

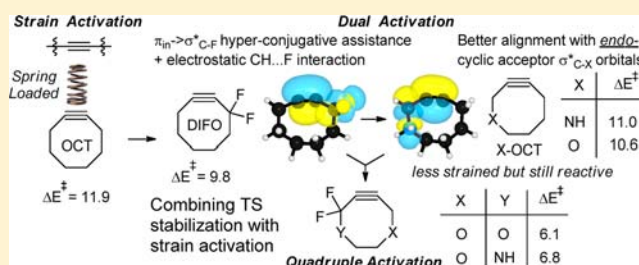
Moderating Strain without Sacrificing Reactivity: Design of Fast and Tunable Noncatalyzed Alkyne–Azide Cycloadditions via Stereoelectronically Controlled Transition State Stabilization

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S Supporting Information

ABSTRACT: Recently, we have identified two strategies for selective transition state (TS) stabilization in catalyst-free azide/alkyne cycloadditions. In particular, the transition states for the formation of both 1,4- and 1,5-isomers can be stabilized via hyperconjugative assistance for the C–N bond formation, whereas the 1,5-TS can be stabilized via C–H...X H-bonding interactions. When the hyperconjugative assistance is maximized by the antiperiplanar arrangement of propargylic σ -acceptors relative to the forming bonds, the combination of these TS-stabilizing effects was predicted to lead to ~ 1 million fold acceleration of the cycloaddition with methyl azide. The present work investigated whether hyperconjugative assistance and H-bonding can be combined with strain activation for the design of even more reactive alkynes and whether reactivity can be turned “on demand.” When stereoelectronic amplification is achieved by optimal positioning of σ -acceptors at the endocyclic bonds antiperiplanar to the breaking alkyne π -bonds, the stabilization of the bent alkyne geometry leads to a significant decrease in strain in cyclic alkynes *without* compromising their reactivity in alkyne–azide cycloadditions. The approach can be used in a modular fashion where the TS stabilizing effects are introduced sequentially until the desired level of reactivity is achieved. A significant increase in reactivity upon the protonation of an endocyclic NH-group suggests a new strategy for the design of click reactions triggered by a pH-change or introduction of an external Lewis acid.



When stereoelectronic amplification is achieved by optimal positioning of σ -acceptors at the endocyclic bonds antiperiplanar to the breaking alkyne π -bonds, the stabilization of the bent alkyne geometry leads to a significant decrease in strain in cyclic alkynes *without* compromising their reactivity in alkyne–azide cycloadditions. The approach can be used in a modular fashion where the TS stabilizing effects are introduced sequentially until the desired level of reactivity is achieved. A significant increase in reactivity upon the protonation of an endocyclic NH-group suggests a new strategy for the design of click reactions triggered by a pH-change or introduction of an external Lewis acid.

INTRODUCTION

The applications of “click chemistry”¹ range from drug design² and chemical biology³ to materials science,⁴ development of sensors,⁵ polymer chemistry⁶ and other molecular sciences. Although the copper-catalyzed variant^{7,8} of the Huisgen azide–alkyne cycloaddition (CuAAC)⁹ is arguably the most widely utilized “click reaction,”¹⁰ the toxicity of copper salts limits the utility of this fast and versatile process for *in vivo* applications.¹¹ In addition, the negative impact of copper salts on the luminescent properties of nanocrystals presents a problem in the application of click chemistry to the functionalization of quantum dots and related nanomaterials.^{12,13}

Bertozzi,¹⁴ Boons,^{3b,15} and others¹⁶ have harnessed the reactivity of activated cyclooctynes (OCT) in strain-promoted¹⁷ azide–alkyne cycloadditions (SPAAC) as metal-free alternatives to the CuAAC with reactivity suitable for a variety of applications (Figure 1).^{18,19} For example, Bertozzi and co-workers demonstrated that intracellular azide–cyclooctyne coupling occurs within hours at room temperature^{3a,20} and enables *in vivo* biological imaging.²¹ Boons introduced dibenzocyclooctyne (DIBO) reagents,¹² where further reactivity enhancements over cyclooctyne are achieved due to an increase in ring strain (more sp^2 -centers) and, in collaboration with Popik,¹⁵ developed a way to generate DIBO photochemically. Rutjes, Van Delft and co-workers introduced additional strain via cyclopropane fusion.^{16a} In an effort to “brush against the line between stability and

reactivity without crossing it,” Bertozzi reported that lactam-based BARAC provides a 10-fold increase in reactivity over DIBO, leading to intracellular coupling within minutes.²²

Although the above examples clearly illustrate the potential of *reactant destabilization* in the design of reactive alkynes,²³ they also illustrate the drawback inherent to this approach: the relatively low stability of the most reactive compounds, some of which “should be stored as a solid at 0 °C protected from light and oxygen.”²² In contrast, *transition state stabilization*, the alternative strategy favored by many of Nature’s powerful catalysts,²⁴ provides reaction acceleration without sacrificing the stability of reactants.

Initial indications that such stabilization is possible were given by the important observation by Bertozzi et al. that the reactivity of OCT is enhanced >50-fold by incorporation of fluorine atoms at the propargylic position (cf. DIFO, Figure 1).²⁵ The ~ 2 kcal/mol decrease in the activation barrier for DIFO relative to cyclooctyne is reproduced by DFT computations.²⁶ Recently, we have shown that the accelerating effects of propargylic fluorine substituents are manifested via different mechanisms: hyperconjugative assistance for 1,4-addition and Me...F interaction for 1,5-addition (Figure 2).²⁷

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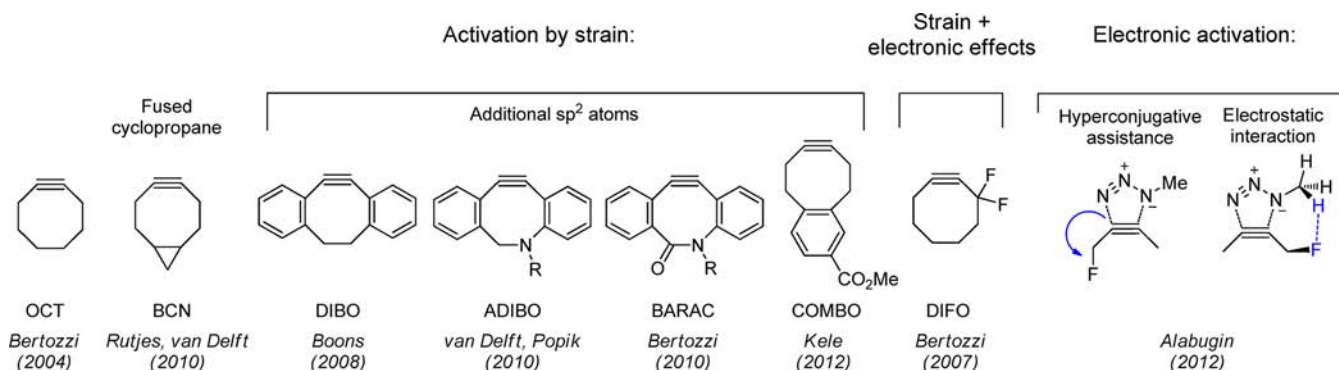


Figure 1. Literature approaches to alkynes with increased reactivity in noncatalyzed cycloaddition with azides.

Electronic effects accelerating DIFO / azide cycloadditions:

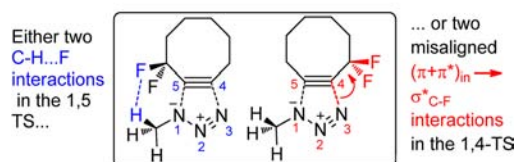


Figure 2. Competing electronic effects responsible for the rate acceleration of DIFO/azide cycloadditions relative to those with OCT.

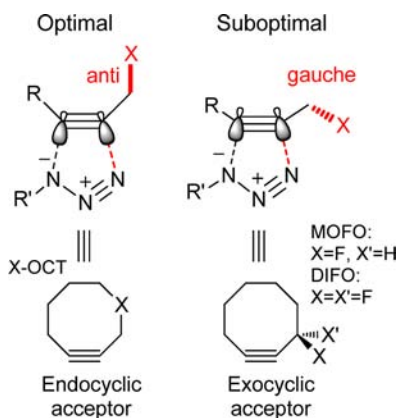


Figure 3. Optimal (antiperiplanar) and suboptimal (gauche) arrangements between propargylic σ -acceptors X and the reacting alkyne π -bond (top). Stereoelectronic differences between the endocyclic and exocyclic acceptors (bottom).

DIFO cannot fully benefit from the combination of the two TS-stabilizing effects identified in our previous work because cyclic restraints render the optimal antiperiplanar position of a C–F bond impossible (vide infra). Each of the two regioisomeric transition states for the methyl azide/DIFO cycloaddition relies mostly on one effect at a time: (a) either C–H...F interactions in the 1,5-TS or (b) imperfect hyperconjugative assistance from the two gauche C–F bonds in the 1,4-TS.

Intriguingly, TS stabilization provided by a *single antiperiplanar* propargylic fluorine substituent in the acyclic substrate (1-fluorobut-2-yne) is *greater* than the TS stabilization provided by *two gauche* fluorines in DIFO. This difference stems from the hyperconjugative origin of TS stabilization which is fully displayed when the proper overlap between orbitals is achieved (Figure 3).²⁸

The greater impact of the antiperiplanar arrangement of the σ^*_{C-F} acceptor and the in-plane alkyne π -system illustrates the stereoelectronic nature of the hyperconjugative assistance. It lowers the TS energy via two effects: (a) decrease in the energy

cost for alkyne bending (distortion energy) needed to reach the cycloaddition TS geometry and (b) assistance to the bond formation. Not only does the alkyne π -orbital donor ability increase upon bending,²⁷ but also the interaction of the alkyne LUMO and azide HOMO leads to orbital mixing which partially redirects the electron density to the alkyne π^* . An appropriately positioned propargylic σ^* or π^* acceptor assists in delocalizing this electron density, facilitating the C...N bond formation and providing selective cycloaddition TS stabilization²⁷ (Figure 4). This interaction is not perfect for DIFO, but is fully manifested when the σ acceptor is antiperiplanar (*app*).

The hyperconjugative assistance can be complemented by the stabilizing C–H...F contacts which can be considered H-bonds with a significant electrostatic component (Figure 5). These two independent mechanisms can be combined to achieve an even larger acceleration once additional σ -acceptors are introduced. Remarkably, the proper positioning of just three C–F bonds at the propargylic carbons eliminates $\sim 80\%$ of the barrier difference between 2-butyne and cyclooctyne without introducing strain destabilization in the reactant.

An intriguing conclusion from these results is that the “economic” utilization of the two electronic effects outlined above leaves free positions at the propargylic carbons which can be further functionalized for additional control, suggesting that even greater reaction acceleration may be possible (Figure 6). In this work, we will investigate whether activation of alkynes via *transition state stabilization* can be combined with *reactant destabilization* for the design of very reactive cycloalkynes with tunable reactivity (Figure 7).

In the first part, we will combine strain with the accelerating effects of *endocyclic* σ -acceptors in the cyclooctyne frame and determine if the two effects are compatible. If two conceptually different accelerating effects can be combined in such a way that selective transition state stabilization via stereoelectronic hyperconjugative effects and electrostatic CH...X interactions can complement reactant destabilization via strain and alkyne distortion, one can achieve the needed compromise between stability and reactivity in the design of alkyne reagents for click chemistry. In the second part, we will show that the combination of effects can indeed lead to extraordinarily low activation barriers for the click cycloadditions.

COMPUTATIONAL DETAILS

The computational analysis of potential energy profiles for azide–alkyne cycloadditions was performed at the B3LYP/6-31G(d) level of theory using Gaussian 03 software.²⁹ For 1,3-dipolar cycloadditions, B3LYP/6-31G(d) and B3LYP/6-31+G(d,p) have mean absolute deviation of 1.5 and 2.6 kcal/mol, respectively, relative to the highly accurate

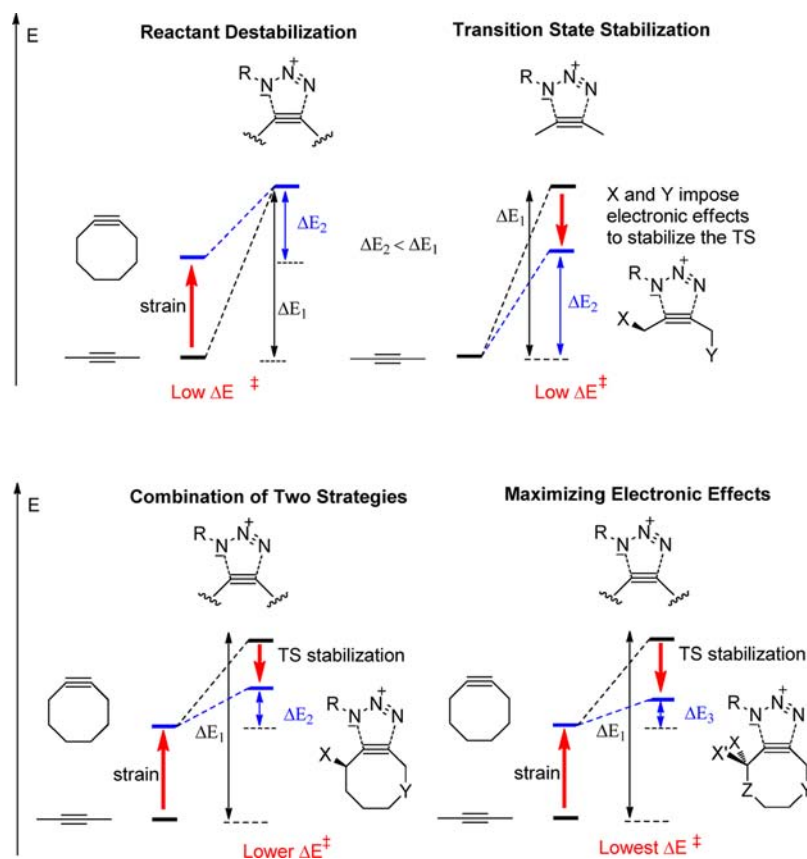


Figure 7. Comparison of alternative strategies for acceleration of copper-free click reactions.

Figure S2 and Table S4). It is possible that by constraining the starting alkynes in the boat conformation even more reactive alkynes could be designed through additional strain activation. Fox and co-workers found that a similar strategy can be effective in tetrazine/trans-cyclooctene cycloadditions.³⁹ We will investigate this possibility in our future work. In the present manuscript, however, all discussion will be centered on chair conformations.

RESULTS AND DISCUSSION

Endocyclic Substitution Alleviates Strain without Sacrificing Reactivity. Reactivity is only one of the challenges in the design of alkynes for click chemistry. Another important challenge is selectivity. Although cycloalkyne strain accelerates cycloadditions, many highly reactive cycloalkynes are relatively unstable and prone to unselective reactivity. In order to understand the effect of heteroatom introduction on the strain in cyclooctyne framework, we had evaluated strain energies in heterocyclooctynes following approach described earlier by Bach^{26d,40} (Table 1).

The ~2 kcal/mol lower strain of DIFO relative to that of cyclooctyne (20.6 and 18.6 kcal/mol, respectively) is counter-intuitive. One would expect DIFO to be more strained than OCT because the fluorinated propargylic carbon of DIFO uses two ~sp² hybrids for making the endocyclic C–C bonds. This hybridization effect (which is a consequence of the Bent's rule)⁴¹ is analogous to adding an sp² carbon in the cyclooctyne framework, something which is usually used to increase strain in cyclooctynes.

The origin for the decreased strain becomes obvious upon the inspection of strain energies in cyclooctynes with endocyclic heteroatoms at the propargylic positions (X-OCT, Table 1). Remarkably, all of the X-Oct alkynes have SEs that are even

lower than the SE of DIFO!⁴² In fact, some of endocyclic heteroatoms bring the SEs close to the 12.4 kcal/mol^{26d,43} SE of cyclooctane.

The low strain reflects the effect of endocyclic hyperconjugation on stabilization of alkyne bending. The lower penalty for the alkyne bending in DIFO is due to hyperconjugative $\pi \rightarrow \sigma^*_{C-F}$ interactions with the exocyclic acceptors.

The greater hyperconjugative effect of a single acceptor C–X bond in X-OCT relative to the effect of two C–F bonds of DIFO illustrates the stereoelectronic nature of this phenomenon, which favors the antiperiplanar donor/acceptor arrangement.

Although endocyclic heteroatoms decrease strain in the cyclooctyne framework, the molecules are still destabilized relatively to Z-cyclooctenes (SE 6.8 kcal/mol) and, as the result, strain should still impose an accelerating effect on the cycloadditions. However, since strain is moderated by the presence of endocyclic heteroatoms, such systems may be easier to prepare and handle. Moreover, the combination of TS stabilization with reactant destabilization by strain may allow one to prepare alkynes which are not only more reactive than DIFO but also may be tunable via conformational and electronic effects.

TS Stabilization in Cycloalkynes with Endocyclic Acceptors. Considering findings from the previous section, one has to wonder whether the decreased strain in X-OCT alkynes may be detrimental for their reactivity in cycloadditions with azides. In this section, we will investigate the effect of stereoelectronically optimized hyperconjugative assistance by endocyclic σ -acceptors.²⁷ On the basis of our previous findings,²⁷ we anticipated substitution at both propargylic carbons to impose an accelerating effect, with the acceptor positioned at

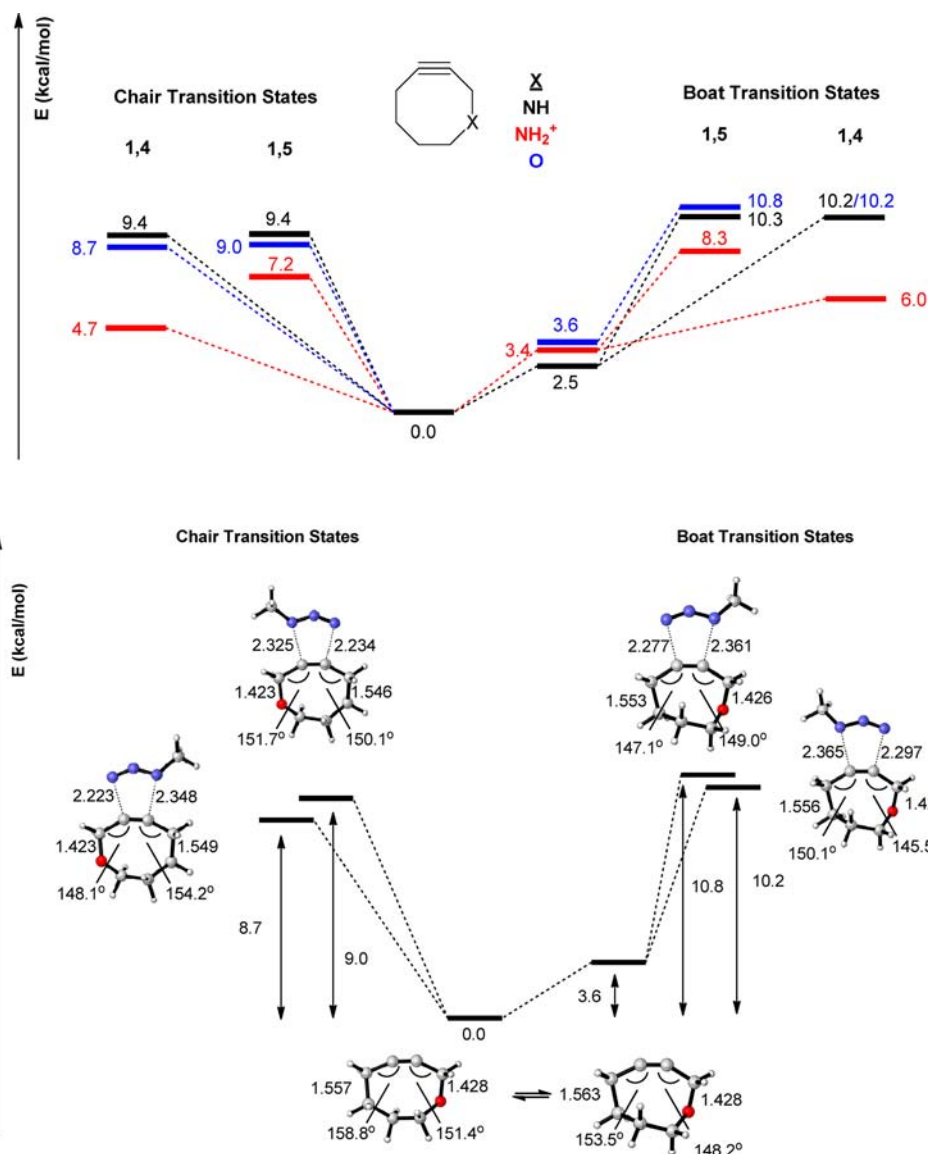


Figure 8. (Top) Relative energies of the chair and boat conformations of heterocycles featuring endocyclic propargylic σ -acceptors and their cycloadditions with methyl azide optimized at the B3LYP/6-31G(d) level of theory. (Bottom) Geometries of the chair and boat TSs for the “1,4” and “1,5” cycloaddition of O-OCT and methyl azide optimized at the B3LYP/6-31G(d) level of theory. Angles are given in degrees, bond distances in angstroms.

the propargylic carbon *opposite* to the azide alkyl group being more effective.

We began our analysis by comparing the effect of a single *endocyclic* acceptor⁴⁴ to the effect of two fluorine atoms in DIFO (Figure 9). The stereoelectronic nature of hyperconjugation suggests that the effect of σ -acceptors will be fully manifested only when they are aligned properly with the donor. As long as C–F bonds in DIFO are misaligned with the reacting alkyne π -system, they cannot impose their accelerating effect to the full capacity. In contrast, *endocyclic* σ -acceptors are antiperiplanar to the in-plane alkyne π -orbital. Although C–F bonds cannot be included into a cycle, we have shown previously that hyperconjugative acceptor ability of some σ -bonds (in particular C–N⁺) can rival the acceptor ability of C–F bonds.⁴⁵

Indeed, the computations predicted significant acceleration as the propargylic CH₂ group of cycloctyne is substituted by heteroatoms (Figure 9, Table 2). In the gas phase, this acceleration surpasses the effect of the *exocyclic* fluorines in DIFO.

Although the barriers become much closer after solvation is incorporated, the effect is still significant. Notably, in the 1,4-TS, a single properly aligned oxygen is as efficient as the two fluorines in DIFO. The extent of *endocyclic* activation is directly proportional to the acceptor ability of the activating group. This opens a number of intriguing approaches for fine-tuning click reactivity via electronic effects of substituents, metal coordination or protonation.⁴⁶ The latter possibility is illustrated by the effect of the endocyclic NH₂⁺ at the propargylic carbon (C–N⁺ is a strong σ -acceptor).^{35,47}

Distortion Analysis. To understand the origin of the accelerating effects deeper, we have utilized distortion analysis which has been used successfully by Houk and co-workers toward a variety of cycloadditions.^{26a,b,48} This analysis dissects the activation barrier for cycloadditions into distortion and interaction energies. Distortion describes the energy penalty for adopting the TS geometry by the reactants, whereas interaction energy reflects energy lowering due to covalent and noncovalent

Table 1. Strain Energies (SEs) of Cyclooctynes Discussed in This Work^a

R	X	Y	SE (kcal/mol)	SE (kcal/mol) H ₂ O ^{b,c}
OCT:				
H	CH ₂	CH ₂	20.4	20.6
DIFO:				
F	CH ₂	CH ₂	19.1	18.6
X - OCT				
H	O	CH ₂	16.3	16.7
H	NH	CH ₂	17.9	18.0
H	NH ₂ ⁺	CH ₂	18.2	16.4
X,Y - OCT				
H	O	O	12.9	13.8
H	NH	NH	18.5	18.3
H	NH ₂ ⁺	NH ₂ ⁺	46.0	20.9
H	O	NH	14.4	14.7
H	O	NH ₂ ⁺	19.0	15.2
Hybrids:				
F	O	CH ₂	15.3	15.5
F	NH	CH ₂	16.4	15.9
F	NH ₂ ⁺	CH ₂	19.9	16.7
F	O	O	14.1	14.1
F	NH	NH	17.4	16.8
F	NH ₂ ⁺	NH ₂ ⁺	46.8	21.0
F	O	NH	16.1	15.8
F	NH	O	16.6	15.6
F	O	NH ₂ ⁺	16.8	13.4
F	NH ₂ ⁺	O	24.0	17.6

^aNote that SE of cyclooctane and Z-cyclooctene is 12.4 and 6.8 kcal/mol, respectively.^{26d} ^bGas phase geometry. ^cCPCM (dielectric continuum solvent model), Radii = UA0.

interaction between the reactants. These results are summarized in Table 2.

As expected for all cyclic alkynes, the distortion energies are small indicating that the reactant geometries are already close to the bent geometry of the cycloaddition TS. The distortion energies for O-OCT and NH-OCT are slightly lower than those in OCT and DIFO, whereas the distortion energy for the NH₂⁺-OCT TS is slightly higher because this molecular structure is influenced stronger by the large interaction energy. Single point solvation correction decreases the interaction energy but it still remains substantial.

Because endocyclic substituents modify both the distortion and the interaction energies, a clear dissection of these effects is difficult, especially considering that azide distortion energies vary as well (from 13.7 to 15.4 kcal/mol in the gas phase). However, the combined distortion energies for all azide/X-OCT transition states are lower than they are for the cyclooctyne TS.

Similar to our earlier findings,²⁷ the increase of TS stabilization through an increase in interaction energies (E_{int} in Table 2) leads to deviations in the usually reliable^{26b} correlation of distortion energies with full activation barriers (Figure 10). The particularly large deviations observed for 1,5 DIFO TS (due to C-H...F interactions described in the introduction) and both 1,4 and 1,5-TS for NH₂⁺-OCT indicate the particularly strong intermolecular interactions between the two reacting species.

Because stabilization energies are greater than alkyne distortions, the NH₂⁺-OCT alkyne has a low overall barrier despite having the greatest distortion energy (the 1,5-TS). Considering the likely diminishing effect of solvation on the stabilization energies, we have fully reoptimized this TS with solvation included. As expected, the distortion decreased significantly (red arrow in Figure 10) when the stabilizing effect of intermolecular electrostatic interactions is diminished because the reacting system has to find a new compromise between the

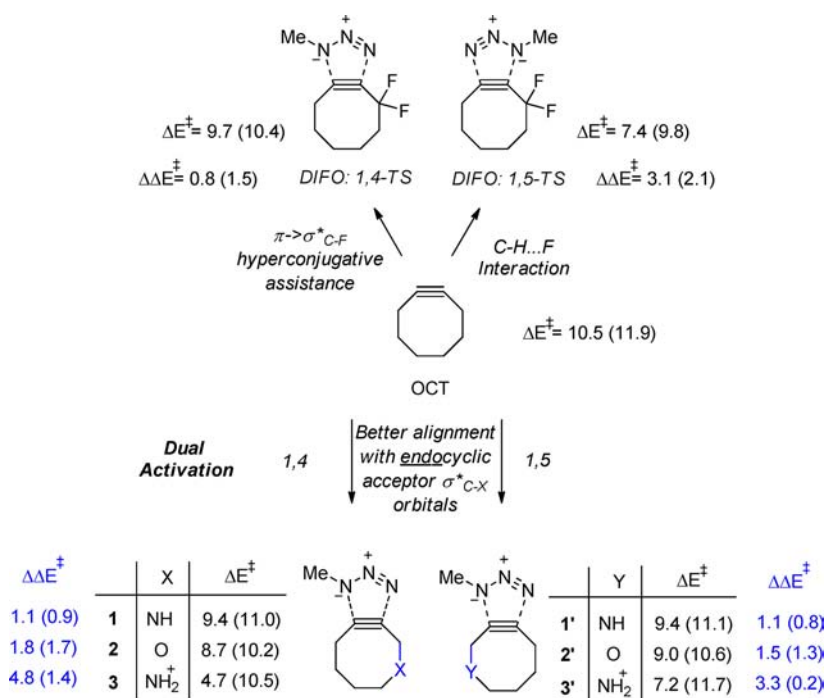



Figure 9. B3LYP/6-31G(d) activation energies of OCT, DIFO and heterocyclooctynes featuring endocyclic propargylic σ -acceptors. CPCM (water) solvation corrections are given in parentheses. $\Delta\Delta E^\ddagger$ values for X-OCT are shown relative to OCT to illustrate the effect of X on reactivity.

Table 2. Activation, Reaction, Distortion, and Interaction Energies for OCT, DIFO, and Heterocyclooctynes Featuring Endocyclic Propargylic σ -Acceptors: Geometries Optimized at the B3LYP/6-31G(d) Level of Theory

 X - OCT	ΔE^\ddagger , kcal/mol	ΔE_{RMS} , kcal/mol	E_{Dist} Alkyne, kcal/mol	E_{Dist} Azide, kcal/mol	E_{Dist} Total, kcal/mol	E_{int} kcal/mol
	Gas phase $H_2O^{a,b}$	Gas phase $H_2O^{a,b}$	Gas phase $H_2O^{a,b}$	Gas phase $H_2O^{a,b}$	Gas phase $H_2O^{a,b}$	Gas phase $H_2O^{a,b}$
Cyclooctyne	10.5	-79.0	2.1	15.3	17.4	-6.9
	11.9	-81.7	1.9	15.5	17.5	-5.6
DIFO	7.4	-81.9	2.3	13.8	16.0	-8.7
1,5	9.8	-82.1	2.1	13.9	16.1	-6.3
DIFO	9.8	-78.5	2.3	14.1	16.5	-6.7
1,4	10.4	-82.1	2.2	14.4	16.6	-6.3
NH-OCT, 1	9.4	-80.4	1.6	14.3	16.0	-6.6
1,4	11.0	-82.9	1.6	14.6	16.2	-5.2
NH-OCT, 1'	9.4	-80.2	1.8	14.4	16.2	-6.7
1,5	11.1	-82.4	1.8	14.7	16.4	-5.3
O-OCT, 2	8.7	-83.4	1.5	13.7	15.2	-6.5
1,4	10.2	-85.2	1.5	13.9	15.4	-5.2
O-OCT, 2'	9.0	-82.7	1.9	13.9	15.7	-6.8
1,5	10.6	-84.8	1.9	14.1	16.0	-5.4
NH ₂ ⁺ -OCT, 3	4.7	-83.5	3.3	13.6	16.9	-12.2
1,4	10.5	-82.6	2.8	13.7	16.5	-6.1
NH ₂ ⁺ -OCT, 3'	7.2	-73.9	3.8	15.4	19.3	-12.0
1,5	11.7	-76.8	3.5	15.6	19.2	-7.5

^aGas phase geometry. ^bCPCM (dielectric continuum solvent model), Radii = UA0.

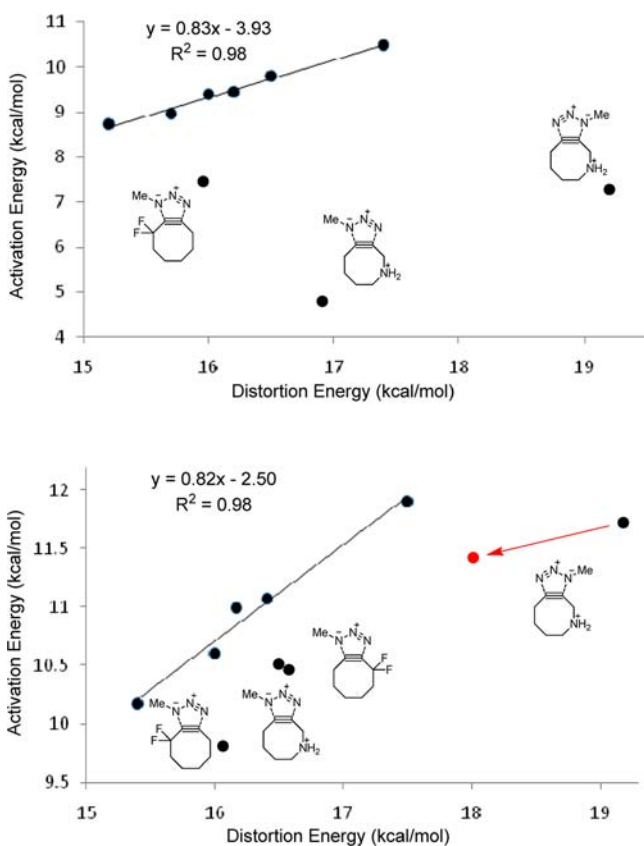


Figure 10. Correlation of the full distortion energy and activation energy cycloadditions between methyl azide with OCT, DIFO, and heterocyclooctynes featuring endocyclic propargylic σ -acceptors (Table 2, B3LYP/6-31G*). (Top) Gas phase data. (Bottom) Single point solvation (water) correction. Shown in red is the shift observed upon optimization in solution (data for all solvent optimizations is given in the Supporting Information Figure S1). The energies below the straight line deviate from the distortion plot due to selective TS stabilization (gas phase: $R^2 = 0.06$, if all nine points are included. CPCM (water): $R^2 = 0.56$, if all nine points are included).

conflicting energetic factors and requirements. Once the system could not benefit as much from the stabilization energy, it readjusted to decrease the distortion energy.

As in our previous work, placement of the propargylic acceptor at the C4 position provides greater stabilization in the TS. This selectivity parallels the acceptor strength, making NH₂⁺-OCT the most regioselective. Formation of the 1,4 regioisomer is more exothermic and has an earlier TS, requiring less energy to distort the azide to the TS geometry. This approach is also favored since the polarization of the alkyne is toward the acceptor moiety and N1 of the azide bears a greater negative charge than N3. In particular, full electrostatic analysis provided in the Supporting Information explains how the unfavorable combination of reactant dipoles renders the 1,5 NH₂⁺-OCT/TS and product less thermodynamically favorable.

NBO Dissection of Hyperconjugative Effects. The stereoelectronic advantage of endocyclic σ -acceptors is illustrated by the NBO plots for the three transition states involving DIFO and NH₂⁺-OCT (Figure 11). The NBO overlap integral, S_{ij} , quantifies the differences. In DIFO, the two σ^*_{C-F} orbitals are positioned in a way where they interact with both in-plane and out-of plane alkyne π -bonds. However, the overlap with the out-of-plane π -system is more efficient (~ 0.2 au for each of the acceptors) than overlap with the in-plane π -system (~ 0.1 au). In the TS, one of the DIFO C-F bonds is reoriented to interact stronger with π_{in} in the DIFO TS, at the expense of weakening the interaction with the π_{out} alkyne orbital.⁴⁹ This, previously unrecognized, conformational effect leads to “switching on” of the $\pi_{in}/\pi_{in}^* \rightarrow \sigma^*_{C-F}$ hyperconjugative assistance in DIFO and illustrates the importance of this TS stabilizing effect. The relatively larger conformational change associated with this stereoelectronic adjustment is consistent with the slightly larger alkyne deformation energy for DIFO⁵⁰ in comparison to the 1,4-TS for the neutral X-OCT alkynes (Table 2) and with the more negative entropy of activation for DIFO in comparison to the other cycloalkynes (see the Supporting Information).

In contrast, overlap of the reacting alkyne π -bond with endocyclic acceptors is already “switched on” in the starting

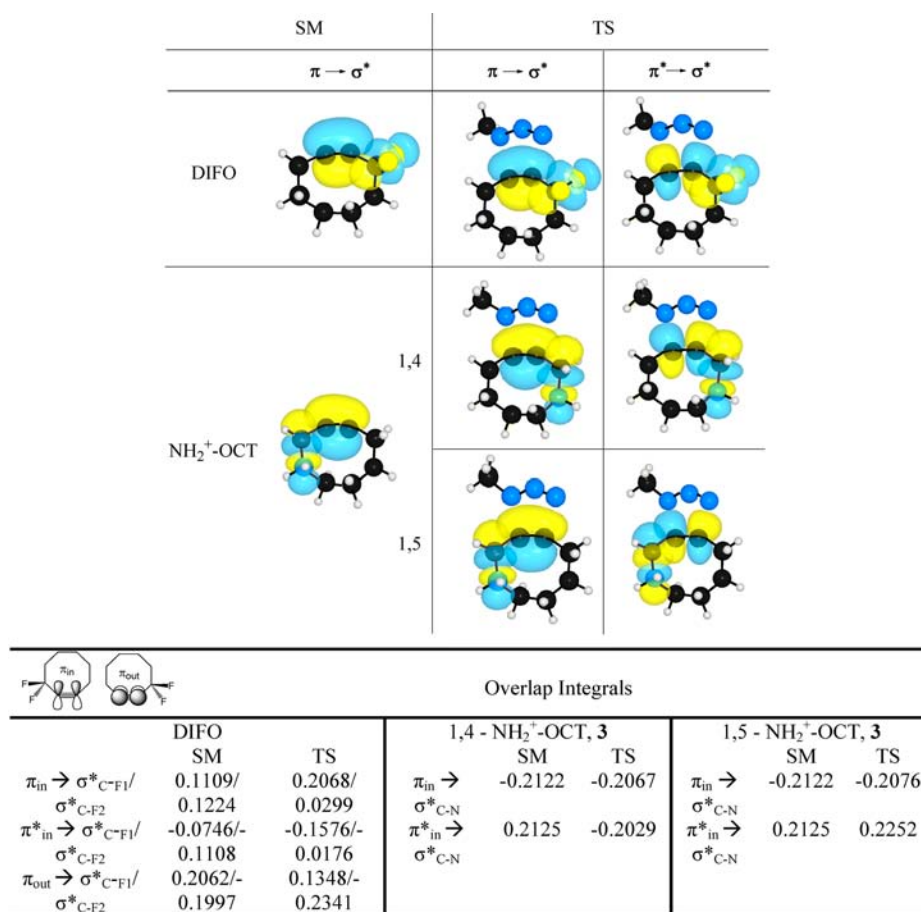


Figure 11. (Top) NBO plots for orbital interactions between the propargylic σ -acceptors and the reacting in-plane alkyne π -bond in the cycloaddition TSs of difluorocyclooctyne and NH₂⁺-OCT with methyl azide. (Bottom) Preorthogonal NBO overlap matrix elements between listed π orbitals and σ^*_{C-X} .

material (Figure 11). Although such stabilization of the reactants may be helpful for the preparation of these cyclic alkynes, this behavior appears to be less favorable than the conformational change in DIFO and would be unproductive unless this interaction gets stronger in the TS despite the overlap staying relatively constant. However, such increase is observed and endo substituents do impose a significant TS stabilizing effect (Table 3). We attribute this effect to two reasons: the lowering

Table 3. NBO Analysis (B3LYP/6-31G(d)) of Hyperconjugative Interactions Involved in the Methyl Azide Cycloaddition with Heterocyclooctynes Featuring Propargylic σ -Acceptors^a

$\pi + \pi^* \rightarrow \sigma^*$ energies, kcal/mol	starting alkyne	alkyne-TS geometry	full TS: alkyne + azide	hyperconjugative TS stabilization
OCT	2.9	3.0 (2.9) ^b	4.2 (3.7) ^b	1.2 (0.8)
DIFO	4.3	4.6 (4.6)	7.1 (6.6)	2.5 (2.0)
NH-OCT	5.1	5.3 (5.2)	5.6 (6.4)	0.3 (1.2)
O-OCT	7.2	7.5 (7.2)	8.8 (9.5)	1.3 (2.3)
NH ₂ ⁺ -OCT	9.2	9.9 (9.6)	17.0 (18.2)	7.1 (8.6)

^aOnly donation from the *in-plane* π -system (both π and π^*) is shown (kcal/mol). Values are for the 1,4-TS (1,5-TS). ^bValues given for each propargylic C-C bond.

of the energy gap between the interacting orbitals^{35,51} and an increase in the alkyne π^* population (as directly follows from

eq 1 given in the Computational Details section). This is readily illustrated by the relative NBO energies of stereoelectronic interactions in reactants and the TS (Table 3).⁵² While the $\pi_{in} \rightarrow \sigma^*_{C-F}$ overlap in DIFO is comparable to the $\pi_{in} \rightarrow \sigma^*_{C-N}$ in the NH₂⁺-OCT, the $\pi^*_{in} \rightarrow \sigma^*_{C-F}$ is much smaller than that of $\pi^*_{in} \rightarrow \sigma^*_{C-N}$ allowing for a greater assistance to bond formation in the latter case (Figure 4).

Let us analyze the reasons for this interesting behavior in more detail. We have reported earlier²⁷ that whereas a modest increase in the $\pi \rightarrow \sigma^*_{C-X}$ stabilization is observed upon bending of acyclic alkynes, a larger increase is found in the full TS where the azide moiety transfers electron density to the properly aligned acceptor via the alkyne π -system. The same is true for cyclic alkynes, except that the hyperconjugation increase associated with the additional reactant bending needed to reach the cycloaddition TS is even smaller. This is not surprising because the reactant geometry is much closer to the TS than it is for acyclic alkynes—very little additional bending is required.⁵³ The stereoelectronic nature is clearly evident when comparing the interactions of the misaligned acceptors in DIFO to those seen for the antiperiplanar arrangement in endo acceptors where the effects are maximized.

On the other hand, hyperconjugative stabilization is significantly increased in the full TS, where the azide is brought into close proximity of the bent alkyne moiety. In this case, the C-N bond forming interactions increase the population of the alkyne π_{in}^* orbital, the latter serving as a very efficient donor in

the interaction with the stereoelectronically aligned σ^* -acceptors (Figure 4, right panel). The increase in this interaction correlates well with the strength of the acceptor, ($\text{NH}_2^+ > \text{O} > \text{NH}$), revealing the potential for “on demand” activation through either protonation or metal coordination.

The NBO analysis also provides insights into the origin of regioselectivity for cycloadditions to X-OCT. Cycloaddition of the parent OCT molecule proceeds via a highly asynchronous TS where the incipient N3–C4 bond distance is considerably shorter than the N1–C5 distance (see Supporting Information for all geometries). In this TS, the propargylic C–C bond at the C4 end is slightly shorter (0.004 Å) than the analogous C5 bond. This observation is consistent with the slightly stronger interaction of the in plane π -system (π and π^*) with the anti-periplanar $\sigma^*_{\text{C5-C}}$ propargylic orbital than with the $\sigma^*_{\text{C4-C}}$ orbital (4.2 vs 3.7 kcal/mol). The analogous interactions in the full TS for the X-OCT alkynes 1–3 consistently suggest that hyperconjugation slightly favors the 1,5-TS and that the lower barriers for the 1,4-TS have to originate from a different factor. Comparison of electrostatic potentials for the alkyne and azide reactants (discussed in the previous section and summarized in the Supporting Information) indicates that 1,5-TS should be disfavored by the dipole–dipole interactions for the neutral alkynes where the heteroatom corresponds to the negative end of the dipole.

Triple Activation/Quadruple Activation. A potentially valuable feature of our approach is that activation can be accomplished in a modular fashion where each set of substituents leads to a progressive decrease in the activation barrier. Alkynes with dual activation are predicted to approach DIFO in reactivity. In this section, we will discuss alkynes with triple and quadruple activation patterns which are predicted to be even more reactive.

Triple activation can be provided in two different ways, illustrated in Figure 12 for X = O, either by introducing a second endocyclic acceptor or by combining hyperconjugative assistance by a single endocyclic acceptor with the C–H...F interactions. Finally, all four effects (strain, two endocyclic $\pi \rightarrow \sigma^*_{\text{C-X}}$ interactions and C–H...F contacts) can be combined in “superactivated alkynes.” These effects can be introduced in a modular way with a predictable outcome.

For example, the C–H...F interactions provide 3.1–3.7 kcal/mol barrier decrease (2.1–2.8 kcal/mol with solvation correction).⁵⁴ The 1,4-endocyclic C–O bonds contributes a little bit less: 1.8–2.4 (1.7–2.4 with solvation) kcal/mol. 1,5-hyperconjugative assistance is the smallest, but still a significant effect on the order of 0.9–1.6 (1.3–1.7 with solvation) kcal/mol.

Expansion of this modular approach to other endocyclic acceptors, X, increases the number of possibilities and provides cyclooctynes with a broad range of reactivities. The relative barrier lowering correlates with the acceptor properties of X: $\text{NH} < \text{O} < \text{NH}_2^+$. Our computational results for these systems are combined in Figure 13.

Because of the additional hyperconjugative assistance to both alkyne bending and bond formation, the activation barriers for systems with two endocyclic acceptors are further lowered both in the gas phase and in the solution. We see here a “superactivated” alkyne ($\text{X} = \text{Y} = \text{NH}_2^+$), appearing to have a negative barrier for the cycloadditions in the gas phase. This unusual result will be discussed below.

Interestingly, the two effects show cooperativity. In compounds 7–11, the exact magnitude of additional barrier lowering by the second acceptor Y depends also on the acceptor ability of

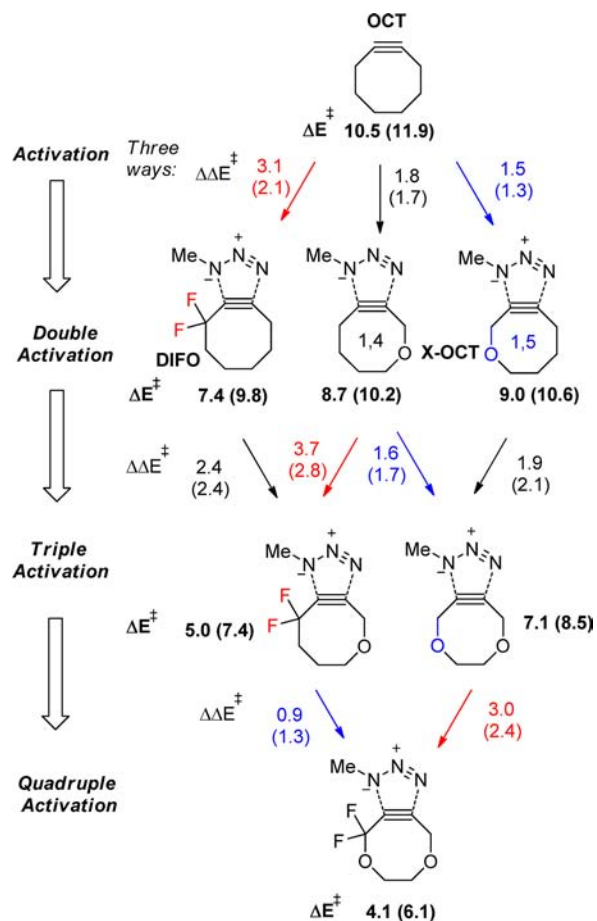


Figure 12. Modularity and cooperativity for the three transition state stabilization approaches for cycloadditions of substituted cyclooctynes and methyl azide. B3LYP/6-31G* activation energies (ΔE^\ddagger) are given in bold, changes in the activation barriers ($\Delta\Delta E^\ddagger$) introduced by an additional level of activation are given near the arrows. CPCM (water) solvation corrections are given in parentheses.

$\sigma^*_{\text{C-X}}$ as well. For instance, the magnitude of additional stabilization gained due to the incorporation of the $\sigma^*_{\text{C-O}}$ acceptor (alkynes 7, 8', and 9, Y = O) into compounds 1–3 increases with the acceptor ability of $\sigma^*_{\text{C-X}}$ (1.4 → 1.7 → 2.4 kcal/mol for NH → O → NH_2^+ in solution). Additionally, the incorporation of different $\sigma^*_{\text{C-X}}$ acceptors (alkynes 7, 8', and 9) into 2' (Y = O) provides greater additional stabilization (1.0 → 2.1 → 2.5 kcal/mol for NH → O → NH_2^+ in solution) than a single $\sigma^*_{\text{C-X}}$ acceptor (0.9 → 1.7 → 1.4 kcal/mol for NH → O → NH_2^+ in solution upon going from OCT to 1, 2, 3).

In addition, examination of the nonsymmetric alkynes (8, X = O, Y = NH vs 8', X = NH, Y = O and 9, X = NH_2^+ , Y = O vs 9', X = O, Y = NH_2^+) reveals the preference for the stronger acceptor to be anti to the azide's substituent, analogous to the preference of a single acceptor to be at the C4 carbon. This is also evident by the larger effect of protonation when the nitrogen is positioned properly (1.5 vs 0.6 kcal/mol in solution for the 8' → 9 and 8 → 9' pairs, respectively).

For the second mode of “triple activation” (“X-OCT+CF₂”), the magnitude of the additional barrier lowering due to fluorination of compounds 1, 2, and 3 also parallels the acceptor ability of X (2.5 → 2.8 → 4.1 kcal/mol for NH → O → NH_2^+ in 4–6), indicating positive synergy between the two effects.

Finally, the combination of strain, C–H...F interactions and both modes of hyperconjugative assistance (*quadruple activation*)

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(54) Note that the effect of two propargylic C–F bonds in the 1,5-TS includes not only the C–H⋯F interactions but also a contribution from 1,5-hyperconjugative assistance. Separation of these effects is not among the aims of the present manuscript.

(55) An example is given in the Supporting Information. The full analysis of these complexes extends beyond the scope of the present manuscript.