

Diazo Esters as Dienophiles in Intramolecular (4 + 2) Cycloadditions: Computational Explorations of Mechanism

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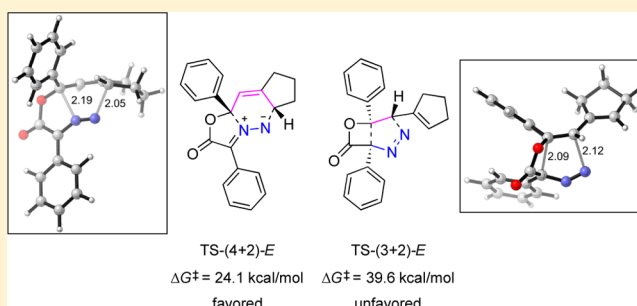
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Supporting Information

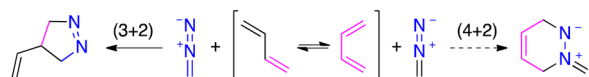
ABSTRACT: The first experimental examples of Diels–Alder (DA) reactions of diazo compounds as heterodienophiles with dienes have been studied with density functional theory (DFT) using the M06-2X functional. For comparison, the reactivities of diazo esters as dienophiles or 1,3-dipoles with 1,3-dienes in intermolecular model systems have been analyzed by the distortion/interaction model. The 1,3-dipolar cycloaddition is strongly favored for the intermolecular system. The intramolecular example is unique because the tether strongly favors the (4 + 2) cycloaddition.



INTRODUCTION

The Diels–Alder (DA) reaction is one of the most important ring-forming reactions in organic synthesis.¹ While DA reactions between dienes and azo compounds are common, reactions of diazo compounds as dienophiles have not been reported until recently.² In contrast, the 1,3-dipolar cycloadditions of diazo compounds to alkenes resulting in the formation of pyrazolines (Scheme 1, left) were discovered by

Scheme 1. Potential Cycloadditions of Dienes with Diazo Compounds

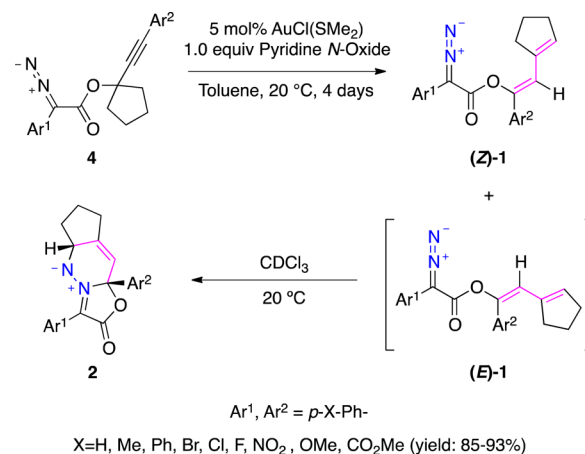


Curtius³ and Buchner⁴ in the 1880s, and identification of this as one of many 1,3-dipolar cycloaddition reactions was made by Huisgen more than 50 years ago.⁵ In the ensuing time, 1,3-dipolar cycloaddition reactions of diazo compounds with alkenes or alkynes have been well developed⁶ and subjected to wide utilization for heterocycle syntheses⁷ with tautomerization or dinitrogen extrusion being potential subsequent processes.⁸ Diazonium ions have been reported as dienophiles,⁹ but diazo esters are well-known to react as dipoles in 1,3-dipolar cycloadditions. This stands in contrast to the cumulenyl ketene and allene counterparts, which generally react as dienophiles or dipolarophiles in (4 + 2) and (2 + 2) cycloaddition reactions.^{10–12}

Recently, Doyle et al. reported the first (4 + 2) cycloaddition of a diazoalkane in which the N=N bond acts as the

dienophile.¹³ Treatment of propargylphenyldiazoacetates **4** with 5 mol % AuCl(Me₂S) in toluene at 20 °C and pyridine-*N*-oxide resulted in the formation of (*Z*)-**1** and products **2** anticipated from the diene-diazo cycloaddition. The (*E*)-1-(1,3-dienyl) aryldiazoacetates (*E*)-**1** (depicted in Scheme 2) undergo intramolecular (4 + 2) cycloadditions to form the azomethine imine 1,3-dipole structures **2**, in moderate to high yields. Cycloaddition is first order in (*E*)-**1**, and both the

Scheme 2. Intramolecular (4 + 2) Cycloaddition Reactions of Dienes with Diazo Compounds



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activation parameters and their Hammett relationships are consistent with those for other intramolecular Diels–Alder reactions.¹⁴ We have undertaken a theoretical study of this reaction and report the factors that lead to this anomalous reaction.

We have employed quantum mechanical calculations to characterize the reaction mechanism and transition states for cycloadditions between 1,3-dienes and diazo esters. We have also applied the distortion/interaction model and FMO analysis to investigate the analogous intermolecular cycloadditions between 1,3-dienes and diazo esters.

COMPUTATIONAL METHODS

All the calculations were performed with Gaussian 09.¹⁵ Geometry optimizations and frequency calculations of reactants, transition states, and products were carried out with the M06-2X density functional^{16,17} with the 6-31G(d) basis set, which has been found to give relatively accurate geometries for cycloadditions.¹⁸ Single-point energies were computed at the more accurate M06-2X/6-311+G(d,p) level using the M06-2X/6-31G(d) geometries. The FMO energy gaps of diazo ester and 1,3-diene were calculated with the Hartree–Fock (HF)^{19–21} method with the 6-31G(d) basis set using the M06-2X/6-31G(d) geometries. Fragment distortion and interaction energies were computed at the M06-2X/6-311+G(d,p) level. Chloroform ($\epsilon = 4.71$, $R_{\text{solv}} = 2.48 \text{ \AA}$) was used in the SMD²² continuum solvation model single-point calculations on gas-phase optimized geometries. All stationary points were verified as minima or first-order saddle points by a vibrational frequency analysis. Optimized structures are illustrated using CYLview.²³

RESULTS AND DISCUSSION

Experimentally, the (*E*)-1-(1,3-dienyl)aryldiazoacetates (*E*)-1 were found to undergo intramolecular (4 + 2) cycloadditions to form the azomethine imine products **2**. The reaction only occurs with the (*E*)-1 isomer, not the (*Z*)-1 isomer.

***E*-Isomer Intramolecular Cycloadditions.** Intramolecular (4 + 2) and (3 + 2) cycloadditions of diazo esters with (*E*)-alkenes are depicted in Figure 1. The observed product from the (4 + 2) cycloaddition reaction is formed with a barrier of

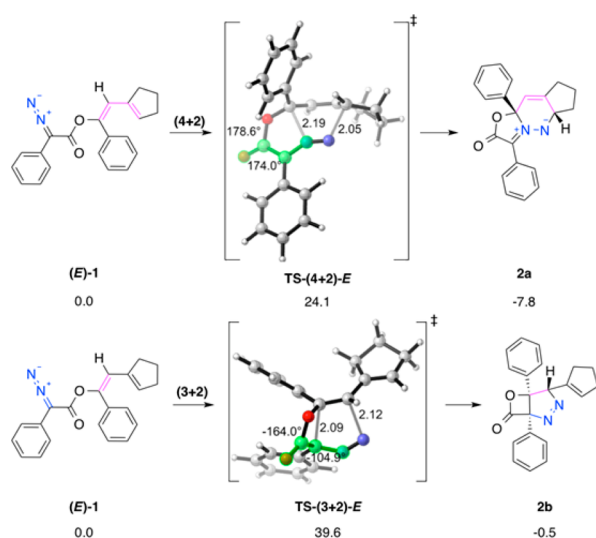


Figure 1. Relative free energies (ΔG_{298}) (in kcal/mol) of intramolecular (4 + 2) and (3 + 2) cycloadditions of diazo ester with (*E*)-alkenes calculated at the M06-2X/6-311+G(d,p)/SMD(chloroform)//M06-2X/6-31G(d) level. Bond lengths in Å and dihedral angle in degree.

only 24.1 kcal/mol in chloroform. The (3 + 2) cycloaddition reaction has a much higher barrier of 39.6 kcal/mol in chloroform. The (3 + 2) cycloaddition at the other double bond was not computed, because it would generate a six-membered ring that contains a *trans* double bond. The product **2b** is predicted to be less stable compared to the (4 + 2) cycloaddition product **2a**. The dihedral angle highlighted in green of TS-(4 + 2)-*E* is 174.0° , close to -177° as in the reactant. The same dihedral angle of TS-(3 + 2)-*E* is -104.9° . This dramatically reduces the conjugation between the ester carbonyl and the diazo group. In fact, when this dihedral angle was constrained to -105° in the reactant, the energy increases by ~ 12 kcal/mol (Figure S2). The dihedral angle of the ester linkage structure of TS-(4 + 2)-*E* is 178.6° , close to the stable *s-trans* conformation (180°) of esters in general. This angle is -164.0° in TS-(3 + 2)-*E*, and it is less stable than TS-(4 + 2)-*E*. The forming five-membered ring of TS-(4 + 2)-*E* is more stable than the forming four-membered ring of TS-(3 + 2)-*E*. This result agrees with the exclusive formation of the (4 + 2) product from the (*E*)-alkene observed in experiment.

(*E*)-Alkene versus (*Z*)-Alkene. Figure 2 shows the most stable structure of (*E*)-alkene and (*Z*)-alkene. The *s-cis*

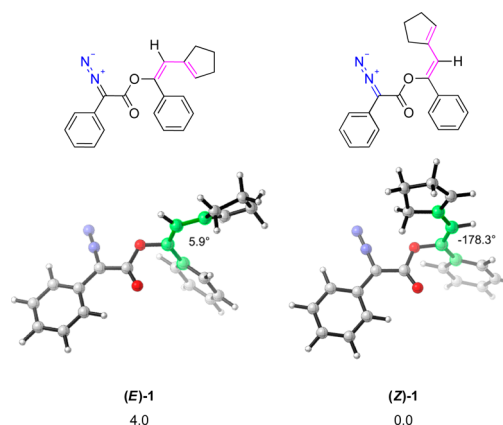


Figure 2. Relative free energies (ΔG_{298}) (in kcal/mol) of (*E*)- and (*Z*)-alkenes calculated at the M06-2X/6-311+G(d,p)/SMD(chloroform)//M06-2X/6-31G(d) level. Dihedral angles in degree.

conformation of (*E*)-1 is less stable than the *s-trans* conformation of (*Z*)-1, because the (*E*)-1 structure has steric repulsion between the phenyl group and the neighboring cyclopentenyl.

Nevertheless, no products from the (*Z*)-alkenes are observed. We explored the possible cycloadditions of the (*Z*)-alkene to understand their lack of reactivity. Figure 3 shows the energetics and transition states of the intramolecular (4 + 2) and (3 + 2) cycloadditions of diazo esters with (*Z*)-alkenes. The transition state of the (3 + 2) cycloaddition in reaction (c) has the lowest energy of 38.5 kcal/mol in chloroform, much too high to be observed under the reaction conditions. The dihedral angles ($C^4-C^1-N^2-C^3$) involving the two forming bonds are -0.6° and 7.4° in reaction (b) and (c), but -49.3° in reaction (a). In a prototypical Diels–Alder transition state, these forming bonds are approximately coplanar (dihedral angle near 0°), to maximize overlap at both termini of the diene. This is not possible in reaction (a), and the TS-(4 + 2)-*Z* dihedral angle is very distorted, and the forming bonds are asynchronous.

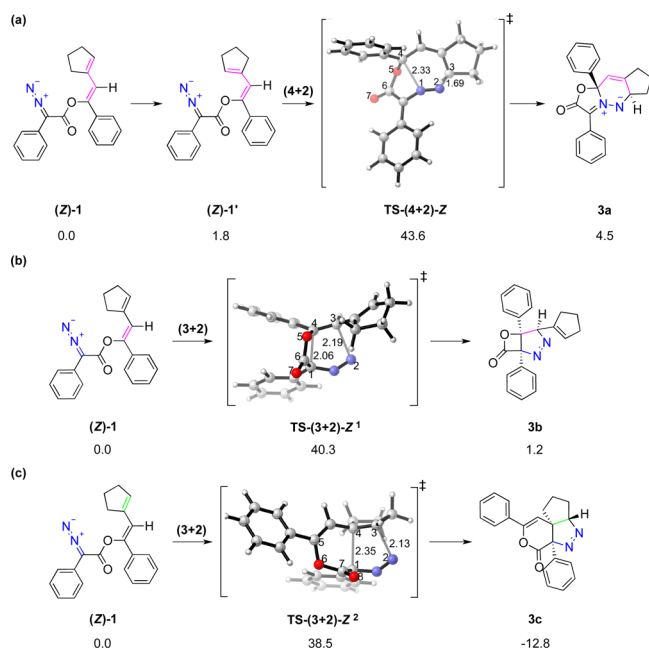


Figure 3. Relative free energies (ΔG_{298}) (in kcal/mol) of intramolecular (4 + 2) cycloaddition for (Z)-alkenes and (3 + 2) cycloaddition across the diazoalkenes 1,3-dipole for different double bonds of (Z)-alkenes calculated at the M06-2X/6-311+G(d,p)/SMD(chloroform)//M06-2X/6-31G(d) level. Bond lengths in Å and relevant dihedral angles are shown in Table 1.

Table 1. Relevant Dihedral Angles of Intramolecular (4 + 2) and (3 + 2) Cycloadditions for (Z)-Alkenes

	Dihedral Angles (deg)	
TSs	C ⁴ -C ¹ -N ² -C ³	C ⁴ -O ⁵ -C ⁶ -O ⁷
TS-(4 + 2)-Z	-49.3 (C ⁴ -N ¹ -N ² -C ³)	137.0
TS-(3 + 2)-Z ¹	-0.6	-173.0
TS-(3 + 2)-Z ²	7.4	101.9 (C ⁵ -O ⁶ -C ⁷ -O ⁸)

The dihedral angle of the ester linkage (C⁴-O⁵-C⁶-O⁷) for TS-(3 + 2)-Z¹ in reaction (b) is -173.0° , close to the stable *s-trans* conformation (180°), but that of TS-(4 + 2)-Z in reaction (a) is 137.0° , and in reaction (c) the dihedral angle (C⁵-O⁶-C⁷-O⁸) is 101.9° , close to the least stable conformation (90°). Each of these has some unfavorable strains due to the tether, and none occurs under the reaction conditions.

Intermolecular (4 + 2) vs (3 + 2) Cycloadditions for (E)-1. To assess the intrinsic barriers of the (4 + 2) and (3 + 2) cycloadditions, we have computed the intermolecular versions of the two reactions. All possible (3 + 2) and (4 + 2) cycloaddition reactions between the truncated reactants were considered (summarized in the Supporting Information). Figure 4 shows the two most stable transition structures for each reaction. The free energy of activation for the (4 + 2) cycloaddition in chloroform is 39.3 kcal/mol, and the (3 + 2) cycloaddition has a barrier of 33.4 kcal/mol. The free energy barrier of the (4 + 2) cycloaddition is now 6 kcal/mol higher than that of the (3 + 2) cycloaddition. That is, the (3 + 2) cycloaddition is strongly favored for the intermolecular reaction, when there are no constraints from the tether. Both of these bimolecular reactions have unfavorable entropies, and their $-T\Delta S^\ddagger$ values are ~ 12 kcal/mol.

D/I Analysis of Intermolecular (4 + 2) and (3 + 2) Cycloadditions. To understand the intrinsic preference for

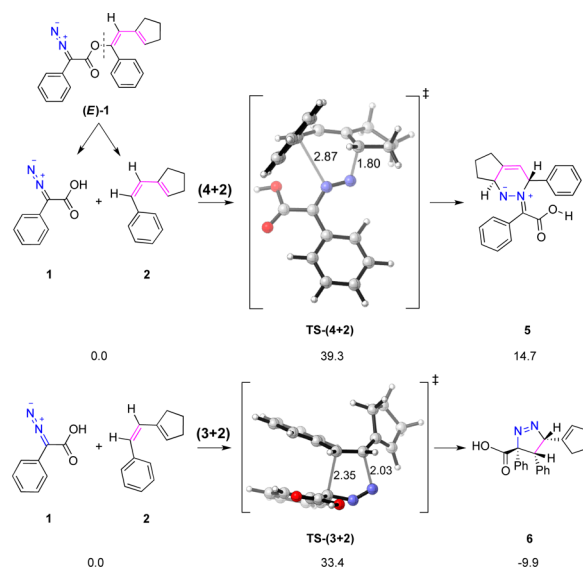


Figure 4. Transition structures and free energies of activation (ΔG_{298}) (in kcal/mol) for the intermolecular (4 + 2) and (3 + 2) cycloaddition reactions of truncated reactants calculated at the M06-2X/6-311+G(d,p)/SMD(chloroform)//M06-2X/6-31G(d) level. Bond lengths in Å.

the (3 + 2) cycloaddition, we analyzed the two transition structures using the distortion/interaction model. The distortion/interaction model,^{24a} or the activation strain model,^{24b} has recently been used to explain the reactivities and selectivities of cycloadditions in bioorthogonal chemistry,²⁵ materials chemistry,²⁶ and organic synthesis.^{27,28} For each reaction, the transition state is separated into two distorted fragments (diazo compound and diene) followed by single-point energy calculations on each fragment. The difference in energy between the distorted fragments and optimized ground-state geometries is the distortion energy of the diazo compound (ΔE_d^\ddagger _diazo) and the diene (ΔE_d^\ddagger _diene). The TS interaction energy (ΔE_{int}^\ddagger) is the difference between the activation energy and the distortion energy ($\Delta E_{int}^\ddagger = \Delta E^\ddagger - \Delta E_d^\ddagger$). The results in Figure 5 show that the distortion energy of TS-(3 + 2) is

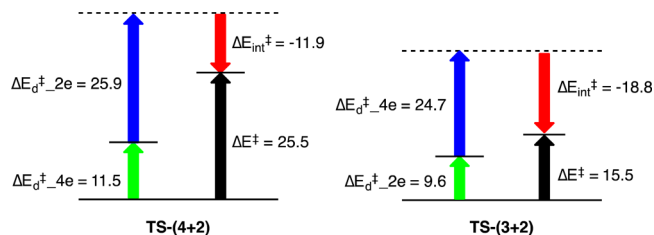


Figure 5. Distortion, interaction, and activation energies for the TS-(4 + 2) and TS-(3 + 2) (green: distortion energy of diene, blue: distortion energy of diazo compound, red: interaction energy, black: activation energy, in kcal/mol).

similar to that of TS-(4 + 2). However, the interaction energy (-18.8 kcal/mol) is more favorable for TS-(3 + 2) compared to that of TS-(4 + 2) (-11.9 kcal/mol). In order to understand the difference, we have analyzed the interaction energies by FMO theory.

Frontier Molecular Orbital (FMO) Analysis. The energies of relevant frontier orbitals were calculated with HF/6-31G(d) based on M06-2X/6-31G(d)-optimized transition

state geometries, because Kohn–Sham orbitals sometimes provide poor estimates of ionization potentials of simple organic molecules.²⁹ Figure 6 shows the HOMO and LUMO of

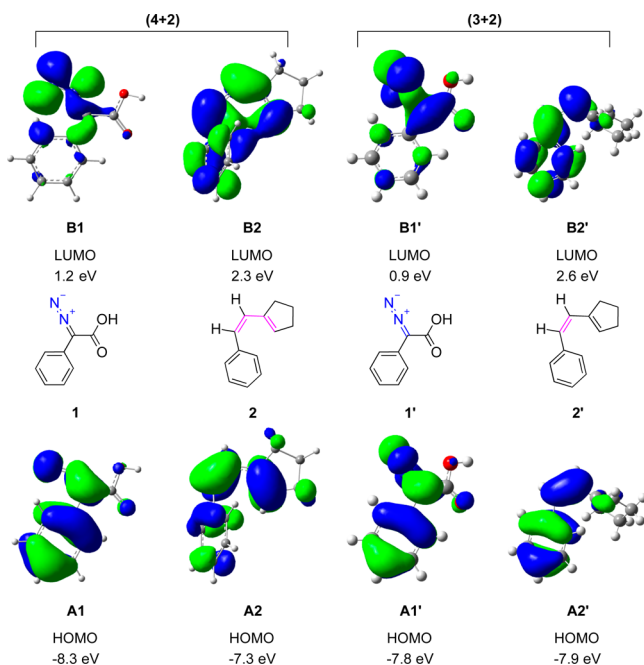


Figure 6. FMO diagram for the distorted reactants of (4 + 2) and (3 + 2) cycloaddition reactions. HF/6-31G(d)//M06-2X/6-31G(d) computed orbital energies.

each reactant distorted into its transition state geometry, for the (4 + 2) cycloaddition and the (3 + 2) cycloaddition. In each case, the LUMO_diazo 1 or 1', HOMO_diene 2 or 2' has the smaller HOMO–LUMO gap. While diazoalkanes are normally nucleophilic, the electron-withdrawing carbonyl group makes the diazo compound more electrophilic. Interestingly, in spite of the smaller FMO gap for the (4 + 2) cycloaddition, the (3 + 2) cycloaddition has a lower energy barrier and greater interaction energy (see Figures 4 and 5). We hypothesize this is due to the superior dipole LUMO–alkene HOMO orbital overlap.

Figure 7 shows qualitatively that there is very large overlap of the 1,3-dipole LUMO (B1') with the HOMO (A2') of the diene for the (3 + 2) cycloaddition. This is mainly due to the absence of a node in the alkene part of the HOMO, and the fact that the middle orbital of the dipole LUMO is small and does

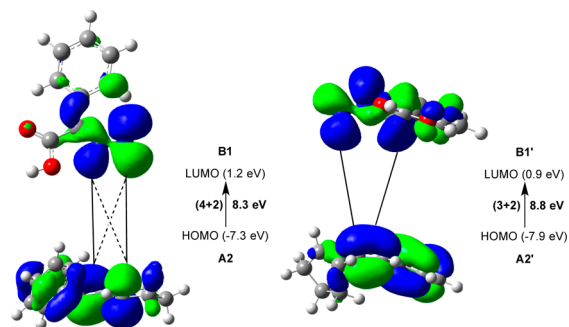


Figure 7. FMO diagram for the distorted reactants of (4 + 2) and (3 + 2) cycloaddition reactions. HF/6-31G(d)//M06-2X/6-31G(d) computed orbital energies.

not interfere with orbital overlap. By contrast, the N=N LUMO of the dipole and the HOMO of the diene contain nodes, and while primary interactions are positive, the secondary overlap represented by the dashed lines is negative, leading to reduced overlap.

Origin of the Preference for the Intramolecular (4 + 2) Cycloaddition to the Diazo Group. We have explained why the (3 + 2) cycloaddition will be favored in the intermolecular analog of the reaction studied here. This preference is overcome in the intramolecular reaction where the diene and diazo units are tethered by an ester linkage. This tether is highly distorted in the transition state, leading to the (3 + 2) reaction, and the (4 + 2) reaction is consequently preferred. As we showed in Figure 1, the stabilizing conjugation of the ester with the diazoalkane is destroyed in TS-(3 + 2)-*E* and the normally planar ester is also distorted significantly from planarity. These distortions are absent in the (4 + 2) pathway, which is consequently preferred in the intramolecular reaction.

CONCLUSION

We have explored diazoester-diene cycloadditions, and found there is an intrinsic preference for diazoesters and dienes to give the 1,3-dipolar cycloaddition. The Diels–Alder reaction of a diene across the N=N bond of a diazoalkene is unfavorable and endergonic. However, the reaction of (*E*)-1 favors the intramolecular (4 + 2) across the diazo N=N bond, because of the lack of strain in the tether and the strong orbital interactions. The *Z*-isomer of the diene is inert to both (3 + 2) and (4 + 2) cycloadditions due to the distortion of the tether required to achieve the transition state geometry. The reactivities of intermolecular cycloadditions are controlled by interaction energies. The intramolecular cycloaddition favors the hetero-DA reactions to the diazo N=N bond because of the high distortion energy of the tethering ester in the (3 + 2) cycloaddition.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12371.

Additional computational results and supplementary computational data such as the energies and Cartesian coordinates of stationary points (PDF)

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Notes

The authors declare no competing financial interest.

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