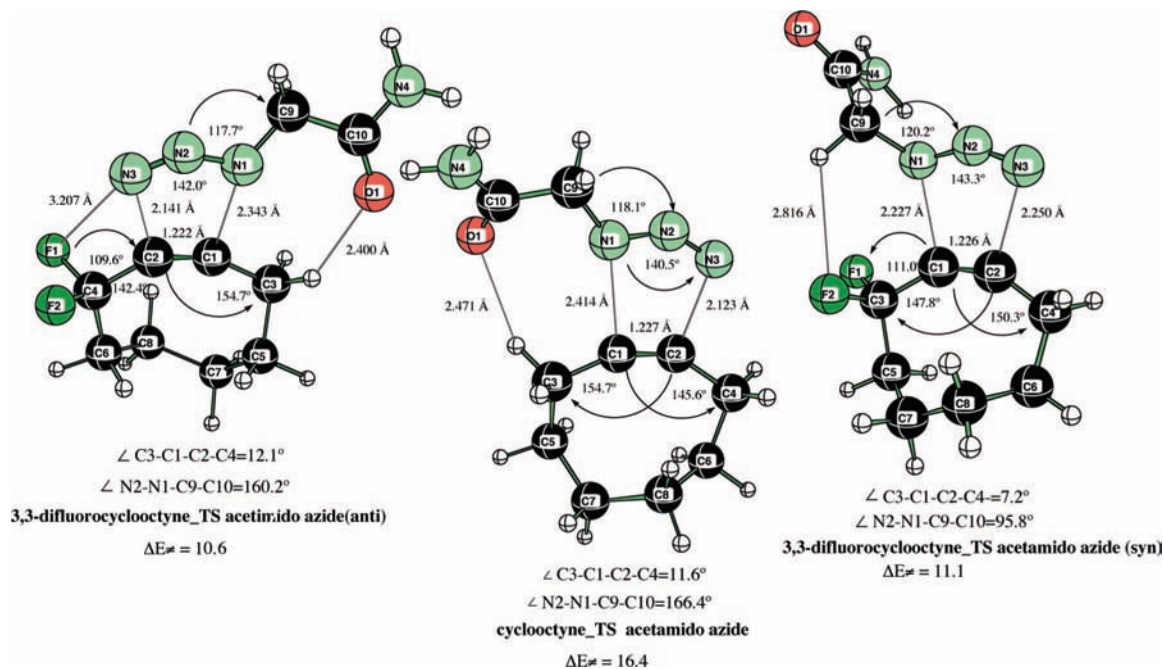


Figure 7. Transition structures for cycloaddition of acetamido azide to cyclooctyne and 3,3-difluorocyclooctyne in syn and anti orientations at the B3LYP/6-311+G(3df,2p) level. The activation barriers are in kcal/mol.

bonding interaction with the azide group in an anti orientation and a similar interaction is noted for the benzyl group of benzyl azide of the syn adduct.

Conclusions

The reactivity of an alkyne toward hydrogenation is inherently greater than that of an alkene ($\Delta\Delta H_{\text{hyd}} \approx 8$ kcal/mol). The

reactivity of an alkyne toward [3 + 2] dipolar cycloaddition is inherently greater than that of an alkene as a consequence of its increased SE and the overall exothermicity (ΔE) of the reaction. However, the corresponding rates of [3 + 2] dipolar cycloaddition of azides for linear disubstituted substrates are comparable ($\Delta\Delta E^\ddagger = 0.3$ kcal/mol). The ring SE in cyclooctyne is only modestly greater than that in *E*-cyclooctene ($\Delta SE =$

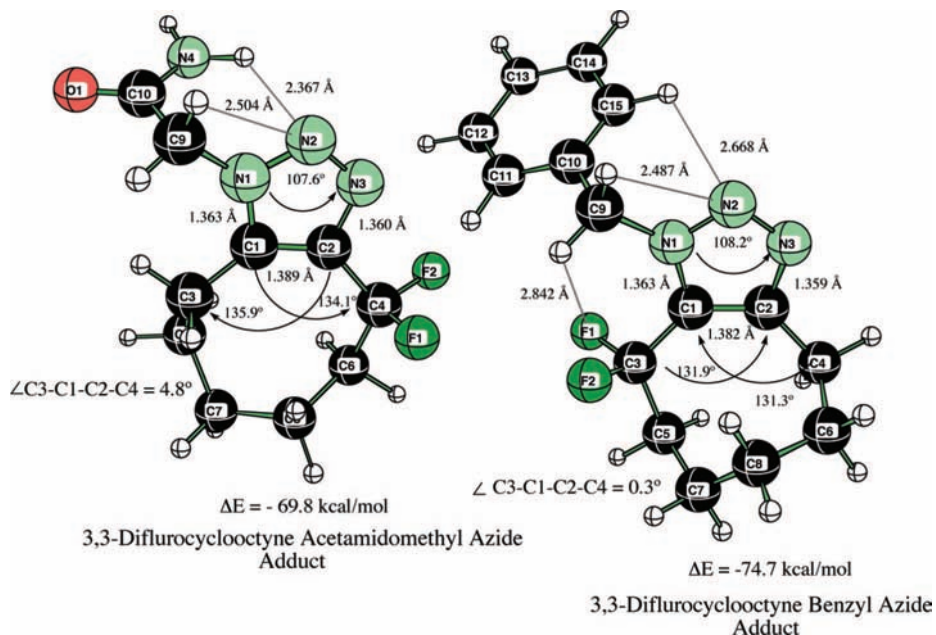


Figure 8. Final products for cycloaddition of acetamido azide and benzyl azide to 3,3-difluorocyclooctyne in anti and syn orientations at the B3LYP/6-311+G(3df,2p) level.

2.0 kcal/mol) and the relative barriers for [3 + 2] dipolar cycloaddition of methyl azide differ by just 3.6 kcal/mol [B3LYP/6-311+G(3df,2p)]. This is a reflection of not only the SE but also the out-of-plane twist of the C=C in the alkyne. The barrier for cycloaddition of benzyl azide DIFO is 2.3 kcal/mol lower than addition to the parent cyclooctyne. The *syn* orientation of the aromatic ring with respect to the CF₂ moiety is favored over the anti TS by 1.6 kcal/mol. By contrast, the anti TS for acetamido azide addition to DIFO (Figure 7) is favored by 0.5 kcal/mol and this TS exhibits a much lower barrier than that for cycloaddition to cyclooctyne ($\Delta\Delta E^\ddagger = 5.8$ kcal/mol) possibly reflecting an intramolecular hydrogen bond of the carbonyl oxygen to an “allylic” C–H bond (2.4 Å).

Computational Methods

Quantum chemistry calculations were carried out using the Gaussian03 program system²⁶ utilizing gradient geometry optimization.²⁷ The standard protocol for G3 calculations as provided in Gaussian 03 was used for most molecules. The Becke three-

parameter hybrid functional combined with the Lee, Yang, and Parr (LYP) correlation functional, denoted B3LYP,²⁸ was employed in the calculations using density functional theory (DFT). In this study we used 6-311+G(d,p) and 6-311+G(3df,2p) basis sets.²⁹ Most of calculations were performed using GridChem computational resources and services, Computational Chemistry Grid³⁰ (www.gridchem.org).

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Supporting Information Available: Total energies, Cartesian coordinates, and complete ref 26. This material is available free of charge via the Internet at <http://pubs.acs.org>

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