

The Nature of the Transition Structures of Triazolinedione Ene Reactions

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Abstract: The ene reactions of triazolinedione (TAD) with propene, *trans*- and *cis*-butene, and tetramethylethylene (TME) have been investigated theoretically with *ab initio* molecular orbital calculations. All geometries were fully optimized at the RHF/6-31G* level, followed by MP2/6-31G* and Becke3LYP/6-31G* single point energy calculations. A stepwise mechanism involving an aziridinium imide (AI) intermediate is predicted. The most stable transition structure for the first step involves a decidedly non-least-motion attack of TAD on the alkene, with methyl group rotation to bring a hydrogen in close proximity to the nitrogen on TAD for favorable electrostatic and secondary orbital interactions. Some isomerization of the AI intermediates is feasible, while reversion to reactants is less favorable than the product-forming hydrogen transfer. The activation energies decrease in the series from propene, to butenes, to TME, as the alkenes become more substituted and electron-rich. Kinetic isotope effects were computed based on the RHF/6-31G* geometries and frequencies, using the Bigeleisen–Mayer equation and the QUIVER program. The calculated isotope effects are in reasonable accord with the experimental measurements. The stabilizing N–H interaction in the first transition structure contributes significantly to the observed isotope effect.

Introduction

Triazolinediones (TAD) are highly reactive neutral electrophiles that exhibit reactivity similar to singlet oxygen,^{1–6} especially in ene reactions with various alkenes.^{1,7–9} The different mechanisms proposed for the ene reaction are shown in Figure 1: (a) a concerted reaction through a cyclic transition state; (b) formation of an open zwitterionic or biradical intermediate; and (c) formation of an aziridinium imide (AI) intermediate. Experimental studies support the formation of an AI intermediate via a stepwise mechanism (Figure 1c). Isotope effect studies on RTAD (R = phenyl, methyl) ene reactions with deuterated tetramethylethylenes and 2-butenes establish rate-determining formation of the aziridinium imide (AI) intermediate (Figure 2).^{1,6,7} Significant intramolecular isotope effects were found with *cis*-related methyl and deuteriomethyl groups, but only a small isotope effect was observed with *trans* groups. AI intermediates have been observed spectroscopically in reactions of biadamantylidene, *trans*-cycloheptene, and *trans*-cyclooctene.^{10–12}

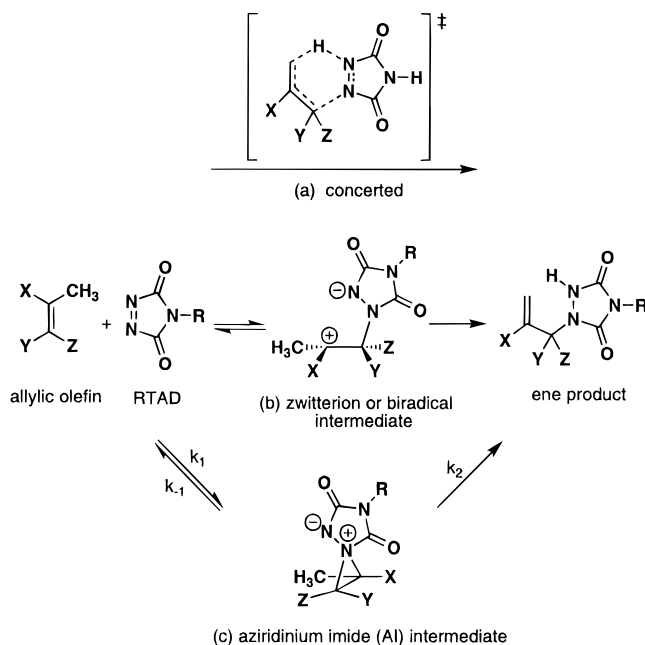


Figure 1. Proposed mechanisms for triazolinedione ene reactions.

Computational Methodology

We have studied TAD ene reactions with several alkenes with RHF/6-31G*, MP2/6-31G*, and Becke3LYP/6-31G* methods.¹³ Reactants, transition structures, intermediates, and products were fully optimized.

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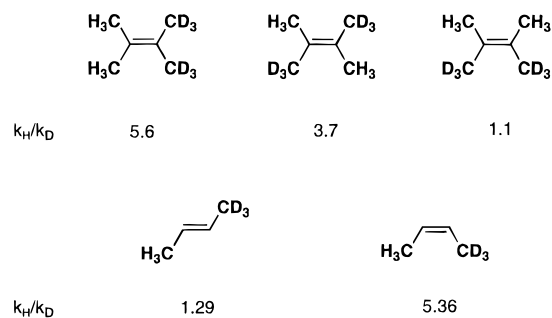


Figure 2. Observed isotope effects in the PTAD ene reaction with tetramethylethylenes¹ and 2-butenes;^{6,7} experimental errors are 5% and 2.0–2.5% of the measured values, respectively.

Harmonic vibrational frequencies were calculated to confirm the nature of all stationary points in this study. Kinetic isotope effects (KIEs) were computed by using the method of Bigeleisen and Mayer,¹⁴ with RHF/6-31G* force constants scaled by 0.9¹⁵ and tunneling corrections.¹⁶

Results and Discussion

The optimized structures for the TAD ene reaction with propene are shown in Figure 3, and the energetics are summarized in Table 1. The transition structure for the formation of the AI intermediate is a highly asynchronous one, reminiscent of the non-least-motion reactions of carbenes with alkenes,^{17–19} and allowing similar orbital interactions. Similar to carbenes, TAD exhibits both electrophilic and nucleophilic character in perpendicular directions. The frontier orbital interactions operating in TS **3** are shown qualitatively in Figure 4. Both an electrophilic (π approach) interaction between the TAD-LUMO and the propene-HOMO and a nucleophilic (σ approach) interaction between the TAD-HOMO and the propene-LUMO can occur. In carbenes, orbital symmetry forbiddenness is avoided by the non-least-motion approach (π approach, then rotation). This non-least-motion approach is favored for the TAD ene reaction also. In TS **3**, the angle of tilt of the TAD ring with respect to the propene plane is approximately 45°. This angle would be expected to be 0° for a pure electrophilic interaction and 90° for a pure nucleophilic interaction. The observed ~45° angle of approach indicates that both types of orbital interactions occur. Furthermore, TAD is pointed “inward”, across the propene face, similar to the geometry calculated for carbene cycloadditions.^{17,18} This “inward” approach maximizes both the electrophilic TAD-LUMO, propene-HOMO interaction and the nucleophilic TAD-HOMO, propene-LUMO interaction.

There are four different approaches of TAD to the alkene plane. TS **3**, shown in Figure 3, is 7.4–9.3 kcal/mol lower than the other three transition structures (Figure 5). Two transition structures lead to AI intermediates which can form products, while the other two give AI intermediates which cannot lead to ene products without first reverting to starting materials or isomerization. The transition states are all unsymmetrical and similar in structure and energy, with the exception of TS **3**, which has the lowest energy. The methyl conformation of TS **3** resembles the maximum in the ground state potential of the methyl group in propene, just as proposed earlier for

Table 1. Calculated Relative Energies (kcal/mol) with Respect to Reactants for the Triazolinedione Ene Reaction with Propene, *trans*- and *cis*-Butene, and Tetramethylethylene

molecule	MP2/6-31G* ^a	B3LYP/6-31G* ^a	$\Delta G^\circ(298\text{ K})^b$
propene			
1st TS 3	2.5	11.0 ^c	26.8
AI 4	-12.7	-3.7 ^c	15.0
TS for isomerization		(3.7) ^d	
2nd TS 5	1.9	4.9 ^c	20.5
ene product 6	-39.1		
<i>trans</i> -butene			
1st TS	0.5	9.8	26.0
AI int.	-13.7	-3.7	15.1
2nd TS	0.8	6.6	22.6
ene product	-37.2		
<i>cis</i> -butene			
1st TS	-0.7	9.2	25.3
AI int	-16.5	-5.9	9.5
2nd TS	-1.0	5.0	20.7
ene product	-40.7		
tetramethylethylene			
1st TS	-6.7	6.9	23.5
AI int	-16.7	-2.3	16.2
2nd TS	-4.1	3.6	20.1
ene product	-42.0		

^a Single point energies on RHF/6-31G* geometries. ^b Free energies are based on Becke3LYP single point energies with RHF/6-31G* corrections for zero-point energy, thermal energy, and entropy. ^c Becke3LYP/6-31G* energies. ^d UBecke3LYP/6-31G* energies.

singlet oxygen reactions.²⁰ In TS **3**, the methyl group is rotated so that one hydrogen is only 2.208 Å away from N2, allowing both favorable electrostatic and secondary orbital interactions to occur. The electrostatic interaction involves the relatively negative N and the positive allylic H, while the stabilizing secondary orbital interaction is shown in Figure 4a. This N–H interaction plays a significant role in stabilizing TS **3** and has a surprisingly important role in the isotope effects of the reaction, as discussed below.

Two isomeric AI intermediates were located. The geometries of both intermediates are consistent with earlier proposals,^{1,2,6–9,21} in that the spiro system has the imide ring perpendicular to the aziridinium ring. AI **4** lies 2.1 kcal/mol below the second isomer (not shown), in which N2 is opposite to the methyl group. Only AI **4** has the proper alignment of the TAD ring and methyl group for hydrogen abstraction to occur, leading to the second transition structure (**5**) of the reaction. The distinguishing feature in TS **3**, the rotation of the methyl group toward N2 on TAD, disappears in AI **4**.

In TS **5**, the three-membered ring is nearly cleaved, and hydrogen transfer to N2 is significant, but less than half-completed.¹⁹ Although hydrogen atom transfer is optimally linear,²² the N1–H–C3 angle is predicted here to be 142°. This value is similar to that calculated in several other intramolecular hydrogen transfer reactions.^{23,24}

We have explored whether the isomeric AI intermediates can interconvert directly via breakage of one C–N bond followed by rotation of the TAD by 180° around the remaining C–N bond. With unrestricted DFT calculations and spin correction,^{25,26} a diradical transition structure (Figure 6) 7.4 kcal/mol higher than the AI intermediate is located; isomerization of the

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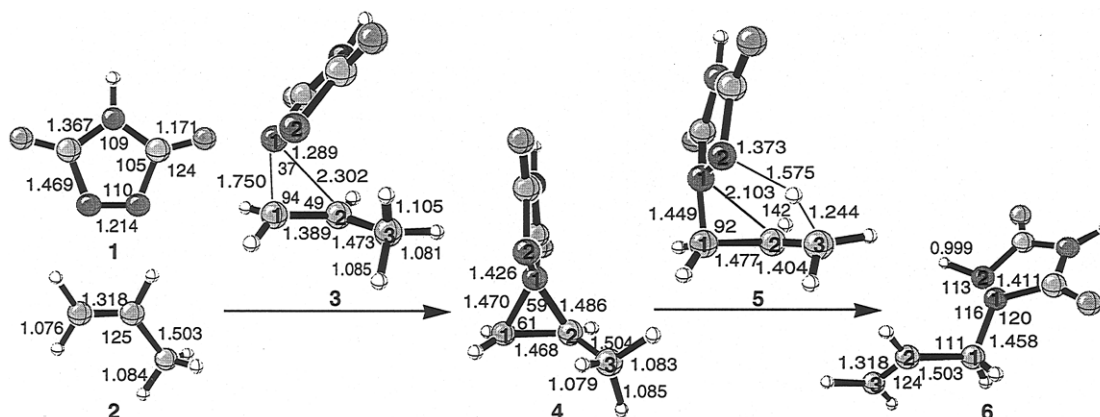


Figure 3. RHF/6-31G* optimized structures for the TAD ene reaction with propene: reactants, transition structures, AI intermediate, and ene product.

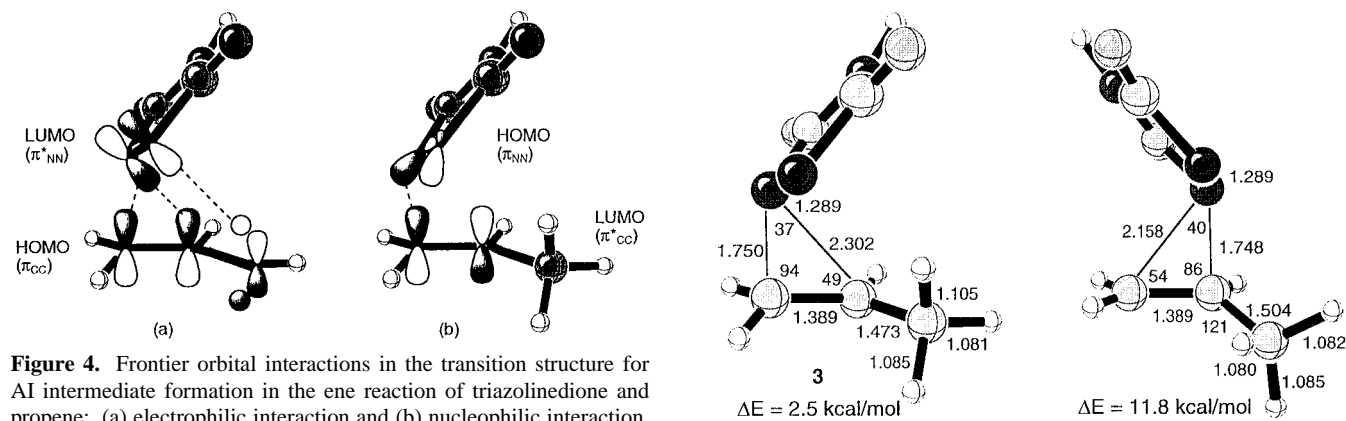


Figure 4. Frontier orbital interactions in the transition structure for AI intermediate formation in the ene reaction of triazolinedione and propene: (a) electrophilic interaction and (b) nucleophilic interaction.

Table 2. Experimental and Calculated (RHF/6-31G*) Intramolecular Kinetic Isotope Effects for Triazolinedione Ene Reactions with *trans*- and *cis*-Butene, and Tetramethylethylene^a

k_H/k_D	exptl ^{1,6,7}	theoretical		
		k_1	k_{-1}	k_2
<i>trans</i> -butene	1.29	1.22 (1.22)	1.22 (1.22)	4.41 (5.60)
<i>cis</i> -butene	5.36	1.00	1.00	4.26 (5.45)
<i>cis</i> -TME- <i>d</i> ₆	1.1	1.10 (1.10)	1.08 (1.08)	4.06 (5.22)
<i>trans</i> -TME- <i>d</i> ₆	3.7	1.00	1.00	3.96 (5.09)
<i>gem</i> -TME- <i>d</i> ₆	5.6	1.00	1.00	5.21 (6.67)

^a Values in parentheses are corrected for tunneling.¹⁶

intermediates and the second step of the reaction have similar energies, and thus some isomerization cannot be ruled out.

For *trans*- and *cis*-butene and for tetramethylethylene (TME), the optimized transition structures and AI intermediates are very similar in geometry to those for propene. The energetics are reported in Table 1. RHF/6-31G* methods overestimate activation energies, MP2 gives barriers that are too low, while B3LYP energies are likely to be closest to experiment.²⁷ For propene, all levels of calculation predict that the first step is rate-determining. The predicted activation energies decrease as the alkenes become more substituted and electron-rich, in agreement with experimental studies.^{6,20} Also, calculated activation barriers are in excellent agreement with experimental results which show that *cis*-butene reacts faster than *trans*-butene.¹ In addition, experimental activation energies for reactions of *trans*-cycloheptene (9.7 and 13.4 kcal/mol) and *trans*-cyclooctene (16.2 kcal/mol) are comparable to those computed here (Table 1).^{11,12}

The calculated kinetic isotope effects (KIEs) of the different steps for the various alkenes are summarized in Table 2 for cases where experimental values are available for comparison.

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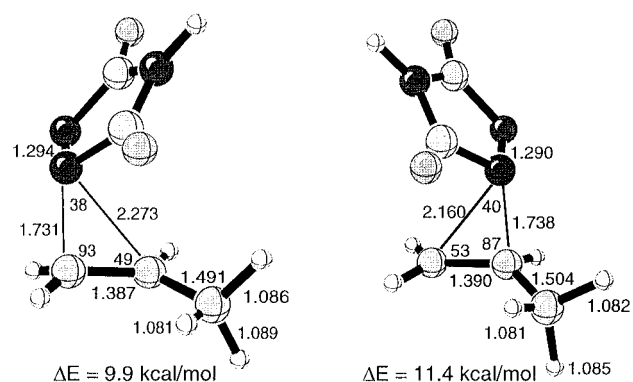


Figure 5. Four optimized transition structures (RHF/6-31G*) for AI intermediate formation in the ene reaction of triazolinedione and propene. MP2/6-31G**/RHF/6-31G* energies relative to reactants are given.

Rate constants k_1 and k_2 correspond to the first and second step, respectively, while k_{-1} refers to the reversion process. The large intramolecular isotope effect in 1,1,1-trideuterio-*cis*-butene (5.36) has been interpreted as being consistent with a stepwise mechanism;^{1,6} indeed, calculations predict 5.45 for the isotope effect of the second (product-determining) step of the reaction. The isotope effect of 1.29 observed with 1,1,1-trideuterio-*trans*-butene was postulated to be a result of either partial reversion of the intermediate to reactants or isomerization of the intermediate, since no isotope effect had been anticipated for the first step.⁶ The computed isotope effect (1.22) for the first step (k_1) is close to the experimentally observed overall k_H/k_D (1.29). The first step is clearly rate-determining, and the experimental result allows for at most a minor amount of isomerization. The isotope effect on the first step comes mainly from a single N–H interaction, which weakens the C–H bond in the transition state. This decrease in C–H bond force constant gives a normal

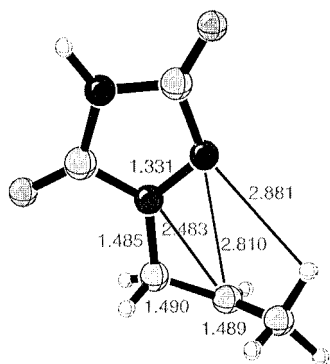


Figure 6. UB3LYP/6-31G* optimized transition structure for the isomerization of AI intermediates.

isotope effect. Thus, this N--H interaction is not only responsible for providing significant stabilization to the first step of the reaction, it is also the origin of the non-trivial isotope effect observed in *trans*-butene. This is contrary to previous suggestions.^{1,6}

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cis-1,1,1,4,4,4-Hexadeuterio-TME is similar to the *trans*-butene case, where the isotope effect of the first step becomes the overall reaction KIE. The experimental and theoretical values are identical. There is no evidence for isomerization. Both *trans*- and *gem*-TME-*d*₆ are similar to the *cis*-butene case; only the isotope effect of the second step contributes to the overall KIE of the reaction. Although both calculated values are larger than the experimental KIEs, the general trend observed is the same: *gem*-TME has a much larger calculated KIE than *trans*-TME. Experimental studies suggested that hydrogen tunneling occurs in *gem*-TME, but not in *trans*-TME.²⁸

In conclusion, our calculations support a stepwise mechanism with the first step being rate-determining. A unique N--H interaction involving both electrostatic and secondary orbital interactions is significant in stabilizing the first transition state and contributes to the overall KIE. The calculated KIEs are in reasonable agreement with experimental values.

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