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Solvent-Dependent Changes in the Triazolinedione–Alkene Ene Reaction Mechanism

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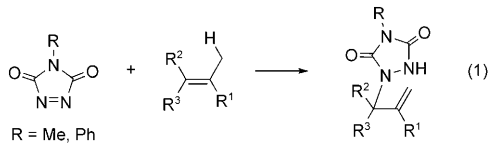
Abstract: The influence of the solvent on the triazolinedione–alkene ene reaction mechanism has been investigated. Both inter- and intramolecular kinetic isotope effects with tetramethylethylenes and 2,2,2-(trideuterio)methyl-7-methyl-2,6-octadiene-[D_3]-1,1,1 provide, for the first time, strong evidence for changes in the mechanism of the reaction on going from non-protic to polar protic solvents. In non-protic polar or apolar solvents, an aziridinium imide that equilibrates to an insignificant extent with an open intermediate (a dipolar or a polarized biradical) is formed irreversibly in the first, rate-determining step of the reaction, which is followed by fast hydrogen abstraction. On the contrary, in polar protic solvents, hydrogen abstraction is rate limiting, allowing the main dipolar intermediate to equilibrate with its open intermediate(s) as well as with the starting reagents.

Keywords: ene reaction · kinetic isotope effects · reaction mechanisms · solvent effects · triazolinediones

Introduction

The ene reaction of triazolinedione[1] (RTAD, R = methyl or phenyl), one of the most reactive neutral enophiles, with alkenes that bear allylic hydrogen atoms, to form *N*-allylurazoles [Eq. (1)] apart from being synthetically useful,[2] has attracted considerable mechanistic[3–9] and theoretical attention[10] for many years. A number of mechanisms and key intermediates (Figure 1) have been proposed for this reaction. Among these, the formation of a closed, three-membered aziridinium imide (AI) intermediate (Figure 1) was the most popular, and initially found support in the results of trapping experiments.[11,12] Subsequently, isotope effect measurements on deuterium-labeled tetramethylethylenes (TMEs)[3,4] and 2-butenes[5,6] also suggested the formation of an AI intermediate in the rate-determining step of the reaction. Thus, large intramolecular kinetic isotope effects (KIEs) were found in the ene reactions of RTADs with the *cis*-related methyl and deuteriomethyl groups in substrates **1** and **2** (H/D isotopic competition; Scheme 1), whereas only a small isotope effect was observed with the *trans*-related groups in compound **3** (no isotopic competition). AI intermediates have also been observed spectroscopically in the reactions of biadamantylidene,[13] *trans*-cycloheptene,[14] and *trans*-cyclooctene[15] with RTADs. Furthermore, because all of the methyl groups of TME are symmetry equivalent, similar isotopic competition would have been expected for substrates **1**, **2**, and **3** in a concerted mechanism; however, this was found not to be the case. On this basis, a one-step mechanism was excluded.



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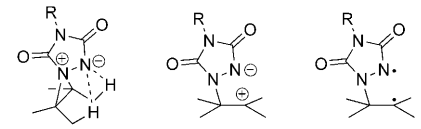

Figure 1. Proposed intermediates for the triazolinedione ene reaction.

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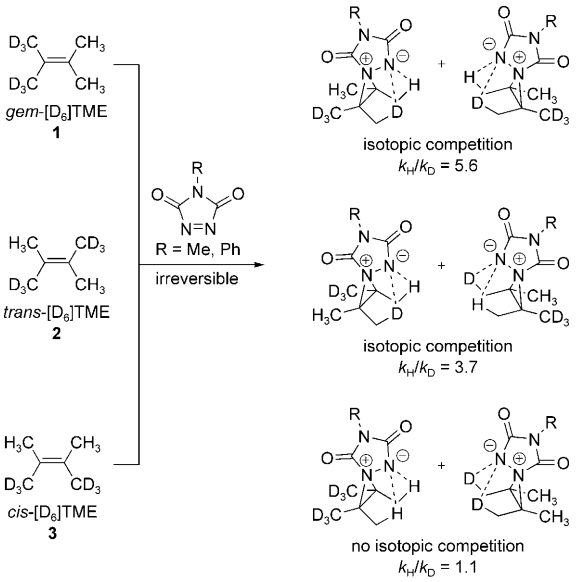
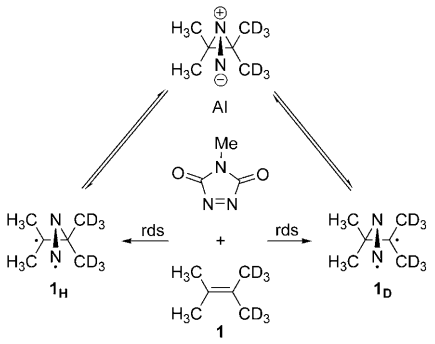


Scheme 1. Reported kinetic isotope effects for the ene reaction of RTADs with deuterium-labeled tetramethylethylenes in $CDCl_3$.

Nevertheless, the AI intermediate was challenged by Singleton and Hang on the basis of experimental and theoretically predicted KIEs, as well as transition-state energy profiles.[10] In their work, an open biradical key intermediate, in rapid equilibrium with an AI, was proposed (Scheme 2).



Scheme 2. Proposed biradical mechanism.

Furthermore, its rotation about the initial alkene double bond was calculated to be restricted. According to this mechanism, H or D abstraction in biradical intermediates $\mathbf{1_H}$ and $\mathbf{1_D}$ (Scheme 2) should not be competitive, and no primary KIE should be expected in the second, fast step of the reaction. To rationalize the large primary KIEs previously found for *gem*-[D_6]TME (**1**; Scheme 1) and *cis*-2-[D_3]butene, fast equilibration of the biradical intermediates $\mathbf{1_H}$ and $\mathbf{1_D}$ with an AI intermediate was proposed. Moreover, since rotation about the C–N bond was also calculated and found to be restricted, the biradical intermediate retains the stereochemical integrity of the AI. Thus, the geminal methyl and deuteriomethyl groups in *cis*-[D_6]TME (**3**; Scheme 1) become non-competitive in the corresponding biradicals, as is observed. The above described biradical mechanism was subsequently challenged by results derived from other stereoisotopic and product studies on the ene reactions of RTADs.[8,9,16–18]

More recently, photochemical formation of the two stereoisomeric AI intermediates from the addition of PTAD to cycloheptene has been reported.[19] These AI intermediates rearrange to the corresponding ene products through their dipolar biradical precursors. Since one of the two dipolar biradical intermediates has the wrong conformation for H abstraction, a 180° rotation about the C–N bond is required to form the biradical conformer suitably predisposed for H abstraction. Although in this particular system the proposed mechanism may well rationalize the obtained results, previous computational work[10] has shown the activation barrier for rotation about the C–N bond in similar biradical intermediates to be energetically unfavorable compared to that of the H abstraction.

In the present study, we report for the first time significant changes in the triazolinedione ene reaction energy profile on going from non-protic to polar protic solvents. This missing mechanistic information may complete the puzzle of this otherwise very well studied reaction that has been a topic of investigation for many years. In particular, we have studied the triazolinedione ene reactions of *gem*-[D_6]TME (**1**), *cis*-[D_6]TME (**3**), and 2,2,2-(trideuterio)methyl-7-methyl-2,6-octadiene-1,1,1-[D_3] ([D_6]DMOD, **4**), as well as the intermolecular isotope effects in the reaction of [D_0]TME versus [D_{12}]TME (**5**; Figure 2), in a variety of solvents. Our new results triggered our long standing interest in this reaction to discuss, along with the present results, previous experimental and theoretical conclusions, and to propose a "unified mechanism" for this classic ene reaction.

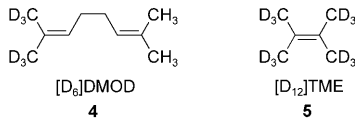
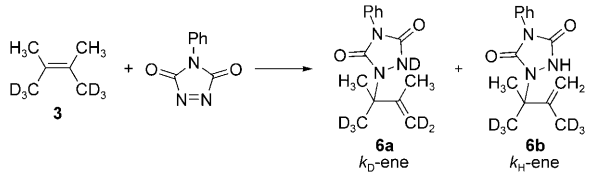


Figure 2. [D_6]DMOD and [D_{12}]TME.

Results

The ene reaction of *cis*-[D_6]TME (**3**) with PTAD was studied in a variety of solvents. As illustrated in Table 1, the primary intramolecular isotope effects in acetone and acetonitrile (entries 3 and 4) are negligible ($k_H/k_D \approx 1.1$), as is also the case in dichloromethane and chloroform (entries 1 and 2). On the contrary, unprecedented large intramolecular isotope effects ($k_H/k_D \approx 2.0$–4.0) were measured in EtOH, MeOH, and MeOH/H_2O (entries 6, 7, and 8). This clearly indicates that solvent properties dictate the PTAD ene reaction mechanism.

Table 1. Intramolecular kinetic isotope effects for the ene reaction of *cis*-[D_6]TME with PTAD.

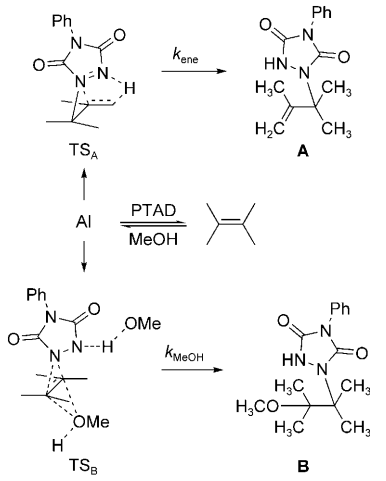


Entry	Solvent	$k_{H\text{-ene}}/k_{D\text{-ene}}$[a,b]	Dielectric constant
1[c]	CH_2Cl_2	1.08±0.1	9.1
2	$CDCl_3$	1.14±0.03	4.8
3	acetone	1.13±0.03	21
4	CH_3CN	1.13±0.03	37
5	DMSO	1.78±0.05	47
6	EtOH[e]	2.10±0.06	24
7	MeOH[e]	2.99±0.09	33
8[d]	MeOH/H_2O[e]	3.96±0.12	N/A

[a] Determined by ^{1}H NMR (500 MHz) spectroscopy. For accurate ^{1}H integrations, a spin-lattice relaxation T1 of 5 s was used. [b] All isotope effects were measured at room temperature at 80% conversion. [c] Ref. [4]. [d] MeOH/H_2O, 4:1. [e] A product ratio of ≈60% ene/≈40% solvent-trapped adduct was formed.

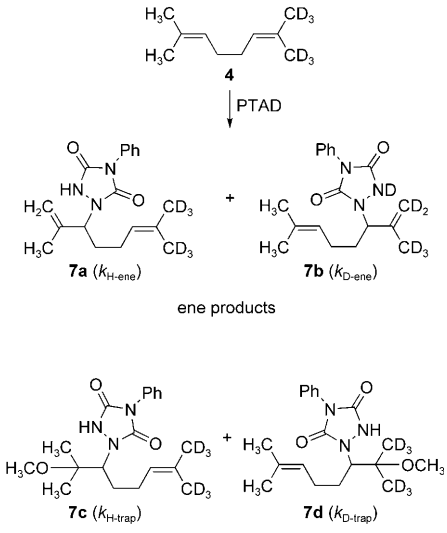
The large isotope effects measured in protic solvents (k_H/k_D ≈2.0–4.0) require reversion of the intermediate(s) to the starting materials and provide, for the first time, evidence that H(D) abstraction occurs in the rate-determining step of the reaction (vide infra). The substantial isotope effect observed in the PTAD ene reaction of **3** carried out in DMSO (entry 5) could be the result of a partial reversion of the intermediate(s) to the starting materials. In an earlier study concerning the addition of MTAD to biadamantylidene (Ad=Ad) to form the corresponding diazetidine, reversion to the starting reagents was proposed.[20] This reaction proceeds through an AI intermediate, which is in equilibrium with an open intermediate (OI) in a variety of solvents. However, in this case, the reaction does not lead to ene products. It also has to be kept in mind that the reaction of PTAD with TME in MeOH affords two products, the ene adduct **A** and the MeOH-trapped adduct **B** (Scheme 3). This reaction has been thoroughly studied in earlier work.[21]

In seeking additional evidence for a solvent-dependent alteration in the mechanism of the alkene ene reaction of RTADs, we studied the reaction between PTAD and [D_6]DMOD (**4**) in CH_2Cl_2 and MeOH. The reason for preparing alkene **4** (Figure 2) is that, unlike **1**, it bears two pairs of geminal methyl and deuteriomethyl groups isolated from each other by four carbon atoms. In the case of an irreversible pathway, these pairs of methyl groups would not be competitive in the second H or D abstraction step, which makes it possible to measure an intramolecular isotope effect that actually simulates the intermolecular one. When PTAD was added to a stirred solution of [D_6]DMOD in MeOH, besides the ene adducts, the MeOH-trapped adducts were also isolated. The obtained KIEs are summarized in Table 2. The insignificant primary isotope effect for the reaction in CH_2Cl_2 (Table 2, entries 1 and 2) suggests that no substantial C–H bond breaking was involved in the rate-determining step of this reaction. In sharp contrast, in the case of methanol as solvent (Table 2, entries 3–6), there is a dramatic increase in the isotope effect (e.g., from $k_{H\text{-ene}}/k_{D\text{-ene}}$ ≈1.10±0.03 to $k_{H\text{-ene}}/k_{D\text{-ene}}$ = 6.0±0.2 at 25 °C). Additionally, as can also be seen in Table 2, the intramolecular primary isotope effect strongly depends on the reaction temperature.



Scheme 3. Trapping and ene adducts for the reaction of PTAD with TME in MeOH.

Table 2. Intramolecular isotope effects in the reaction of [D_6]DMOD with PTAD.



Entry	Solvent	T [°C]	$k_{H\text{-ene}}/k_{D\text{-ene}}$[a,b]	$k_{H\text{-trap}}/k_{D\text{-trap}}$[a,b]
1	CH_2Cl_2	25	1.09±0.03	–
2	CH_2Cl_2	0	1.16±0.03	–
3	MeOH[c]	40	4.7±0.1	1.65±0.05
4	MeOH[c]	25	6.0±0.2	1.70±0.05
5	MeOH[c]	0	9.1±0.3	1.70±0.05
6	MeOH[c]	−35	23.3±0.7	1.80±0.05

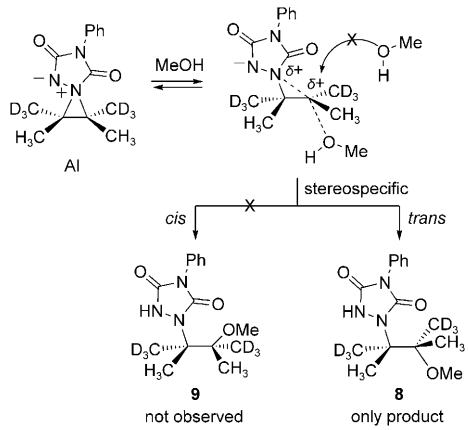
[a] Determined by ^{1}H NMR (500 MHz) spectroscopy. For accurate ^{1}H integrations, a spin-lattice relaxation T1 of 5 s was used. [b] Conversion 25%. [c] The percentage ratios of ene:trap in entries 3–6 are 45:55, 37:63, 25:75, and 18:82, respectively.

For example, $k_{H\text{-}ene}/k_{D\text{-}ene}$ is 4.7 at 40 °C, whereas at lower temperatures (entries 4–6) the $k_{H\text{-}ene}/k_{D\text{-}ene}$ ratio is abnormally large, reaching a value of 23.3 at −35 °C, which is more than three times the magnitude of that at room temperature. To a first approximation, the maximum isotope effect, corresponding to the zero-point energy difference for the C–H and C–D stretches in the transition state, is calculated to be about 7.4 at room temperature.[22] In the present system, however, the measured $k_{H\text{-}ene}/k_{D\text{-}ene}$ values are substantially larger than 7.4 at low temperatures, and they decrease sharply with an increase in temperature. These results may be attributed to extensive hydrogen tunneling along the reaction coordinate. In our earlier work, we showed that a similar hydrogen tunneling takes place in the ene reaction of PTAD with *gem*-[D_6]TME (**1**).[23]

To shed more light on the nature of the intermediate in MeOH, we also studied the β-secondary KIEs in the addition reaction of MeOH and PTAD to [D_6]DMOD (**4**). The molar ratio of the two isomeric methanol adducts **7c** and **7d** (Table 2, entries 3–6) was found to be proportional to the isotopic ratio $k_{H\text{-}trap}/k_{D\text{-}trap}$.

Moreover, we studied the β-secondary KIEs in the addition reaction of MeOH and PTAD to *gem*-[D_6]TME (**1**). Compared to the β-secondary KIEs measured in the addition reaction of MeOH and PTAD to [D_6]DMOD (**4**), the isotope effects for *gem*-[D_6]TME (**1**) were found to be slightly smaller ($k_{H\text{-}trap}/k_{D\text{-}trap} = 1.60 \pm 0.05$ and 1.64 ± 0.05 at 25 and 0 °C, respectively).

We also examined the stereochemistry of the MeOH adduct of PTAD and *cis*-[D_6]TME (Scheme 4). The

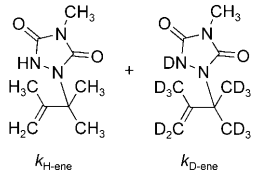


Scheme 4. Stereospecific addition of MeOH and PTAD to *cis*-[D_6]TME (**3**).

^{1}H NMR spectra of the methanol-trapping reactions of *cis*-[D_6]TME show only one methyl signal at $\delta = 1.26$ ppm, attributable to the methyl group adjacent to the oxygen atom of diastereomer **8**. As illustrated in Scheme 4, two methyl resonances for the methyl group adjacent to the oxygen atom (i.e., one for the methyl group of **8** and one for that of **9**) would have been expected in the case of top and bottom MeOH attack on an open zwitterionic intermediate. However, only the stereospecific adduct **8** was observed.

In this context, the intermolecular isotope effects for the equimolar competition between [D_{12}]TME and [D_0]TME in dichloromethane and MeOH (ene path) were also measured. As illustrated in Table 3, the primary intramolecular

Table 3. Intermolecular kinetic isotope effects for the reaction of [D_0]TME/[D_{12}]TME with MTAD.



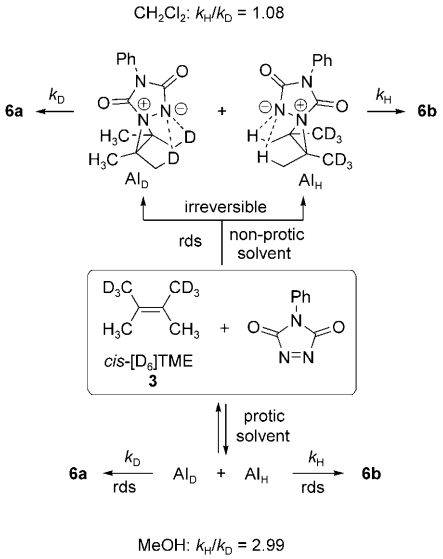
Entry	Solvent	T [°C]	$k_{H\text{-}ene}/k_{D\text{-}ene}$[a,b]
1	CH_2Cl_2	25	1.06 ± 0.03
2	CH_2Cl_2	0	1.08 ± 0.03
3	MeOH	25	2.25 ± 0.07
4	MeOH	0	4.02 ± 0.12

[a] Determined by ^{1}H NMR (500 MHz) spectroscopy. For accurate ^{1}H integrations, a spin-lattice relaxation T1 of 5 s was used. [b] Conversion 25 %.

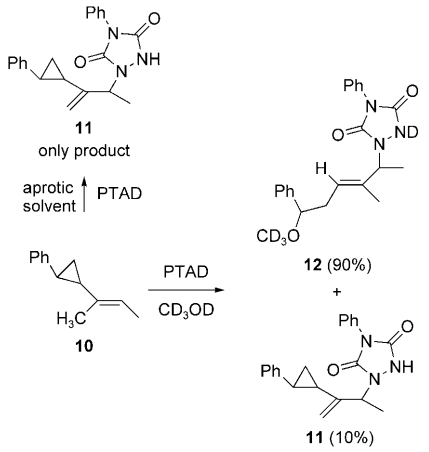
isotope effects in dichloromethane (entries 1 and 2) are again negligible ($k_H/k_D \approx 1.1$). On the contrary, large intramolecular isotope effects ($k_H/k_D \approx 2.2$–4.0) were measured in MeOH (entries 3 and 4), signifying a change in the energy profile of the reaction. It should also be noted that besides the ene product (≈60 % at 25 °C) the known solvent-trapped adduct (≈40 % at 25 °C) was formed in MeOH.

Discussion

A mechanism that could account for the observed KIEs when the PTAD ene reaction of *cis*-[D_6]TME is carried out in protic or non-protic solvents is presented in Scheme 5. In aprotic solvents, the irreversible formation of the intermediates leads to ene products **6a** and **6b** without isotopic competition. Also, in aprotic solvents, the previously proposed equilibration of AI with an OI, biradical,[10] or polarized biradical[19] cannot be excluded as a mechanistic possibility. In this case, the requirement for restricted rotation about the previous double bond or C–N bond of the OI must be met.[10] However, the extent of AI equilibration with an OI, as well as the lifetime of the OI, depend on the particular system and the polarity of the aprotic solvent. Our previous results[17] concerning the PTAD ene reaction in aprotic solvents suggest a rather "tight" AI intermediate with minimal, if any, equilibration with an open intermediate. In this recent work,[17] the vinylcyclopropyl moiety, as in substrate **10**, was used as a probe to test the nature of the PTAD–alkene ene reaction intermediate (Scheme 6). In aprotic sol-



Scheme 5. Proposed mechanism for the ene reaction of *cis*-[D_6]TME with PTAD.



Scheme 6. The vinylcyclopropyl moiety as a mechanistic probe.

vents, this reaction afforded only the ene adduct **11**, via the aziridinium imide as the major intermediate, whereas in protic solvents a dipolar intermediate was favored, which was trapped by the cyclopropyl moiety to form the corresponding cyclopropyl-rearranged, solvent-trapped adduct **12**. Had the AI been in equilibrium to a significant extent with a dipolar or polarized biradical intermediate in non-protic solvents, a cyclopropyl rearrangement (within the limits of the rate of phenylcyclopropyl ring-opening, $3\times10^{11}\ s^{-1}$) would have been observed, contrary to the experimental findings. These observations also support the intermediacy of an AI in aprotic solvents, whereas in protic solvents an OI (zwitterion or dipolar biradical) is indicated.

Proposed energy diagrams for the ene reactions of RTADs with alkenes in protic and non-protic solvents are presented in Figure 3. The shift from energy diagram A to B, on going from non-protic to polar protic solvents, may be

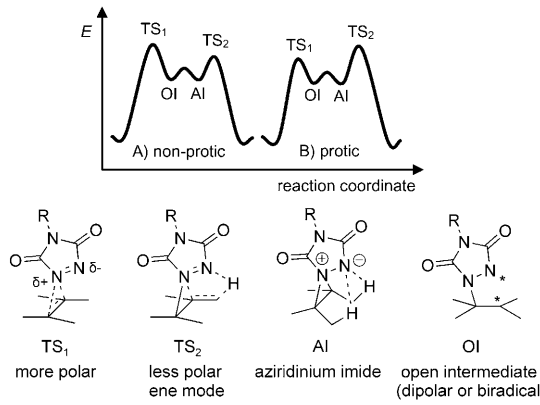


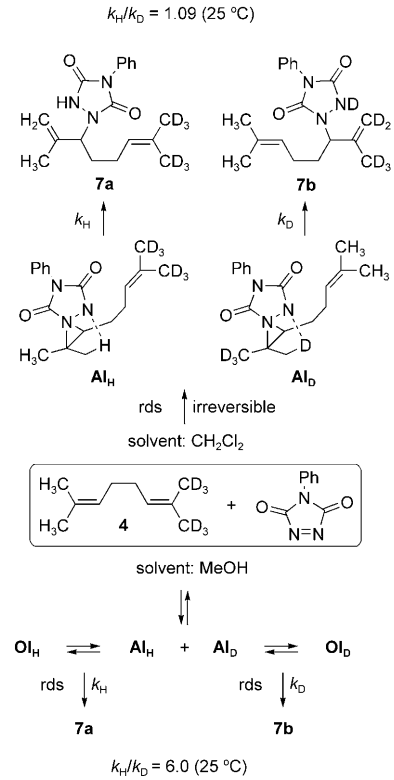
Figure 3. Proposed energy profiles for the triazolinedione ene reaction in non-protic (A) and protic solvents (B).

rationalized in terms of a more pronounced charge separation for the first transition state and a polar/protic solvent stabilization. As a result, the first transition state (TS_1, more polar) in diagram B is of lower energy than the second one (TS_2, less polar), and so the latter becomes the rate-limiting step. In the case of the reaction of *cis*-[D_6]TME (**3**) with PTAD in DMSO, the lower but still substantial KIE of 1.78 suggests an intermediate energy profile, with its two transition states TS_1 and TS_2 being of roughly equal energy.

Before we continue discussing our present results, it is useful to mention the key aspects of the MeOH trapping experiments. The **A**/**B** product ratio (Scheme 3) depends on the reaction temperature. For example, at −78 °C the MeOH adduct **B** is essentially the only product, whereas above the isokinetic temperature, 13.8 °C, adduct **A** predominates, a 78:22 ratio of ene/trapping products being obtained at 60 °C. The activation parameters $\Delta\Delta H_{AB}^{\neq}$ and $\Delta\Delta S_{AB}^{\neq}$ have been calculated as 5.2 kcal mol^{-1} and 17.9 cal mol^{-1} K^{-1}, respectively.[21] The enthalpy of activation favors the formation of the MeOH adduct **B**, whereas the entropy favors the formation of the ene product **A**. These results are rather expected because of the bimolecularity of the path leading to the MeOH adduct **B** through transition state TS_B versus the monomolecular path leading to the ene product **A** via TS_A (Scheme 3). These earlier results indicate that the large entropy factor $\Delta\Delta S_{AB}^{\neq}$ dictates $\Delta\Delta G_{AB}^{\neq}$ changes in the competing reactions and, consequently, controls the remarkable variations in the reactivity of the two competing paths. It was proposed that the common intermediate of the two competing pathways is the aziridinium imide; however, our present results could also be rationalized in terms of an aziridinium imide in equilibrium with its open intermediate (zwitterion or polarized biradical).

As regards the reaction between PTAD and [D_6]DMOD (**4**) in dichloromethane (Table 2, entries 1 and 2), a tight AI intermediate (in partial equilibrium with an open intermediate) is most probably formed in the rate-limiting step, and this is then followed by a second, product-determining step leading to the ene products without isotopic competition. The sharp increase in the isotope effect with methanol as

the solvent (Table 2, entries 3–6) again suggests reversible formation of the intermediates, revealing a change in the energy profile on going from a non-protic (A) to a protic solvent (B) in Figure 3. The two proposed mechanistic pathways, which involve: a) the reversible, in MeOH, formation of an aziridinium imide in equilibrium with its open intermediate (OI_H or OI_D), and b) the irreversible, in CH_2Cl_2, formation of an aziridinium imide through the ene reaction of [D_6]DMOD with PTAD, are presented in Scheme 7.



Scheme 7. Mechanistic possibilities for the ene reaction of [D_6]DMOD with PTAD in CH_2Cl_2 and MeOH.

In the MeOH trapping experiments with [D_6]DMOD, the β-secondary KIE (≈1.10 per deuterium) may be attributed to a rather loose S_N2 dipolar transition state (Figure 4; TS_3 and TS_4), which is characterized by a small degree of C–O bond making and extensive C–N bond breaking. In transition state TS_3, hyperconjugative effects involving the six hydrogen atoms of the two methyl groups, as opposed to the six deuterium atoms in TS_4, are expected to give a normal and large β-secondary KIE (k_H/k_D ≈1.05–1.10 per deuterium), as is found experimentally. Similar isotope effects have been reported in the dipolar cycloaddition of tetracyanoethylene to 2,4-hexadiene.[24] If the transition states in Figure 4 were of a tight S_N2 type, the measured β-secondary isotope effects would have been unity or slightly inverted because of a steric deuterium kinetic isotope effect (see below).[22,25] In accordance with the above hypothesis, the recently reported thermodynamic parameters $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ for the reaction of PTAD with 2-methyl-2-butene in nucleophilic solvents were found to be in favor of an "S_N2-like" transition state.[26] Moreover, the β-secondary KIEs measured in the MeOH trapping experiments with *gem*-[D_6]TME again support a loose S_N2 dipolar transition state. As a final note, although the present β-secondary KIEs in the reactions of *gem*-[D_6]TME and [D_6]DMOD can be satisfactorily rationalized by a loose S_N2 dipolar transition state (Figure 4), an open zwitterionic or a polarized biradical mechanism cannot be excluded.

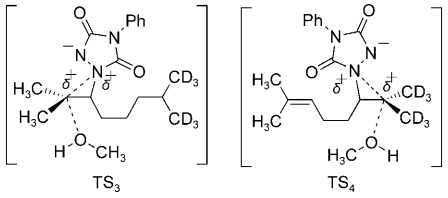
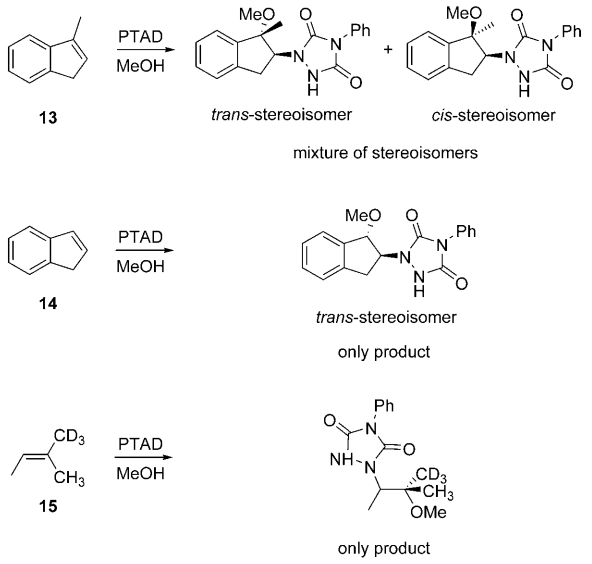


Figure 4. Proposed transition states for the addition reaction of MeOH and PTAD to [D_6]DMOD.

It has also been observed that, in contrast to the reaction of 2-methylindene (**13**), there is no loss of stereochemistry in the addition of MeOH and PTAD to 2-butenes (*cis* and *trans*), 1-methylcyclopentene, indene (**14**), and 2-methyl-2-butene (**15**) (Scheme 8).[27] To rationalize the formation of only one stereoisomer, a rather tight AI intermediate that does not equilibrate to any significant extent with a zwitterionic intermediate has been proposed. The loss of stereochemical integrity observed in the case of methyl-substituted indene (**13**; Scheme 8) was attributed to the fact that this AI intermediate can yield a highly stable, tertiary benzylic carbocation. It was therefore concluded that the stability of the AI intermediate and its equilibration with the open intermediate depends on the particular system.[27]



Scheme 8. MeOH and PTAD addition reactions with 2-methylindene (**13**), indene (**14**), and 2-methyl-2-butene (**15**).

With regard to the MeOH adduct of PTAD and *cis*-[D_6]TME (Scheme 4), the retention of the stereochemical integrity at the reaction center reveals the stereospecific character of the trapping reaction, similar to previous observations for the addition of MeOH and PTAD to 1-methylcyclopentene, 2-methyl-2-butene (**15**), *cis*- and *trans*-2-butenes, and indene.[27]

Finally, in the intermolecular competition between [D_{12}]TME and [D_0]TME, the absence of a KIE when the reaction is carried out in CH_2Cl_2 (Table 3, entries 1 and 2) demonstrates that once the aziridinium imide or/and open intermediate is formed, only one kind of isotope (either H or D, non-competing) is available for abstraction in an irreversible mode. In contrast to the hitherto accepted mechanism for the ene reaction of RTADs, the KIEs observed in MeOH (Table 3, entries 3 and 4) again suggest reversible generation of the aziridinium imide. The difference in the measured isotope effects in these two solvents, which are aprotic and protic, is again consistent with the proposed energy profiles A and B illustrated in Figure 3.

Conclusion

Unlike the results in non-protic solvents, the large, non-stereochemically dependent kinetic isotope effects measured in the RTAD–alkene ene reactions of TMEs and [D_6]DMOD in polar protic solvents are suggestive of rate-determining H(D) abstraction. This is a clear reversal of what has hitherto been known for the otherwise extensively studied RTADs–alkene ene reaction mechanism. These results have led us to a "unified" mechanism, whereby the stability of the aziridinium imide intermediate and its equilibration with the open intermediate depends on the solvent and the particular system. In aprotic solvents, a rather tight aziridinium imide intermediate is envisaged, with insignificant equilibration to its open intermediate (in this case, retention of configuration), whereas in protic solvents one may envisage a loose aziridinium imide in extensive equilibrium with its open intermediate (dipolar or polarized biradical) and the starting reagents. In this case, large KIEs, independent of the relative isotope stereochemistry, were recorded.

Experimental Section

General considerations: ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz (125 MHz for ^{13}C) spectrometer from samples in $CDCl_3$ solutions. Chemical shifts are reported in ppm downfield from Me_4Si by using the residual solvent peak as an internal standard. Isomeric purities were determined by ^{1}H NMR and by GC on a 50 m HP-5 capillary column connected to a 5971 A MS detector. Vapor-phase chromatographic separations were performed on a GOW MAC 55 chromatograph with a thermal conductivity detector. TLC was carried out on SiO_2 (silica gel F_{254}). Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–400 mesh ASTM). During work-up of the reaction mixtures, organic extracts were dried over anhydrous $MgSO_4$. Solvents were evaporated in a rotary evaporator.

General procedure for the triazolinedione–alkene ene reactions: A freshly prepared solution of RTAD (0.025 and 0.08 mmol for inter- and intramolecular competitions, respectively) in the appropriate solvent (1 mL) was added to a solution of the alkene (0.1 mmol) in 2 mL of same solvent. Once the reaction was complete (as determined by the disappearance of the characteristic pink color of the RTAD), the solvent and the residual alkene were removed in a rotary evaporator. The last traces of solvent were removed under high vacuum and the ^{1}H NMR spectrum of the products was recorded in $CDCl_3$ solution.

(*Z*)-2,3-Dimethyl([D_6]-1,1,1,4,4,4)-2-butene (*cis*-[D_6]TME): This deuterium-labeled alkene was prepared according to the procedure reported in the literature,[28] as detailed below:

(*Z*)-2,3-Dimethyl-2-butenedioic acid dimethyl ester (dimethyl dimethylmaleate): Dimethylmaleic anhydride (4.36 g, 34.4 mmol) was refluxed in methanol (80 mL) for 90 min. The solution was then cooled to 0 °C and titrated with diazomethane in diethyl ether until a yellow color persisted. The solvents were evaporated and the yellow oil was filtered through silica gel (12 g) with diethyl ether to yield 5.92 g of dimethyl dimethylmaleate (34.4 mmol, 100 %). ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C, TMS): $\delta =$ 1.94 (s, 6H), 3.75 ppm (s, 6H).

(*Z*)-2,3-Dimethyl([D_4]-1,1,4,4)-2-butene-1,4-diol: Aluminum chloride (1.41 g, 10.6 mmol) was added in small portions to an ice-cooled suspension of lithium aluminum deuteride (1.34 g, 32 mmol) in absolute diethyl ether (160 mL). After stirring the deuteride mixture at room temperature for 30 min, it was cooled to 0 °C, whereupon a solution of dimethyl dimethylmaleate (3 g, 17.5 mmol) in diethyl ether (15 mL) was added dropwise. The reaction mixture was stirred for a further 2 h at room temperature. Acid work-up afforded 1.65 g of the desired alcohol (14 mmol, 80 %). ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C, TMS): $\delta = 1.75$ ppm (s, 6H); MS: *m*/*z* (%): 138 (4) [M^+], 119 (17), 102 (52), 87 (97), 72 (100), 58 (40), 45 (54).

(*Z*)-1,4-Dichloro-2,3-dimethyl([D_4]-1,1,4,4)-2-butene: Me_2S (1.06 g, 16.6 mmol) was added dropwise to a solution of *N*-chlorosuccinimide (2.24 g, 16.8 mmol) in CH_2Cl_2 (100 mL) at 0 °C. Upon stirring for 15 min, a precipitate was formed. The mixture was cooled to −20 °C, whereupon a solution of the above diol (1 g, 8.2 mmol) in CH_2Cl_2 (40 mL) was added dropwise. The resulting mixture was kept at 0 °C for 2 h, and then saturated aqueous NaCl solution (100 mL) and ice (100 g) were added, the organic phase was separated, and the aqueous layer was extracted with Et_2O. The organic layers were washed separately with H_2O and stripped of solvent to yield a total of 1.04 g of the desired dichloride, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C, TMS): $\delta = 1.83$ ppm (s, 6H); MS: *m*/*z* (%): 158 (24) [M^+], 156 (39), 123 (31), 121 (100), 107 (25), 105 (80), 91 (23), 85 (38), 69 (47), 55 (26).

(*Z*)-2,3-Dimethyl([D_6]-1,1,1,4,4,4)-2-butene (*cis*-[D_6]TME): A Schlenk flask, connected to a rotaflo trap that was cooled to −78 °C, was charged with lithium aluminum deuteride (290 mg, 7 mmol) in dry triglyme (12 mL) under Ar. The flask was cooled to −25 °C, whereupon a solution of the above dichloride (1 g, 6.6 mmol) in dry triglyme (5 mL) was added over a period of 10 min by means of a syringe. The mixture was stirred at −25 °C for 1 h and at room temperature for a further 2 h. With the help of a slow stream of Ar, and by heating the reaction mixture to 110 °C, the alkene was collected in the trap together with some solvent. This mixture was further purified by preparative GC to afford 286 mg (50 %) of *cis*-[D_6]TME. ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C, TMS): $\delta = 1.64$ ppm (s, 6H); MS: *m*/*z* (%): 90 (79) [M^+], 75 (84), 72 (100), 59 (19).

2,2,2-(Trideuterio)methyl-3-methyl-2-butene-[D_3]-1,1,1 (*gem*-[D_6]TME): This deuterium-labeled alkene was prepared according to the procedure reported in the literature,[29] as detailed below:

2,2-Dimethyl-3-hydroxy-3-(trideuterio)methyl-butyric acid-[D_3]-4,4,4: A flame-dried, 500 mL three-necked round-bottomed flask, equipped with a magnetic stirrer, a reflux condenser, and an addition funnel, was charged, under N_2, with a solution of dry diisopropylamine (14 mL, 100 mmol) in dry THF (100 mL). After cooling the solution to −78 °C, *n*BuLi (1.6 M in *n*-hexane, 62.5 mL, 100 mmol) was added dropwise. The mixture was left for 1 h at room temperature and then cooled to −78 °C once more. Next, isobutyric acid (4.41 g, 50 mmol, 1 M solution in dry

THF) was added dropwise. The resulting mixture was left for 1 h at room temperature and then cooled to 0 °C, whereupon [D_6]acetone (3.7 mL, 50 mmol) was added as a 2.5 M solution in dry THF. After stirring at room temperature for 12 h, the reaction mixture was poured onto ice and transferred to a separatory funnel. After several extractions with Et_2O, the aqueous layer was acidified with 6 N HCl and extracted with Et_2O (5×50 mL). The combined extracts were dried and the solvent was evaporated to afford the β-hydroxy acid (6.5 g, 85 %), which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C, TMS): δ = 6.01 (br s, 2H; COOH + OH), 1.26 ppm (s, 6H).

3,3-Di(trideuterio)methyl-4,4-dimethyl-β-lactone: A single-necked 500 mL round-bottomed flask, equipped with a magnetic stirrer, was charged with the above β-hydroxy acid (1.52 g, 10 mmol) in dry pyridine (60 mL). The solution was cooled to 0–5 °C, *p*-toluenesulfonyl chloride (3.8 g, 20 mmol) was added, and the resulting mixture was stirred for 10 min. The flask was then sealed and left in a freezer for 12 h. Thereafter, the reaction mixture was poured onto crushed ice (four to five times greater in volume) and extracted with Et_2O (5×50 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution and H_2O, dried, and stripped of solvent to afford the β-lactone (0.7 g, 52 %). ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C, TMS): δ = 1.30 ppm (s, 6H).

2,2,2-(Trideuterio)methyl-3-methyl-2-butene-[D_3]-1,1,1 (*gem*-[D_6]TME): The above β-lactone (0.5 g, 3.72 mmol) was placed in a Schlenk flask, which was connected to a rotaflo trap cooled to −78 °C. The flask was heated at 160 °C, which resulted in decomposition of the β-lactone to the deuterated alkene and CO_2. With the help of a slow stream of N_2, the alkene (0.26 g, 77 %) was collected in the trap. ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C, TMS): δ = 1.66 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, 26 °C, TMS): δ = 123.4, 123.2, 20.3, 19.4 ppm (septet, ^1J(C,D) = 19 Hz).

Methyltriphenylphosphonium iodide: A flame-dried, 100 mL round-bottomed flask, equipped with a magnetic stirrer, was charged with iodomethane (1.24 mL, 20 mmol), triphenylphosphine (3.93 g, 15 mmol), and toluene (50 mL). The solution was stirred at room temperature for 12 h and the white solid product was washed with hot toluene to afford 5.76 g of methyltriphenylphosphonium iodide (14.25 mmol, 95 %). ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C, TMS): δ = 3.23 (d, 3H, ^3J(H,H) = 8 Hz), 7.75 ppm (m, 15H).

2,2,2-(Trideuterio)methyl-7-methyl-2,6-octadiene-[D_3]-1,1,1 ([D_6]DMOD): A flame-dried, 100 mL round-bottomed flask, equipped with a magnetic stirrer, was charged with a solution of methyltriphenylphosphonium iodide (3.32 g, 8.2 mmol) in dry THF (20 mL) under Ar. The solution was cooled to 0 °C, and then 1.6 M *n*BuLi (5.15 mL, solution in hexanes) was added dropwise. The orange solution was left at room temperature for 30 min, cooled to 0 °C, and then a solution of 5-bromo-2-methyl-2-pentene (1.1 mL, 8.2 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h, cooled to 0 °C, and then 1.6 M *n*BuLi solution (5.15 mL) was added dropwise. The resulting mixture was stirred at room temperature for 15 min, cooled to 0 °C, and then [D_6]acetone (3 mL, 40 mmol) was added. The solution obtained was concentrated to a volume of 10 mL, pentane (40 mL) was added, and the mixture was stirred for 30 min. Filtration, evaporation of the solvents, and purification of the residue by preparative GC afforded 472 mg of the desired **4** (3.28 mmol, 40 %). ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C, TMS): δ = 5.12 (t, 2H), 2.73 (t, 4H), 2.02 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, 26 °C, TMS): δ = 131.51, 131.34, 124.46, 28.39, 28.36, 25.72, 24.80 (septet, ^1J(C,D) = 19 Hz), 17.70, 16.80 ppm (septet, ^1J(C,D) = 19 Hz); MS: *m*/*z* (%): 144 (13) [M^+], 126 (2), 101 (5), 88 (10), 75 (84), 69 (100), 45 (24).

2,3-Dimethyl-2-[D_{12}]butene ([D_{12}]TME): This deuterium-labeled alkene was prepared according to the procedure reported in the literature,[30] as detailed below:

2,3-Dimethyl-2,3-[D_{12}]butanediol ([D_{12}]pinacol): A flame-dried 100 mL round-bottomed flask, equipped with a magnetic stirrer, a reflux condenser, and an addition funnel, was charged with magnesium turnings (1.6 g, 65.8 mmol) and dry benzene (16 mL). A solution of mercury(II) chloride (1.8 g) in [D_6]acetone (10 mL, 138 mmol) was added gradually through the addition funnel. When the first vigorous reaction subsided, a mixture of [D_6]acetone (5.2 mL) and dry benzene (4 mL) was added, and the flask was heated over a water bath until no further reaction was evident (about 3 h). H_2O (4 mL) was then added through the addition funnel; the reaction mixture was heated for a further 1 h, cooled to about 50 °C, and filtered. The solid was returned to the flask and heated with fresh benzene (10 mL) to dissolve any remaining pinacol. The combined filtrates were then concentrated to half of the original volume in order to remove the acetone; the remaining benzene solution was treated with H_2O (6 mL) and cooled to 10–15 °C. Pinacol hydrate was precipitated, which was collected by filtration and washed with benzene (6.5 g, 43 % based on the magnesium used). The pinacol hydrate was then dehydrated and distilled to anhydrous pinacol (2.5 g). MS: *m*/*z* (%): 130 (0.1) [M^+], 112 (2), 94 (5), 65 (100), 46 (26), 33 (10).

2,3-Dimethyl-2-[D_{12}]butene (5, [D_{12}]TME): A Schlenk flask, which was connected to a rotaflo trap cooled to −78 °C, was charged with [D_{12}]pinacol (2.2 g, 16.95 mmol) and ethyl orthoformate (2.52 g). The flask was heated from 125 °C to 140 °C over a period of 8 h, during which time ethanol (1.9 mL) was distilled off. The remaining colorless liquid (2-ethoxy-4,4,5,5-tetramethyl-1,3-[D_{12}]dioxolan) was heated at 150–160 °C for 10 h, during which time CO_2 was evolved and 2.2 mL of distillate was collected. This distillate, which consisted mainly of [D_{12}]TME and ethanol, was further purified by preparative GC to afford **5** (800 mg, 6.15 mmol). ^{13}C NMR (125 MHz, $CDCl_3$, 26 °C, TMS): δ = 123.4, 19.4 ppm (septet, ^1J(C,D) = 19 Hz); MS: *m*/*z* (%): 96 (40) [M^+], 78 (86), 62 (17), 46 (100), 42 (27).

2,3-Dimethylbut-2-[D_0]ene ([D_0]TME): This compound was purchased from Aldrich. ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C, TMS): δ = 1.66 ppm (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$, 26 °C, TMS): δ = 123.4, 20.3 ppm.

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