

Isotope Effects and the Mechanism of Triazolinedione Ene Reactions. Aziridinium Imides Are Innocent Bystanders

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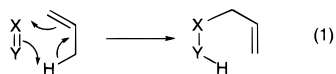
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Abstract: Kinetic isotope effects were determined for the ene reactions of 4-phenyl-1,2,4-triazoline-2,5-dione with 2-methyl-2-butene and 2-methyl-1-pentene. In each case highly inverse ($k_H/k_D = 0.87–0.88$) vinylic deuterium isotope effects were observed. Large ^{13}C isotope effects were observed for the less-substituted olefinic carbons of each alkene and much smaller effects were found in the more-substituted olefinic carbon. Becke3LYP calculations of the mechanistic pathway for the ene reaction of 1,2,4-triazoline-2,5-dione with isobutene, 2-methyl-2-butene, and tetramethylethylene predict a new mechanism for these reactions involving an open biradical as the key intermediate. This biradical may either form the ene product or reversibly form an intermediate aziridinium imide. The validity of these calculations is supported by a comparison of experimental and theoretically predicted isotope effects. A curved Arrhenius plot of product ratios was found for the ene reaction of 2-methyl-1-pentene in the presence of methanol. This is inconsistent with a simple two-step ene mechanism involving only an aziridinium imide intermediate, but the curvature of this plot could be modeled well by the theoretical mechanism using enthalpy and entropy parameters close to theoretically predicted values. A variety of observations associated with these reactions are examined and found to support the new mechanism.

Introduction

An ene reaction is the addition of an electrophilic double or triple bond to an alkene with concomitant transfer of an allylic hydrogen. Despite the simple formal description of the bonding changes in these reactions (eq 1) and the fact that they are



allowed pericyclic processes, these synthetically important reactions have often been shown to involve complex mechanisms. This includes ene reactions of singlet oxygen,¹ nitroso compounds,² selenium dioxide,³ acylium ions,⁴ and Lewis acid-catalyzed ene reactions.⁵

A central component of mechanistic studies of ene reactions has been the observation of deuterium kinetic isotope effects (KIEs). The observation of a large ($k_H/k_D > \sim 2$) KIE is indicative of hydrogen transfer in the rate-limiting step and has often been taken as evidence for a concerted mechanism,⁶ while the absence of a substantial deuterium KIE is the signature of a stepwise mechanism. Stepwise ene reactions that lack an *intermolecular* deuterium KIE may still exhibit an *intramolecular* KIE if a hydrogen is transferred in the product-determining step. The observation of intramolecular KIEs has provided information about the nature of the intermediates in many of the stepwise ene reactions, and this is the basis for the “Stephenson isotope effect test”.⁷

The reactions of 1,2,4-triazoline-3,5-diones (TADs) have attracted interest owing to their expected similarity to singlet oxygen and their multiform high reactivity in Diels–Alder reactions,⁸ ene reactions,⁹ [2 + 2] cycloadditions,¹⁰ and even ring-openings of strained C–C single bonds.¹¹ The ene reactions of TADs were quickly recognized as stepwise processes on the basis of trapping experiments.^{10,12} Deuterium KIE studies have backed this conclusion and provided more detailed information on the mechanistic pathway. In a Stephenson isotope effect test on the reaction of RTAD [R = phenyl (PTAD) or methyl (MTAD)] with *cis*-, *trans*-, and *gem*-substituted tetramethylethylene-*d*₆ (**1a–c**), Greene and co-workers observed a significant intramolecular KIE only with **1b** and **1c** (Scheme 1).¹³ This observation indicates that the product-determining step involves a choice of reaction modes between *cis*-oriented CH₃ and CD₃ groups, and was taken as implicating the intermediacy of the aziridinium imide (AI) **2**.

This two-step mechanism involving an AI has been supported by both experimental and theoretical studies. Foote has observed KIEs for the reaction of PTAD with *cis*- and *trans*-2-butene-*d*₃ and, in concordance with the Green studies, observed a substantial intramolecular KIE only with the *cis* isomer. An AI

(1) Frimer, A. A.; Stephenson, L. M. In *Singlet O₂*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; pp 68–87.

(2) Seymour, C. A.; Greene, F. D. *J. Org. Chem.* **1982**, *47*, 5226.

(3) Stephenson, L. M.; Speth, D. R. *J. Org. Chem.* **1979**, *44*, 4683–9.

(4) Beak, P.; Berger, K. R. *J. Am. Chem. Soc.* **1980**, *102*, 3848–56.

(5) Snider, B. B.; Ron, E. *J. Am. Chem. Soc.* **1985**, *107*, 8160.

(6) Achmatowicz, O., Jr.; Szymoniak, J. *J. Org. Chem.* **1980**, *45*, 4774.

(7) Kwart, H.; Brechbiel, M. W. *J. Org. Chem.* **1982**, *47*, 3355. Dai, S.-H.; Dolbier, W. R., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 3953.

(7) (a) Grdina, B.; Orfanopoulos, M.; Stephenson, L. M. *J. Am. Chem. Soc.* **1979**, *101*, 3111–2. (b) For earlier work on intramolecular isotope effects, see: Dai, S.-H.; Dolbier, W. R., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 3946.

(8) Burrage, M. E.; Cookson, R. C.; Gupte, S. S.; Stevens, I. D. R. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1325.

(9) Pirkle, W. H.; Stickler, J. C. *J. Chem. Soc., Chem. Commun.* **1967**, 760.

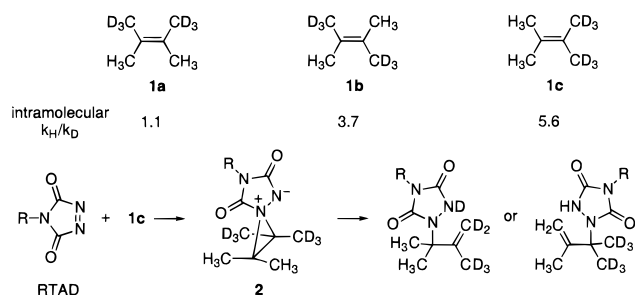
(10) von Gustorf, E. K.; White, D. V.; Kim, B.; Hess, D.; Leitich, J. *J. Org. Chem.* **1970**, *35*, 1155.

(11) Amey, R. L.; Smart, B. E. *J. Org. Chem.* **1981**, *46*, 4090.

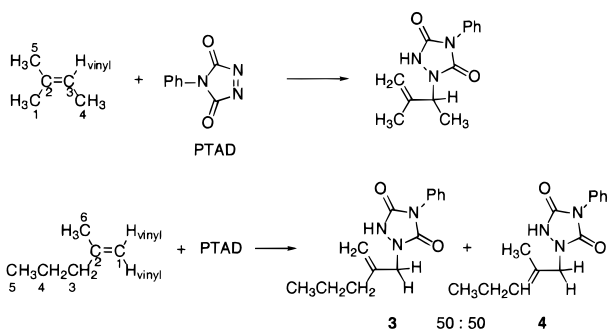
(12) Turner, S. R.; Guilbault, L. J.; Butler, G. B. *J. Org. Chem.* **1971**, *36*, 2838.

(13) (a) Seymour, C. A.; Greene, F. D. *J. Am. Chem. Soc.* **1980**, *102*, 6384. (b) Cheng, C.-C.; Seymour, C. A.; Petti, M. A.; Greene, F. D.; Blount, J. F. *J. Org. Chem.* **1984**, *49*, 2910.

Scheme 1



has been directly observed spectroscopically in reactions of RTAD with biadamantylidene,¹⁴ *trans*-cycloheptene,¹⁵ and *trans*-cyclooctene.¹⁶ Interestingly, the AI intermediate formed from *trans*-cycloheptene is *cis*-fused. Ab initio calculations by Houk and Foote at the RHF/6-31G* level (with higher-level energy calculations) have characterized transition states for the reaction of alkenes with TAD and for the formation of the ene product, as well as the AI intermediate with various alkenes.¹⁷



It has at times been proposed that other intermediates play a role in the reactions of alkenes with TADs, but the two-step mechanism for the ene reaction of TADs with alkenes through an AI intermediate is well-accepted. The results here conflict with this view. We report the results of a combined experimental and theoretical study of these reactions which suggest that the AI is an innocent bystander in the ene reaction, and that an alternative mechanism provides explanations for the diverse observations associated with these reactions. These results have implications toward the mechanisms of other reactions of TADs and other ene reactions.

Results

Experimental Isotope Effects. Our initial aim was to study with isotope effects the synchronicity of C–N bond formation in the reaction of PTAD with alkenes, as we presumed that the transition state involved AI formation. This requires the use of unsymmetrically substituted alkenes because symmetrical alkenes would necessarily exhibit symmetrical KIEs due to averaging. 2-Methyl-2-butene was chosen for study because its ene reaction with PTAD produces a single product in quantitative yield,¹⁸ and it was thought that the initial addition of PTAD to this unsymmetrical alkene would be dominated by a single

Table 1. Experimental and Calculated KIEs ($k^{12}C/k^{13}C$ or k_H/k_D , 25 °C) for the Ene Reactions of 2-Methyl-1-pentene and 2-Methyl-2-butene with PTAD

	exptl: 2-methyl-1-pentene		calcd: 5	
	expt 1 ^a	expt 2 ^a	Becke3LYP	RHF
C1	1.036(4)	1.036(4)	1.037	1.047
C2	1.003(3)	1.003(1)	1.009	1.011
C3	1.001(2)	1.000(2)	1.001	1.001
C(4)	1.00 (assumed)			
C6	1.002(2)	1.000(2)	1.001	1.001
H _{vinyl}	0.87(1)	0.87(1)	0.862	0.841
C3HD	1.04(1)	1.04(1)	1.026	1.016
C6H ₂ D	1.01(1)	1.03(1)	1.026	1.016

	exptl: 2-methyl-2-butene		calcd (all Becke3LYP)		
	expt 3 ^a	expt 4 ^a	7	8	9
C1	1.000(1)	1.001(1)	1.001	1.002	0.997
C2	1.014(3)	1.013(2)	1.009	1.010	1.039
C3	1.026(3)	1.025(3)	1.038	1.036	1.010
C4	1.00 (assumed)		0.998	0.999	1.001
C5	1.003(2)	1.004(2)	1.001	1.001	0.998
H _{vinyl}	0.87(2)	0.88(2)	0.869	0.854	1.025
C1H ₂ D	1.02(2)	1.01(2)	1.045	1.007	0.971
C5H ₂ D	1.01(2)	1.00(2)	1.004	1.039	0.970
C4H ₂ D	1.00 (assumed)		0.973	0.977	1.049

^a Experiments 1–4 were taken to 66%, 70%, 75%, and 67% (all ±3%) completion, respectively.

regioisomeric transition state. This assumption was not supported by later results (vide infra) and we therefore also studied the reaction of PTAD with the more unsymmetrical 2-methyl-1-pentene. Although the reaction of 2-methyl-1-pentene forms two products, the stereoisomeric pathways for formation of these two products should involve very similar transition states in the first mechanistic step.

The ¹³C and ²H KIEs for these reactions were determined combinatorially at natural abundance.¹⁹ Reactions of 2-methyl-2-butene on a 0.5-mol scale with PTAD were carried out in 1,4-dioxane at 25 °C, and were taken to 75(±3)% and 67(±3)% conversion. The unreacted 2-methyl-2-butene was then recovered by vacuum transfer followed by fractional distillation. The resulting material was analyzed by ¹³C and ²H NMR compared to a standard sample of the original 2-methyl-2-butene. The changes in ¹³C and ²H isotopic composition were calculated by using the C4 methyl group as “internal standard” with the assumption that their isotopic composition does not change. Similarly, reactions of 2-methyl-1-pentene on a 0.4-mol scale with PTAD were taken to 66(±3)% and 70(±3)% conversion and the recovered unreacted alkene was compared to the original alkene using the C4 methylene group as standard.²⁰ From the changes in isotopic composition, the KIEs were calculated in the previously reported fashion.¹⁹

The results are summarized in Table 1. In accord with previous observations, no primary deuterium KIE was observed. The most notable features of the KIEs were the substantial difference in C1 and C2 ¹³C KIEs for 2-methyl-1-pentene and the highly inverse H_{vinyl} deuterium KIE.

Theoretical Calculations. These experimental KIEs suggested in a qualitative fashion that the reaction of PTAD with 2-methyl-1-pentene involved extremely asynchronous C–N bond formation, if an AI were being formed at all. The results with 2-methyl-2-butene, particularly the less differing ¹³C KIEs at the olefinic carbons, qualitatively suggested a less asynchro-

(14) Nelsen, S. F.; Kapp, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 5548.

(15) Squillacote, M.; Mooney, M.; De Felippis, J. *J. Am. Chem. Soc.* **1990**, *112*, 5364.

(16) Poon, T. H. W.; Park, S. H.; Elemes, Y.; Foote, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 10468.

(17) Chen, J. S.; Houk, K. N.; Foote, C. S. *J. Am. Chem. Soc.* **1997**, *119*, 9852.

(18) Ohashi, S.; Leong, K.; Matyjaszewski, K.; Butler, G. B. *J. Org. Chem.* **1980**, *45*, 3467.

(19) Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357.

(20) C4 was chosen as standard due to an overlapping impurity in the ¹³C NMR which prevented the accurate integration of C5.

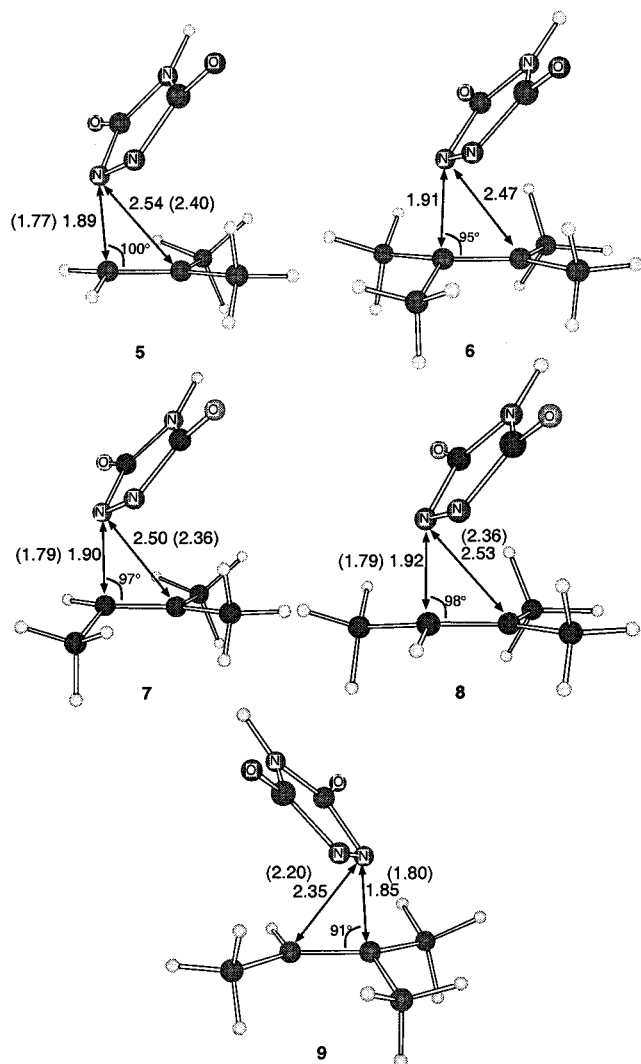


Figure 1. Becke3LYP transition structures for the reaction of TAD with isobutene, 2-methyl-2-butene, and tetramethylethylene. RHF distances are shown in parentheses.

nous formation of the two new C–N bonds and seemed reconcilable with the prior calculational results. However, a more detailed interpretation of the KIEs with the aid of calculations supports a very different picture of the reaction mechanism.

The complete mechanistic pathways for the reaction of the unsubstituted TAD with isobutene, 2-methyl-2-butene, and tetramethylethylene were studied in HF and Becke3LYP calculations using a 6-31G* basis set. Transition structures for the initial attack of TAD on these alkenes are shown in Figure 1. Only one low-energy transition structure was found with isobutene and tetramethylethylene (**5** and **6**, respectively), while three stereoisomeric/regioisomeric low-energy transition structures were found with 2-methyl-2-butene (**7–9**).²¹ All of these first-step transition structures involve a very unsymmetrical attack on the alkene. However, the transition structure with isobutene differs little from those with 2-methyl-2-butene, in contrast to what was qualitatively suggested by the experimental KIEs above (considering isobutene as a good model for 2-methyl-1-pentene). A better explanation for the differing KIEs for 2-methyl-1-pentene versus 2-methyl-2-butene will be discussed below. At the RHF level, the first-step transition

(21) A fourth regioisomeric transition structure in which N2 is anti to C4 was higher in energy (5.4 kcal/mol at the Becke3LYP level) and was not considered further.

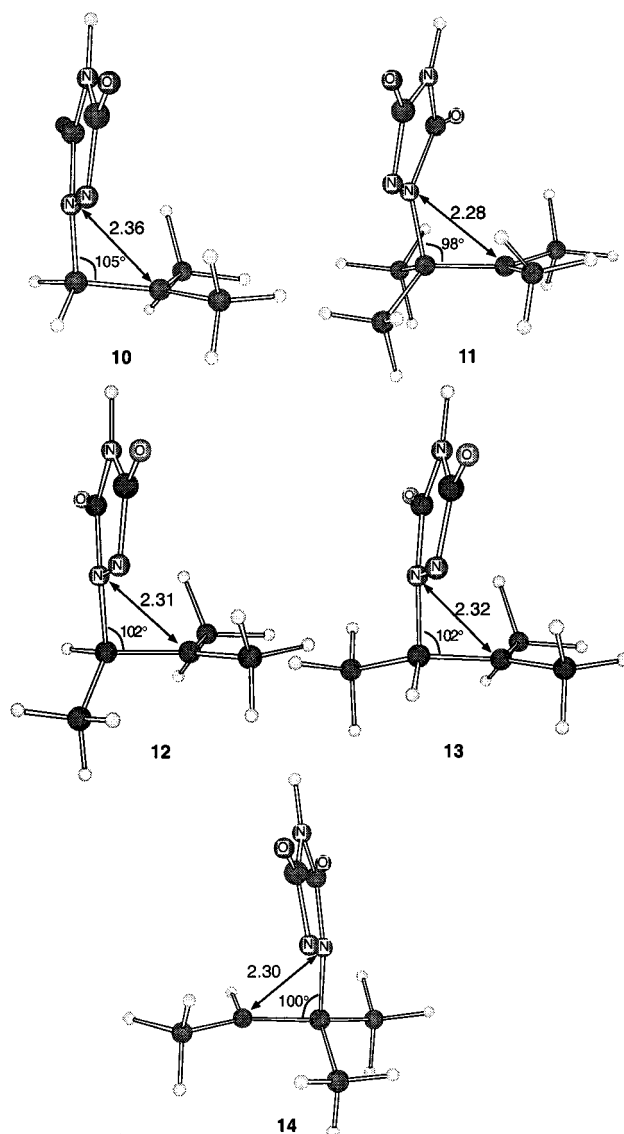
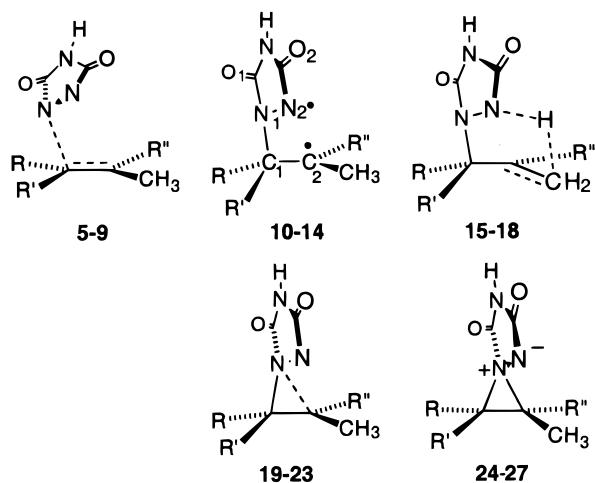


Figure 2. UBcke3LYP intermediate structures for the reaction of TAD with isobutene, 2-methyl-2-butene, and tetramethylethylene.

structures closely resemble that calculated by Houk and Foote for reaction of TAD with propene,¹⁷ but the Becke3LYP structures show significantly less sign of bond formation between the attacking nitrogen of TAD and the distal olefinic carbon. Most notably, examination of the atomic motion associated with the transition vectors for **5–9** suggested that the attacking TAD nitrogen was undergoing bond formation with only one of the olefinic carbons: the angle of attack of the TAD nitrogen on the olefinic carbons was in each case actually increasing in the transition vector.

Based on these observations, an IRC analysis of structures **7** and **8** was performed. In intriguing contrast with the standard mechanism for these reactions, **7** and **8** did not lead to AI intermediates. Instead, open structures in which the attacking TAD nitrogen has bound to only one of the olefinic carbons were formed. Corresponding to each of the first-step transition structures, the open structures **10–14** in Figure 2 were found.

Structures **10–13** are minima in both restricted and unrestricted Becke3LYP calculations, while **14** could be found only in unrestricted calculations. None of these structures correspond to minima at the RHF level. The unrestricted structures have biradical character, having an S^2 of 0.42–0.63 and having Mulliken spin densities of 0.6–0.74 on the unbonded of the



	R	R'	R''
5 10 15 19 24	H	H	CH ₃
6 11 16 20 25	CH ₃	CH ₃	CH ₃
7 12 17 21 26	H	CH ₃	CH ₃
8 13 18 22 27	CH ₃	H	CH ₃
9 14 23	CH ₃	CH ₃	H

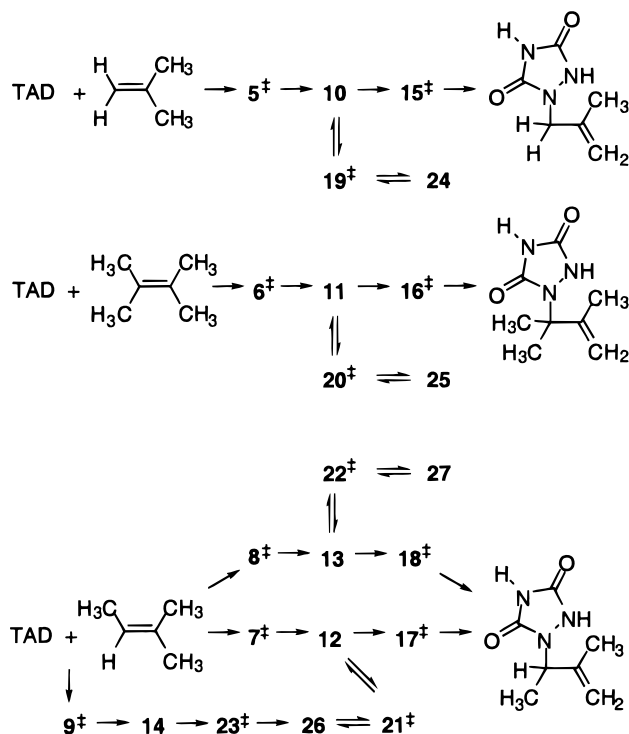


Figure 3. Intermediates, transition structures, and reaction pathways for the ene reactions of TAD with isobutene, 2-methyl-2-butene, and tetramethylethylene. Complete structures are given in the Supporting Information.

original olefinic carbons, and we will describe these structures as biradicals. The restricted structures (see Supporting Information) exhibit slightly greater charge separation, with $\approx 0.5 e^-$ charge transfer from the 2-methyl-2-butene to the TAD in a Mulliken analysis. The moderate zwitterionic character exhibited by the restricted structures would likely be enhanced in solution reactions, but in the calculations falls well short of the degree of charge transfer expected in a zwitterion.

The remainder of the reaction pathway is illustrated in Figure 3 (and shown in detail in the Supporting Information). The

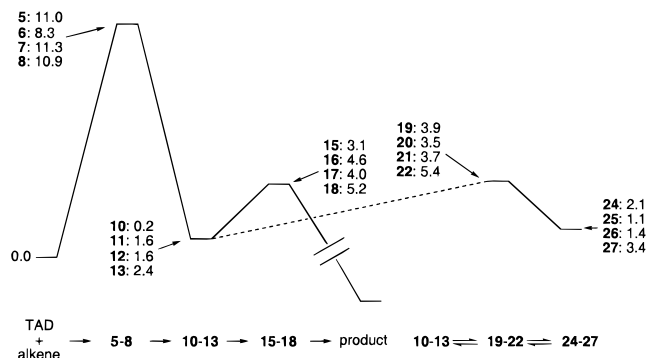


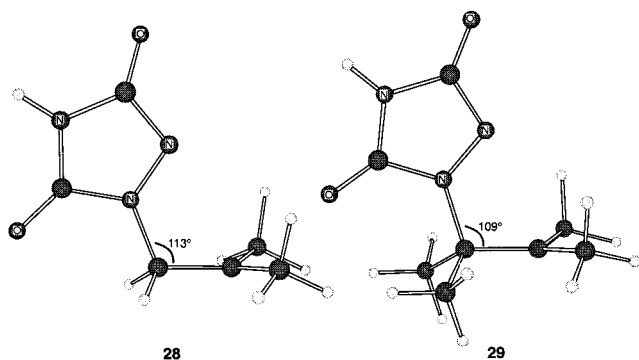
Figure 4. Energetic profile predicted for the reactions of TAD with isobutene, 2-methyl-2-butene, and tetramethylethylene, in kcal/mol relative to starting material energies. ((U)Becke3LYP/6-31G* + ZPE).

observed ene products are predicted to be formed via transition states 15–18. In contrast to the literature mechanism, an IRC analysis links these transition states to the biradicals 10–13, not to AIs 24–27. The biradicals may either form product or close reversibly to the AIs via transition states 19–23; in the case of 14 closure to the AI 26 is predicted to be strongly favored (but see the discussion of 14 below) and none of the regiochemically reversed product is formed experimentally.

A key question is whether the biradicals 10–14 correspond to true minima in reality on the free energy surface. Considering the restricted Becke3LYP calculations predict 10–13 to be minima: 10, 11, 12, and 13 are 1.8, 1.2, 0.9, and 1.8 kcal/mol lower in energy (including ZPE) than the transition states 19, 20, 21, and 22, respectively, leading to AIs. The introduction of solvent benzene by an SCICPM model with the restricted structures lowers the barrier for ring closure slightly, from 0.9 to 0.6 kcal/mol with 12. The use of unrestricted Becke3LYP calculations lowers the energy of 10–13 but has no impact on 19–22, so it raises the barriers to AI formation (including ZPE) to 3.8, 1.9, 2.1, and 3.1 kcal/mol, respectively. It should be noted that the use of unrestricted DFT calculations is problematical. Addressing the energetics from a different direction, a CASSCF calculation (2 electron, 2 orbital) found a 3.5 kcal/mol barrier for AI formation from 10. Entropy is also predicted to favor the open intermediates over their transition states for ring closure by 3–6 eu at the (U)B3LYP level, raising the free-energy well for 10–13 by an additional 0.9–1.8 kcal/mol. All of these factors suggest that 10–13 correspond to real minima on the free energy surface. The reality of biradical 14 is uncertain, as it is predicted to exist only in the unrestricted calculations and even then only faces a 0.6 kcal/mol barrier for ring closure to the AI 26. The lower stability of 14, if it is real, may be the result of involving a secondary carbon radical instead of the tertiary carbon radicals in 10–13.

The energetics for the mechanistic pathways (not including 9, 14, and 23) at the (U)Becke3LYP(+ZPE) level are summarized in Figure 4. In each case the first step is predicted to be rate limiting and the barriers for the remaining steps are low. The biradicals are predicted to be roughly comparable in energy to the AIs. Entropy is predicted to favor biradical 10 over AI 24 substantially (5.2 eu), though the entropy differences in the other cases are small. The relative enthalpic barrier for product formation versus AI formation from the biradical intermediates depends on the starting alkene. Based on the predicted energies here, much of the ene product from isobutene would form without the intermediacy of an AI intermediate, while tetramethylethylene would be expected to repeatedly visit the AI side path before product formation.

The barrier for N_1-C_1 or C_1-C_2 rotation in the open biradicals **10–14** is of interest owing to implications regarding the intramolecular isotope effects. The barrier for conformational isomerization in biradicals, such as the conversion of **12** into **13**, has often been assumed to be low. However, Houk and Foote found that the transition structure for isomerization of aziridinium imide intermediates with propene was 7.4 kcal/mol (UB3LYP + spin correction).¹⁷ This is substantially higher than the barrier for formation of the ene products. The search for the rotational transition structures with more alkyl groups on the alkene proved difficult: in many attempts to find a transition structure for the isomerization of **12** and **13** the search invariably fell into transition structures for the formation of the ene product, the diazetidone, or an oxazoline from C_2-O_1 bond formation. However, the transition structure **28** was located for conformational isomerization in **10**. Structure **28** has C_s symmetry and results from rotation about the C_1-N_1 bond in **10**. The barrier for this conformational isomerization is 3.9 kcal/mol (UB3LYP + zpe), which is 1.0 kcal/mol higher than the barrier predicted for formation of the ene product (cf. Figure 4). The corresponding C_s -symmetric structure **29** for rotation about the C_1-N_1 bond in **11** is a shallow minimum (ν for rotation = 16 cm^{-1}) which is 5.5 kcal/mol above **11**. If conformational isomerization in **11** must proceed through **29** (our search of the energy surface has not been sufficient to establish this), then the barrier would be predicted to be at least 2.5 kcal/mol higher than the barrier for formation of the ene product.



Calculated versus Experimental Isotope Effects. The comparison of experimental and calculated KIEs has been found to provide a sensitive measure of the transition state geometry and the accuracy of calculated transition structures. Toward that end, KIEs were predicted for each of the transition structures **5** and **7–9** by the method of Bigeleisen and Mayer²² from the scaled theoretical vibrational frequencies,²³ and tunneling corrections were applied using the one-dimensional infinite parabolic barrier model.²⁴ The results are shown in Table 1.

Using isobutene as a calculational model for 2-methyl-1-pentene, the Becke3LYP structure of **5** provides very good predictions of the experimental KIEs. The large C1 and H_{vinyl} KIEs are predicted within experimental error, and only the C2 KIE prediction differs substantially from the experimental value. The error at C2 is larger than errors observed in previous predicted ^{13}C KIEs based on Becke3LYP transition structures,^{25–27} but it is notable that the experimental value of 1.003 for C2 is

Table 2. Weighted-Average Calculated KIEs ($k^{12}\text{C}/k^{13}\text{C}$ or $k_{\text{H}}/k_{\text{D}}$, 25 °C) for the Ene Reaction of 2-Methyl-2-butene with TAD

	weighted av			weighted av	
	A ^a	B ^a		A ^a	B ^a
C1	1.001	1.000	H_{vinyl}	0.865	0.907
C2	1.010	1.017	$C1H_2D$	1.020	1.013
C3	1.036	1.030	$C5H_2D$	1.026	1.007
C4	0.998	0.999	$C4H_2D$	0.978	0.996
C5	1.001	1.000			

^a Weighted averages **A** and **B** are based on a Boltzmann distribution of **7**, **8**, and **9** using energies at the Becke3LYP/6-31G* +ZPE level for **A** and the MP4(SDQ)/6-31G//Becke3LYP/6-31G*+ZPE level for **B**, including a $-T\Delta S$ correction. See the Supporting Information for weighted-average predictions based on energies calculated in other ways.

lower than the predicted KIE of 1.009. The RHF structure, which shows greater bond formation to C2, results in less accurate prediction of the experimental KIEs.

The prediction of KIEs for the reaction of 2-methyl-2-butene is more complicated. The calculations of Houk and Foote had predicted that the TAD addition to propene would be extremely regioselective, with attack at the more substituted olefinic carbon disfavored by 8.9–9.3 kcal/mol at the MP2/6-31G**/RHF/6-31G* level.¹⁷ In contrast, we find here that transition state **9** is comparable in energy to **7** and **8** and should contribute to the observed KIEs. The degree of this contribution affects the predicted KIEs tremendously. A large contribution from **9** would result in C2 and H_{vinyl} KIE predictions that are too high and a C3 KIE prediction that is too low, opposite in direction from the errors in the predictions for **7** and **8**. In principle a total prediction can be based on a Boltzmann distribution of **7**, **8**, and **9**. In practice a problem is that small changes in the predicted relative energies of **7**, **8**, and **9** have large effects on the predicted KIEs and these predicted energies vary substantially with the theoretical level of the calculation. Table 2 shows two sets of predictions based on energies at the Becke3LYP/6-31G*+ZPE level and at a MP4(SDQ)/6-31G**/Becke3LYP/6-31G*+ZPE level including a correction for the relative entropies of **7**, **8**, and **9** to approximate their relative free energy. The predictions for these two sets nearly bracket the experimental values. However, the predicted KIEs vary with basis set, calculational level, and whether ZPE, thermal factors, and entropy are included. Nonetheless, it appears that a combination of **7**, **8**, and **9** can result in a reasonable agreement of the predicted KIEs with the experimental values. In contrast, RHF calculations, which predict direct formation of the aziridinium imides intermediates, result in KIE predictions which are in weak agreement with the experimental values at any weighting of contribution from the transition state isomers (see the Supporting Information.)

Methanol Trapping of Intermediates. Triazolinedione ene reactions carried out in the presence of methanol result in the formation of methanol adducts (e.g., **30**) in addition to the regular ene product. Except when a highly stable cation could be formed, an anti addition of the TAD and methoxy groups is observed. This has been concluded to result from methanol attack on an aziridinium imide intermediate²⁸ and is evidence

(22) (a) Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, *15*, 261. (b) Wolfsberg, M. *Acc. Chem. Res.* **1972**, *5*, 225.

(23) The calculations used the program QUIVER (Saunders, M.; Laidig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1989**, *111*, 8989) with Becke3LYP frequencies scaled by 0.9614 (Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502).

(24) Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman & Hall: London, 1980; pp 60–63.

(25) Beno, B. R.; Houk, K. N.; Singleton, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 9984–5.

(26) Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 3385–6.

(27) DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907–9908.

(28) Smonou, I.; Khan, S.; Foote, C. S.; Elemen, Y.; Mavridis, I. M.; Pantidou, A.; Orfanopoulos, M. *J. Am. Chem. Soc.* **1995**, *117*, 7081.

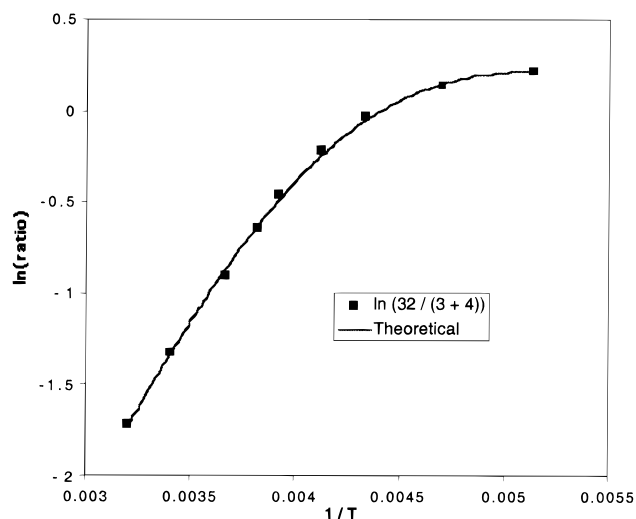
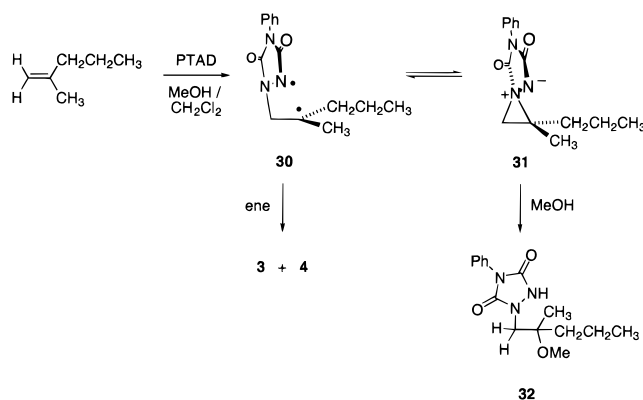


Figure 5. Logarithmic plot of the ratio of **32**:(**3** + **4**) versus temperature, and theoretical curve modeled on the mechanism of Scheme 2 (see text).

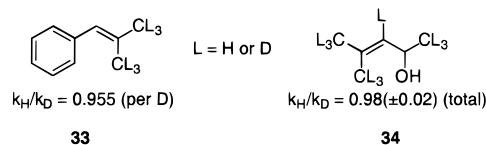
Scheme 2



against the initial involvement of a zwitterion. Although a concerted $\text{A}_{\text{D}}\text{E}_3$ -type addition of TAD and methanol might also explain the anti addition, we have noted that the reaction of PTAD with tetramethylethylene is qualitatively faster in CH_2Cl_2 than in methanol (complete in 4 min versus 13 min respectively at -78°C). This argues against methanol involvement in the rate-limiting step. Because the transition state for methanol attack would be entropically disfavored relative to the unimolecular formation of the ene product, there is a strong dependence of the product distribution on temperature with the methanol adducts being favored at low temperature.²⁹

If these reactions involve as predicted an intermediate biradical that may form either the ene product or an aziridinium imide (Scheme 2), one might expect that a portion of the ene product not formed via the aziridinium imide would not be intercepted by methanol. To test the idea, the reaction of 2-methyl-1-pentene with PTAD was studied in a 1:1 mixture of methanol: CH_2Cl_2 . As the temperature is decreased from 40°C to -78°C , the methanol adduct **32** increases from 15% to 55% of the total product. However, there is a definite leveling off or break in the curve in a logarithmic plot of the ratio of **32**:(**3** + **4**) as the temperature is decreased (Figure 5).

This plot was found to be modeled well by the mechanism of Scheme 2, varying the $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$ for the partitioning of **31** and the $\Delta\Delta H^\ddagger$ for partitioning of **30**, fixing the $\Delta\Delta S^\ddagger$ for the partitioning of **30** at the predicted value for **15** versus **19** of



2.3 eu (favoring formation of **31**). The best-fit values were $\Delta\Delta H^\ddagger = -4.6$ kcal/mol (favoring the methanol adduct) and $\Delta\Delta S^\ddagger = -17$ eu for the partitioning of **31** and $\Delta\Delta H^\ddagger = 0.3$ kcal/mol for the partitioning of **30** (favoring ene product formation). The last value may be compared with a predicted energy difference of 0.8 kcal/mol for **15** versus **19**.

Discussion

The calculational results predict a new mechanism for the ene reaction of alkenes with TADs as shown in Figure 3. In this mechanism, the ene product is formed via the open biradical intermediates **10**–**14**, and the aziridinium imides **24**–**27** are “innocent bystanders” and not on the direct pathway between starting materials and products. However, the aziridinium imides can be formed because the overall barrier for their formation from **10**–**14** is comparable to the barrier for product formation. In this way the aziridinium imides can have an impact on the experimental observations (vide infra).

The ultimate test of this mechanism is the degree to which it can reconcile the diverse experimental observations in these reactions. We discuss here in turn each of these observations and their consistency with the mechanism of Figure 3.

Intermolecular KIEs. The isotope effects observed with 2-methyl-1-pentene are qualitatively consistent with the formation of a biradical intermediate, and are inconsistent with a transition state involving synchronous or moderately asynchronous formation of two C–N bonds of an aziridinium imide. The good correspondence of calculated and experimental KIEs supports the proposition that the Becke3LYP calculations provide a reasonably accurate description of the first step in the reaction pathway. With 2-methyl-1-pentene the only significant error is at C2. The predicted KIE for C2 (1.009) is greater than the observed value (1.003), and the direction of this error is suggestive of less bond formation to C2 in the actual transition state than depicted in the calculated structure **5**. This error thus adds support for the formation of a biradical intermediate.

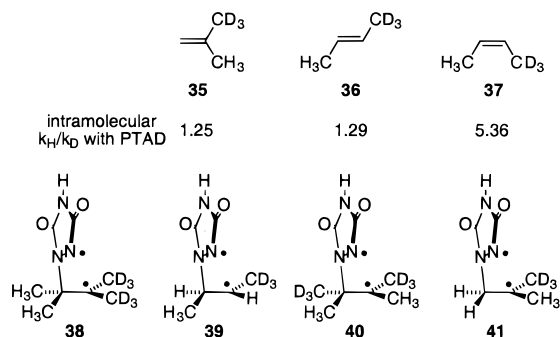
For 2-methyl-2-butene the agreement between the predicted and experimental KIEs is harder to evaluate due to the difficulty of accurately weighing the contributions of three possible transition structures **7**–**9**. No weighting of the isotope effects calculated for **7**–**9** perfectly predicts the ^{13}C KIEs observed for 2-methyl-2-butene: at best the experimental and weighted calculated KIEs differ by 0.3–0.4%. However, this problem seems related to the incorrect prediction of the C2 KIE above with 2-methyl-1-pentene. Allowing for an over-prediction for **7**–**9** of the ^{13}C KIEs at the distal olefinic carbons by replacing the predicted KIEs of 1.009–1.010 with 1.003, a 70:30 mixture of (**7** + **8**):**9** would give KIEs of 1.014 and 1.026 for C2 and C3 of 2-methyl-2-butene, respectively, in perfect agreement with the experimental results. This exercise in numerology is hardly convincing. However, it does show that the KIEs observed with 2-methyl-2-butene are consistent with the picture painted by the 2-methyl-1-pentene KIEs of a TAD attack on alkenes that is highly unsymmetrical, and plausibly more unsymmetrical than the Becke3LYP calculated structures.

Several other studies have reported intermolecular KIEs or intramolecular KIEs that effectively represent intermolecular

(29) Elemes, Y.; Orfanopoulos, M. *Tetrahedron Lett.* **1991**, *32*, 2667.

KIEs. In the reaction of MTAD with β,β -dimethylstyrene (**33**) a significant inverse k_H/k_D of 0.955 per deuterium was observed within the methyl groups.³⁰ This may be compared with the deuterium KIEs of 0.970 and 0.971 predicted for the C1 and C5 methyl groups in transition state **9**, assuming that the MTAD would preferably attack the β carbon to form the more stable open biradical. The ene product could then be formed after ring closure to the aziridinium imide and ring opening to the opposite biradical. A recent report of an overall k_H/k_D of 0.98 ± 0.02 in the ene reaction of MTAD with **34** attributed the isotope effect to a mixture of rate-limiting steps with a counterbalancing inverse isotope effect for a step forming the aziridinium imide and a normal isotope effect for the hydrogen-transfer step.³¹ A much simpler explanation is that the transition state for reaction of **34** resembles **7** or **8**: the predicted KIEs for the combination of vinylic and C1/C5 deuterium substitution in **7** and **8** are 1.00 and 0.98, respectively, in perfect agreement with the KIE in **34**.³²

Intramolecular KIEs. Outside of providing some support for the accuracy of the Becke3LYP calculations, the intermolecular KIEs here provide no direct information about the rest of the reaction pathway. The intramolecular KIEs of Greene for **1** were originally interpreted as *excluding* biradical intermediates such as **10–14**. The same is true with the KIEs observed by Foote for butene isomers **35–37**. The assumption in this interpretation is that a biradical intermediate such as **38** or **39** would have no choice of isotopes in the product-determining step and so exhibit a small intramolecular KIE, while **40** or **41** could choose between reaction of H and D and so exhibit large intramolecular KIEs. This is opposite of the experimental observations. However, this idea assumes that the reactions of a singlet biradical including the 1,2 shift of the TAD ring will be slower than a relatively hindered bond rotation, which is contrary to the theoretical predictions here.

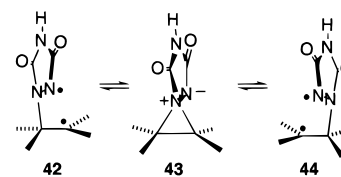


The results here highlight an important limitation to the interpretation of the results of a Stephenson isotope effect test. If the equilibrium between open biradical intermediates **42** and **44** is more rapid than product formation or C–N bond rotation, then the Stephenson isotope effect test will show results similar to those observed for **1**, and will appear to implicate an intermediate with the symmetry of **43**, without **43** being on the direct pathway to product.

(30) Stratakis, M.; Orfanopoulos, M.; Foote, C. S. *J. Org. Chem.* **1998**, *63*, 1315.

(31) Vassilikogiannakis, G.; Stratakis, M.; Orfanopoulos, M.; Foote, C. S. *J. Org. Chem.* **1999**, *64*, 4130.

(32) A slightly differing allylic alcohol in ref 30 exhibited a k_H/k_D of 1.15 ± 0.02 , attributed to reversible formation of the aziridinium imide followed by rate-limiting hydrogen abstraction. This is rather surprising; considering the magnitude of the observed intramolecular isotope effects (3.7 or greater), the presence of only a very small amount of reversibility in the first step would account for the slightly elevated k_H/k_D .



The isotope effect of 1.25 for **35** is notable because it is significantly greater than the unity value expected for a mechanism involving direct formation and reaction of an aziridinium imide. Houk and Foote explained such isotope effects based on a hydrogen-bond-like interaction between a TAD nitrogen and the methyl groups present at the transition state for TAD addition to the alkene.¹⁷ Such an interaction appears to be present in **5–9**, but the predicted isotope effect in **35**, when based solely on the transition structure **5** for the first mechanistic step, is only 1.12 for the RHF structure and 1.15 for the Becke3LYP structure. A plausible explanation for the higher observed isotope effect is a small amount of rotation in **10**, as **28** is predicted to be only 1.0 kcal/mol higher than the transition structure **15** for ene product formation. Based on the energy of **29**, rotation in tetramethylethylene should be negligible. In keeping with this, the isotope effect seen with **1a** is only 1.1.

The intramolecular isotope effect for the reaction of **1c** with PTAD was intriguingly found by Orfanopoulos to exhibit activation parameters indicative of substantial tunneling.³³ The isotope effects and contribution of tunneling appeared to vary little in solvents ranging from CCl_4 to acetonitrile. These observations would be somewhat surprising if the last step in the ene reaction occurred directly by proton transfer in the aziridinium imide. It has been noted previously that a relatively small proportion of reactions involving the redistribution of charge, such as any proton transfer, exhibit significant tunneling effects.³⁴ This is thought to result from the importance of solvent reorganization in such reactions,³⁵ and the effect of solvent and steric bulk on tunneling in proton transfers has been discussed.³⁴ The significant tunneling with little effect of solvent is readily consistent with hydrogen atom transfer within a biradical.

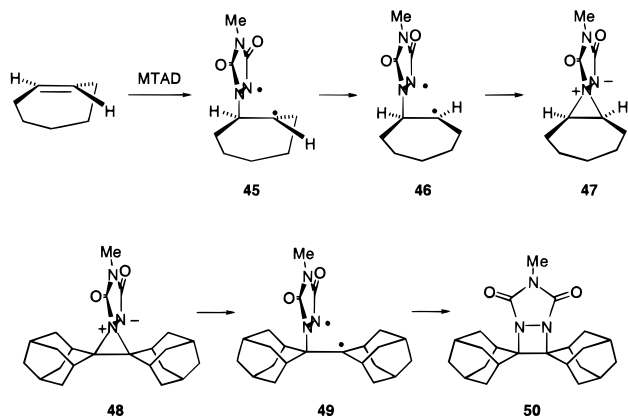
The Observation of Aziridinium Imides. The prior spectroscopic observations of aziridinium imides establishes incontrovertibly that aziridinium imides can be formed in the reactions of RTAD with alkenes. The spectroscopically observed aziridinium imides must be more stable than the corresponding open biradicals but the experimental observations associated with these reactions suggest the importance of open intermediates as well. This is most obvious for the formation of the *cis* aziridinium imide **47** from the reaction of *trans*-cycloheptene with MTAD.¹⁵ Although the initial intermediacy of a trans-bicyclic aziridinium imide intermediate cannot be excluded, it would have to open rapidly at -135°C to biradical intermediate **45** to explain the exclusive observation of the *cis* structure **47**. With *trans*-cyclooctene the resulting aziridinium imide is *trans*, but the multiple products observed in this case were proposed to result from an open zwitterionic intermediate.¹⁶ The ultimate product in the reaction of adamantylideneadamantane with MTAD is the diazetidene **50**. A consistent explanation for the formation of **50** from the observed intermediate aziridinium imide **48** is that it too reacts via a thermally accessible open structure **49** which ring closes to form a four-membered ring.

(33) Elemes, Y.; Orfanopoulos, M. *J. Am. Chem. Soc.* **1992**, *114*, 11007.

(34) Caldin, E. F.; Mateo, S. *J. Chem. Soc., Faraday Trans.* **1975**, *71*, 1876.

(35) (a) Kurz, J. L.; Lurz, L. C. *J. Am. Chem. Soc.* **1972**, *94*, 4451. (b) Borgis, D.; Hynes, J. T. *J. Phys. Chem.* **1996**, *100*, 1118.

The intermediacy of open biradicals also provides a simple explanation for the many other observations of diazetidines in the reactions of alkenes with RTAD.



Reactivity. Ene reactions of simple alkenes with RTAD exhibit a characteristic reactivity trend with increasing alkyl substitution in which each additional alkyl group, in any position, increases the rate of reaction. It is sufficient to note here that the activation energy for formation of the Becke3LYP transition structures leading to the open intermediates reasonably reflects the experimental trends. It was found previously that Becke3LYP single-point energies for the RHF transition structures in the reaction of TAD with propene, *trans*-butene, *cis*-butene, and tetramethylethylene also reproduced the trend in the observed reactivities. Thus, the relative reactivity of alkenes would seem to not be a good diagnostic of whether aziridinium imides or open structures are the initial intermediates.

$k_{\text{rel}}(\text{expt})$	1	33	1500
$E_{\text{act}}(\text{calc, Becke3LYP})$	11.1	10.5	7.9

Solvent Effects. The general observation in reactions of RTAD with alkenes is that there is little effect of solvent polarity.^{13,36} There is no simple correlation of reaction rates with solvent polarity scales and, in fact, reactions are generally faster in CH_2Cl_2 or benzene than in acetonitrile. Solvent effects on the ene reaction with 3-hexene, diazetidine formation with chloroethyl vinyl ether, and the Diels–Alder reaction with 1,3-cyclooctadiene are all very similar.^{13,36,37} The lack of a substantial rate increase with solvent polarity has been taken as evidence against the direct formation of a 1,4-dipolar intermediate. Surprisingly the same observation has not been taken as incongruous with direct formation of an aziridinium imide, describable as either a 1,2- or 1,4-dipole.

One approach to interpreting the solvent polarity observation is to compare the predicted effect of a polar solvent on the relative stability of the RHF transition structures (which lead directly to an aziridinium imide) with the effect predicted for the Becke3LYP transition structures (which lead to the biradical intermediates). Using an SCICPM model, the barrier for reaction of TAD with 2-methyl-2-butene via **8** is predicted to increase slightly (0.1 kcal/mol) going from benzene to acetonitrile. In contrast, the barrier via the corresponding RHF transition structure is predicted to decrease significantly (1.3 kcal/mol)

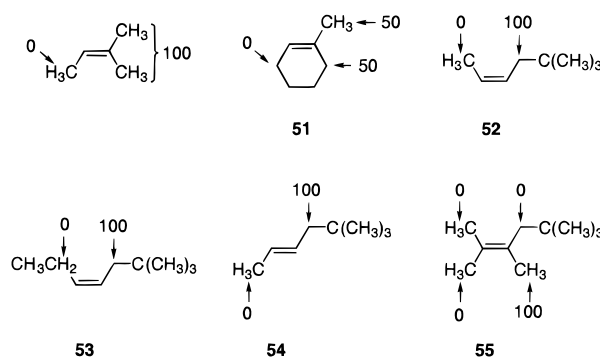
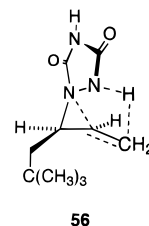


Figure 6. Regioselectivity in some ene reactions of PTAD with alkenes. The position from which a hydrogen has been abstracted in the ene product is shown. Results are taken from refs 18 and 38.

going from benzene to acetonitrile. The Becke3LYP predictions are thus in better accord with the experimental observations.

Regiochemistry. The ene reactions of PTAD with alkenes follow several distinctive regiochemical trends (Figure 6).^{18,38} Simple trisubstituted alkenes react with exclusive hydrogen abstraction from the more substituted end of the double bond. For 1,2-disubstituted alkenes there is high selectivity for hydrogen abstraction from the bulkier alkyl group. However, if a methyl group is geminal to the bulky group, there is a strong preference for abstraction at the geminal methyl group.

The preference for reaction at the bulkier group in *cis*-1,2-disubstituted alkenes has been rationalized as the result of nonbonding interactions between the bulky group and the TAD ring in the transition state for the disfavored hydrogen abstraction from the less bulky group. The origin of this substantial steric interaction is subtle if there is direct formation of the ene product from an aziridinium imide, as in **56**, but any steric interaction would be expected to be greater in a transition state from an open biradical.

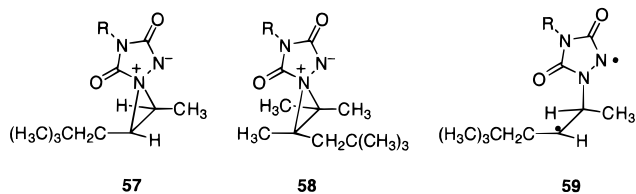


The regiochemistry of the reactions of **54** and **55** seems particularly difficult to rationalize by the standard aziridinium imide mechanism. In either case, formation of the “wrong” aziridinium imides **57** and **58** in an irreversible first step would necessarily result in regioisomeric products that are not observed. There is no obvious potential origin for such selectivity in the formation of the aziridinium imides, particularly in light of the fact that the disfavored aziridinium imides **57** and **58** are opposite in orientation of the TAD ring with respect to the neopentyl group. However, the intermediacy of an open biradical would allow the regioselectivity of these reactions to be expressed at the stage of the product-forming step, with selective formation of open biradicals such as **59** having the TAD ring away from the neopentyl group. Having no favorable alternative except reversible formation of **57**, **59** would eventually undergo the C–N bond rotation that allows the formation of the observed product.

(38) (a) Orfanopoulos, M.; Elemes, Y.; Stratakis, M. *Tetrahedron Lett.* **1990**, *31*, 5775. (b) Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3180. (c) Elemes, Y.; Stratakis, M.; Orfanopoulos, M. *Tetrahedron Lett.* **1989**, *30*, 6903.

(36) Hall, J. H.; Jones, M. L. *J. Org. Chem.* **1983**, *48*, 822.

(37) Isaksen, H.; Snyder, J. P. *Tetrahedron Lett.* **1977**, 889.



Trapping of Intermediates. The logarithmic plot of a ratio of products versus temperature should be linear or nearly linear whenever the product ratio is determined by a simple competition between two transition states.³⁹ Thus the partitioning of an aziridinium imide intermediate between forming the methanol adduct **32** and the ene products **3** and **4** would be expected to lead to a linear plot in Figure 5 if the aziridinium imide is formed directly. A linear plot would also be expected if formation of the aziridinium imide from an open biradical intermediate is much faster than formation of the ene product. However, when aziridinium imide and ene product formation are competitive the curvature of Figure 5 is the expected result. The excellent match-up of the experimentally observed product ratios with the theoretically modeled curve shows that the mechanism in Scheme 2 is consistent with these observations. It should be noted that other complex mechanisms might also explain the curvature in this Arrhenius-type plot: the basic requirements being that there be an intermediate that is not trapped by methanol (this weighs against a zwitterionic species) and that at least *three* transition states are important in determining the product ratio. However, it is striking that this curvature may be reproduced with $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$ values for the partitioning of **30** that are close to those theoretically predicted in the model **10**.

Conclusions

The theoretical results here predict a new mechanism for ene reactions of triazolinediones involving an open biradical as the key intermediate. This biradical may either form the ene product or reversibly form an intermediate aziridinium imide. The formation of the aziridinium imide would thus be a shunt off the main ene mechanistic pathway.

The isotope effects here support the basic features of Becke3LYP-predicted transition structures for these reactions. If the predicted structures err, the isotope effects suggest they err toward underpredicting the asymmetry of the attack of PTAD on alkenes. It should be recognized that these intermolecular isotope effects pertain only to the transition state for the first step in the reaction pathway and provide no direct information about the rest of the mechanism. However, the comparison of experimental and predicted isotope effects suggests that RHF calculations which predict the direct formation of aziridinium imides are inadequate for these reactions, while supporting the greater accuracy of the Becke3LYP structures.

The other experimental observations with triazolinedione ene reactions may be divided into categories depending on whether they are merely consistent with the intermediacy of a biradical or else favor the biradical mechanism over the direct involvement of aziridinium imides. The pattern of intramolecular

(39) When one of the products is formed by a process that involves substantial tunneling, as possible here (see ref 33), the tunneling could lead to curvature in such an Arrhenius plot over a very wide temperature range (see: Jonsson, T.; Glickman, M. H.; Sun, S.; Klinman, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10319). However, Arrhenius plots for hydrogen-transfer reactions are usually linear over a normal temperature range, and a plot of $\ln k_H/k_D$ versus $1/T$ from 25 to -60 °C for reactions of **1c** in CH_2Cl_2 (using data from ref 33) shows no significant curvature. Therefore tunneling in the formation of the ene product is unlikely to account for the large curvature seen in Figure 5.

isotope effects observed with **1** is in the former category: the direct formation and reaction of aziridinium imides would provide a simpler explanation for the Stephenson isotope effect results, but the predicted difficulty of rotation of the open biradicals allows this mechanism to account for the intramolecular isotope effects. The biradical mechanism is favored by observations of solvent effects, regioselectivity, the formation of the *cis* aziridinium imide **47** from *trans*-cycloheptene, and tunneling in the intramolecular isotope effects for **1c**. Finally, the curved Arrhenius plot in the trapping of intermediates by methanol appears inconsistent with the simple two-step mechanism through an aziridinium imide, and provides the strongest classical experimental support for the biradical mechanism. Overall, the new mechanism is both supported by theory and provides the most consistent explanation for the diverse observations associated with these reactions.

Experimental Section

Ene Reactions of PTAD. As an example procedure, 72 g (0.41 mol) of freshly prepared⁴⁰ PTAD in 450 mL of 1,4-dioxane was added slowly to a mixture of 36.94 g (0.528 mol) of 2-methyl-2-butene, 15.92 g (0.161 mol) of 1,2-dichloroethane (used as GC internal standard), 5.035 g (36.5 mmol) of 1,4-dimethoxybenzene (used as NMR internal standard), and 385 mL of 1,4-dioxane in a water bath at 25 °C. After 2 h the reaction was found to be $75 \pm 3\%$ complete by NMR. (The percent conversion determined by GC agreed with this result within the standard error.) Vacuum transfer of the volatiles from the reaction mixture using a water aspirator followed by fractional distillation using a 10-cm Vigreux column afforded 4.8 g of 2-methyl-2-butene (bp 38–40 °C, >98% pure by GC).

An analogous reaction of 2-methyl-2-butene taken to $67 \pm 3\%$ conversion afforded 6.5 g of the starting alkene. Analogous reactions of 2-methyl-1-pentene were taken to $70 \pm 3\%$ and $66 \pm 3\%$ completion, and afforded 8.1 and 11.9 g, respectively, of recovered 2-methyl-1-pentene (>98% purity by GC in each case).

NMR Measurements. NMR measurements were taken on neat samples of 2-methyl-2-butene or 2-methyl-1-pentene in 10-mm NMR tubes filled to a constant height of 5 cm. A T1 determination by the inversion–recovery method was carried out for each NMR sample, and the T1 for each NMR signal remained constant within experimental error from sample to sample.

The ^{13}C spectra were recorded at 100.58 MHz with inverse gated decoupling, using 175 s delays between calibrated 45° pulses for 2-methyl-2-butene and 120 s delays between calibrated 45° pulses for 2-methyl-1-pentene. For 2-methyl-2-butene an acquisition time of 5.499 s was used and 197440 points were collected, and for 2-methyl-1-pentene an acquisition time of 6.278 s was used and 262144 points were collected. The ^2H spectra were recorded at 61.395 MHz with calibrated 45° pulse widths, using an acquisition time of 7.951 s and a 10.0-s delay between pulses for 2-methyl-2-butene, and using an acquisition time of 4.983 s and a 9.0-s delay between pulses for 2-methyl-1-pentene. Integrations were determined numerically using a constant region for each peak that was ≈ 5 times the peak width at half-height on either side of the peak. A zeroth-order baseline correction was generally applied, but in no case was a first-order (tilt) correction applied. The results for all reactions are summarized in the Supporting Information.

Acknowledgment. We thank NIH grant No. GM-45617 and The Robert A. Welch Foundation for support and NSF grant No. CHE-9528196 and the Texas A&M University Supercomputing Facility for computational resources.

Supporting Information Available: Energies and full geometries of all calculated structures and NMR integration results for all reactions (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(40) Adams, C. E.; Aguilar, D.; Hertel, S.; Knight, W. H.; Paterson, J. *Synth. Comm.* **1988**, *18*, 2225.