ORGANIC LETTERS
2000
Vol. 2, No. 15
2245−2248

Isotope Effects and *syn* Selectivity in the Ene Reaction of Triazolinedione with Conjugated Enones: Aziridinium Imide or an Open Intermediate Mechanism?

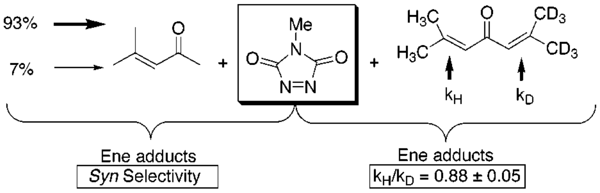
Georgios Vassilikogiannakis, Manolis Stratakis,* and Michael Orfanopoulos*

Department of Chemistry, University of Crete, 71409 Iraklion, Crete, Greece

orfanop@chemistry.uch.gr

Received April 26, 2000

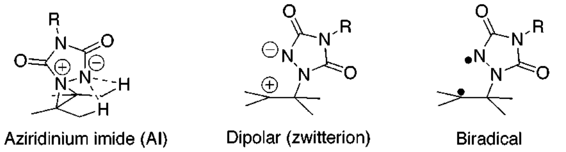
ABSTRACT



The ene reaction of 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) with phorone-d_6 (5-d_6) shows an inverse β-secondary isotope effect and with mesityl oxide-d_3 (7-d_3) proceeds with 93% *syn* selectivity. These results are consistent with a mechanism involving the formation of an aziridinium imide intermediate in the rate-determining step. An open biradical or dipolar intermediate is excluded by them.

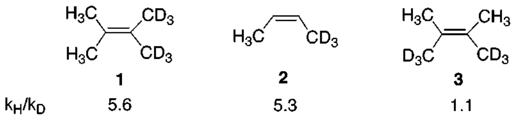
The ene reaction of triazolinediones (RTAD, R = methyl or phenyl) with akenes has attracted considerable mechanistic and theoretical attention.[1−10] For simple alkenes, among the various mechanistic pathways (Scheme 1), the formation of an aziridinium imide type intermediate, AI, via a stepwise mechanism is the most popular and has found much experimental[1−8] and theoretical[9] support.

Scheme 1. Proposed Intermediates for Triazolinedione Ene Reactions



The AI[1,2] and the analogous perepoxide[11] intermediates were established by using Stephenson's tetramethylethylene-d_6 isotope effect test.[12] That mechanism provided a reasonable explanation for the isotope effects found in the reaction of PTAD with tetramethylethylenes-d_6[1] and *cis*-2-butene-d_3[2] (Scheme 2). For example, large intramolecular isotope effects were found in reactions of PTAD with *cis*-related methyl and deuteriomethyl groups in compounds **1** and **2**, whereas

Scheme 2. Reported Isotope Effects in the PTAD Ene Reaction with Tetramethylethylenes-d_6 and *cis*-2-Butene-d_3



---

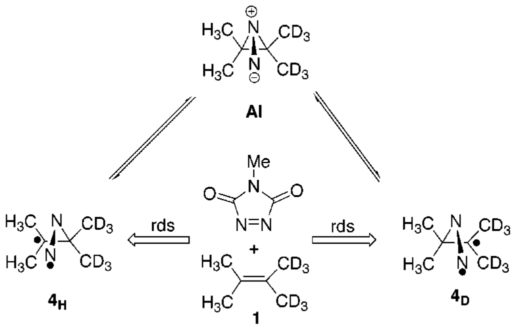
(1) Seymour, A.; Greene, F. D. *J. Am. Chem. Soc.* **1980**, *102*, 6384−6385.
(2) Orfanopoulos, M.; Smonou, I.; Foote, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 3607−3614.
(3) Orfanopoulos, M.; Stratakis, M.; Elemes, Y.; Jensen, F. *J. Am. Chem. Soc.* **1991**, *113*, 3180−3181.
(4) Elemes, Y.; Foote, C. S. *J. Am. Chem. Soc.* **1992**, *114*, 6044−6050.
(5) Clennan, E. L.; Koola, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 3802−3803.

10.1021/ol000109b CCC: $19.00

only a small isotope effect was observed with *trans* groups in compound **3** (Scheme 2). Later on, the AI intermediate was also observed spectroscopically.[13−15]

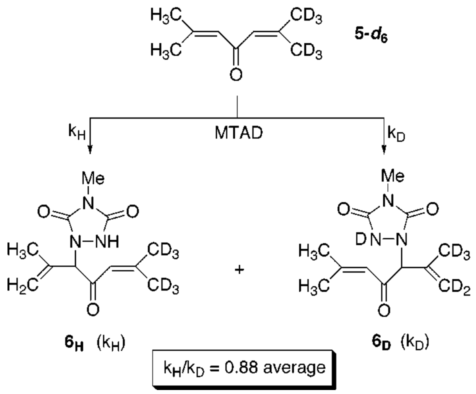
The AI intermediate was challenged recently by Singleton and Hang[10] on the basis of experimental and theoretically predicted isotope effects, as well as transition state energy profiles. They proposed an open biradical as the key intermediate in the rate-determining step of the ene reaction. Its barrier to rotation for certain substrates was calculated to be slightly higher (1−2.5 kcal) than the calculated energy of hydrogen abstraction through the ene mode; thus rotation around the previous alkene double bond is restricted. According to that mechanism (Scheme 3), biradical intermediates $\mathbf{4_H}$ and $\mathbf{4_D}$ should not compete for H or D abstraction, and no primary isotope effect should have been expected in the second fast step of this reaction. However, to rationalize the large primary isotope effects found earlier for tetramethylethylenes-d_6[1] and *cis*-2-butene-d_3,[2] compounds **1** and **2**, a fast equilibration of biradical intermediates $\mathbf{4_H}$ and $\mathbf{4_D}$ with an AI intermediate was proposed. Furthermore, the biradical intermediate retains the stereochemical integrity of the AI, since lamination around the C−N bond was also calculated and found to be restricted. Thus, the geminal methyl and deuteriomethyl groups in alkene **3** become noncompetitive in the corresponding biradicals. As a result, such a biradical intermediate that carries on well-defined stereo and energy requirements cannot be excluded by Stephenson's isotope effect test.

Scheme 3. Proposed Biradical Mechanism



To test this new biradical mechanism, we decided to isolate the geminal methyl from the deuteriomethyl groups in tetramethylethelene-d_6 by the intervention of a carbonyl functionality (Scheme 4). For this purpose, 2,6-dimethylhepta-2,5-diene-4-one-*1,1,1,2′,2′,2′*-d_6 (phorone-d_6, **5-*d*₆**) was prepared by aldol condensation between the kinetic enolate of mesityl oxide and acetone-d_6 and subsequent dehydration of the resulting *β*-keto alcohol {GC−MS ($C_9H_8D_6O$) *m/z* (%) 144 ([M^+], 15)}. Reactions of PTAD with a series of conjugated enones, α,*β*-unsaturated esters and lactones, have been reported earlier. However, the proposed mechanisms were not clear.[16−18]

Scheme 4. Intramolecular Secondary Isotope Effect in the Addition of MTAD to **5-*d*₆**



Unlike the tetramethylethylene-d_6 test,[12] phorone-d_6 fulfills the requirement that the two pairs of geminal methyl groups (protio and deuterio) will not be competitive in the second H or D abstraction step. It is assumed that the reaction is irreversible, like the reactions of simple alkenes. This requirement should hold, even in the case that a fast equilibration of the proposed biradical intermediate with the AI intermediate applies.

Phorone-d_6 reacts with MTAD in a 1:1 molar ratio at ambient temperature. This reaction gave exclusively the ene adducts in a variety of solvents (Scheme 4). When the reaction was carried out in MeOH, some unidentified byproducts, most probably MTAD−MeOH adducts, were formed. Solvent polarity did not affect substantially the relative reaction rates, judging from the ^1H NMR analysis of ene product formation (reactions were completed between 12 and 14 h). In all cases, the reaction products were purified by flash column chromatography, by using a mixture of hexane/ethyl acetate (2:1) as eluent. The ^1H NMR spectra of the ene adducts were taken in deuterated benzene as solvent {HRMS (MALDI) calcd for $C_{12}H_{11}D_6O_3N_3Na$ [$M + Na^+$] 280.1533, found 280.1541}.

---

(6) Smonou, I.; Khan, S.; Foote, C. S.; Elemes, Y.; Mavridis, I. M.; Pantidou, A.; Orfanopoulos, M. *J. Am. Chem. Soc*. **1995**, *117*, 7081−7087.

(7) Stratakis, M.; Orfanopoulos, M.; Foote, C. S. *J. Org. Chem*. **1998**, *63*, 1315−1318.

(8) Vassilikogiannakis, G.; Stratakis, M.; Orfanopoulos, M.; Foote C. S. *J. Org. Chem*. **1999**, *64*, 4130−4139.

(9) Chen, J. S.; Houk, K. N.; Foote, C. S. *J. Am. Chem. Soc*. **1997**, *119*, 9852−9855.

(10) Singleton, D. A.; Hang, C. *J. Am. Chem. Soc*. **1999**, *121*, 11885−11893.

(11) A perepoxide intermediate was proposed in the analogous singlet oxygen−alkene ene reactions: (a) Stephenson, L. M.; Grdina, M. B.; Orfanopoulos, M. *Acc. Chem. Res*. **1980**, *13*, 419−425. (b) Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595−1615.

(12) Grdina, M. B.; Orfanopoulos, M.; Stephenson, L. M. *J. Am. Chem. Soc*. **1979**, *101*, 3111−3112.

(13) .Poon, T. H. W.; Park, S.; Elemes, Y.; Foote, C. S. *J. Am. Chem. Soc*. **1995**, 117, 10468−10473.

(14) Squillacote, M.; Mooney, M.; De Felipis, J. *J. Am. Chem. Soc*. **1990**, 112, 5364−5365.

(15) Nelsen, S. F.; Kapp, D. L. *J. Am. Chem. Soc*. **1985**, 107, 5548−5549.

(16) Shiloff, J. D.; Hunter, N. R. *Tetrahedron Lett*. **1976**, 3773−3774.

(17) Hoye, T. R.; Bottorff, K. J.; Caruso, A. J.; Dellaria, J. F. *J. Org. Chem*. **1980**, *45*, 4287−4292.

(18) Hunter, N. R.; Krawchuk, B. R.; Shiloff, J. D. *Can. J. Chem*. **1982**, *60*, 835−839.

Whereas tetramethylethylene-d_6, (substrate **1**, Scheme 3), gave a 5.6 k_H/k_D isotope effect, phorone-d_6 gave no primary isotope effect. Instead a substantial β-secondary isotope effect was found in a variety of reaction solvents. These results are summarized in Table 1.

Table 1. Secondary Isotope Effects in the Ene Reaction of MTAD with Phorone-d_6

solvent	$k_H/k_D{}^a$
C_6D_6	0.90 ± 0.05
$CDCl_3$	0.90 ± 0.05
$(CD_3)_2CO$	0.87 ± 0.05
DMSO-d_6	0.86 ± 0.05
CD_3OD	0.88 ± 0.05

[a] Determined by ^{1}H NMR integration of the proper hydrogen signals.

The inverse isotope effect, k_H/k_D, is the result of an intramolecular isotopic competition between the two double bonds (d_0 and d_6, Scheme 4) of phorone-d_6, and was proportional to the ratio of $\mathbf{6_H}/\mathbf{6_D}$ adducts. It was measured by ^{1}H NMR integration of the methyl group of $\mathbf{6_H}$ at 1.60 ppm and methyl groups of $\mathbf{6_D}$ at 1.33 and 1.98 ppm, (Figure 1).

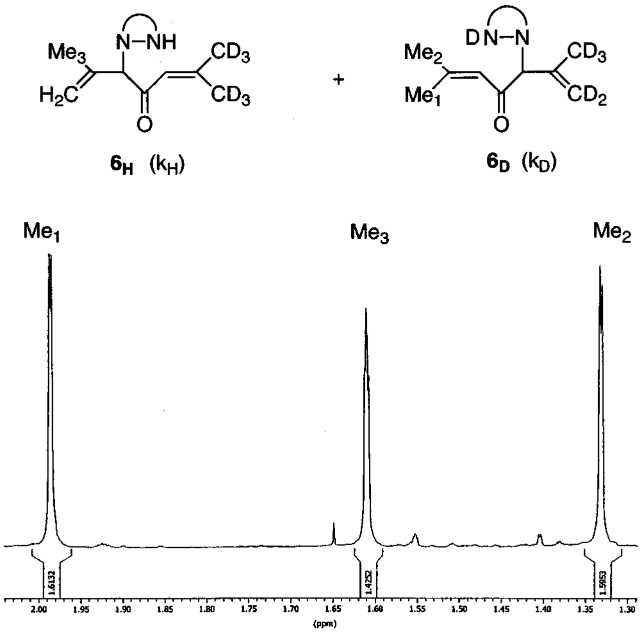
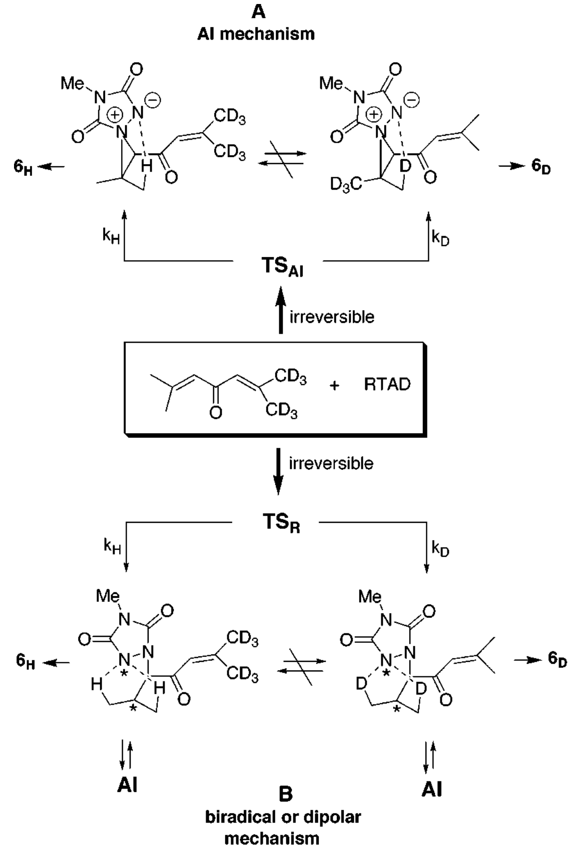


Figure 1. ^{1}H NMR determination of k_H/k_D by the integration of the proper methyl absorptions of products $\mathbf{6_H}$ and $\mathbf{6_D}$. In this case, the reaction was run in MeOH solvent. The chemical shift of the methyl groups in $\mathbf{6_D}$ was assigned by NOE experiments.

Scheme 5. Ene Reaction of MTAD with (*Z*)-Mesityl Oxide-d_3



To rationalize these results, two mechanistic possibilities are presented in Scheme 5: (a) an AI intermediate (**A**) and (b) a dipolar or a biradical intermediate (**B**). The absence of a primary isotope effect indicates the irreversible formation of an intermediate. This intermediate, AI or biradical/dipolar, was formed in a rate-determining step and preceded the H or D abstraction mode. Because the two sets of the methyl groups in **5-*d*$_6$** (protio and deuterio) are separated by the carbonyl functionality no intramolecular competition is allowed, in the second, H or D abstraction step of the ene reaction. Furthermore, the substantial inverse β-secondary isotope effect found consistently in these solvents (Table 1), excludes the formation of a biradical or a dipolar transition state $\mathbf{TS_R}$ in a rate-limiting step. In transition state $\mathbf{TS_R}$, leading to a dipolar intermediate, the hyperconjucative effect involving the six hydrogen atoms in one double bond (terminal protio methyl groups) of **5-*d*$_6$**, versus the six deuterium atoms in the other double bond (terminal deuterio methyls), is expected to give a normal and large β-secondary isotope effect ($k_H/k_D \approx 1.05-1.1$ per deuterium atom),[19] as found recently in a typical dipolar cycloaddition[20] of TCNE to 2,5-dimethyl-2,4-hexadiene. In the case of a biradical transition state $\mathbf{TS_R}$, a smaller but still normal isotope effect is expected ($k_H/k_D \approx 1.02-1.05$ per deuterium atom). It is important to note here that the well established [2 + 2] photocycloaddition of enones and dienones to C_{60} proceeds via a biradical intermediate.[21,22] When this reaction was run

---

(19) Matsson, O.; Westway, K. C. *Adv. Phys. Org. Chem.* **1996**, *31*, 143–248.

(20) Vassilikogiannakis, G.; Orfanopoulos, M. *Tetrahedron Lett.* **1996**, *37*, 3075–3078.

(21) Schuster, D. I.; Cao, J.; Kaprinidis, N.; Wu, Y.; Jensen, A. W.; Lu, Q.; Wang, H.; Wilson, S. R. *J. Am. Chem. Soc.* **1996**, *118*, 5639–47.

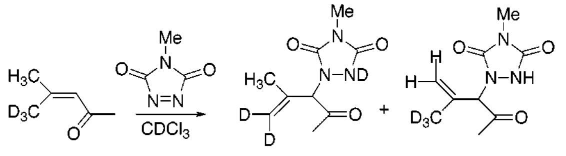
with phorone-d_6 as the dienone component, a normal β-secondary isotope effect ($k_H/k_D \approx 1.1$)[23] was found. Also, the formation of the *tert*-butyl radical from the decomposition of the perester of pivalic acid[24] proceeds with a normal β-secondary isotope effect of 1.19 (2% per deuterium atom).

Concerning mechanism **B**, we must emphasize that a tertiary radical is more stable than a secondary α-carbonyl radical.[22,25] It is therefore unreasonable to explain the observed inverse isotope effects by assuming an α-carbonyl radical formation with simultaneous bond formation between the nitrogen of PTAD and the disubstituted carbon of phorone-d_6. These results are consonant with a S_N2 type addition of MTAD to one of the double bonds of phorone, leading to the AI intermediate in the rate-determining step. In this transition state, the steric interactions in going from the less crowded ground state (sp^2 hybridization) to a more crowded transition state (sp^3 hybridization) would lead to a substantial inverse isotope effect, as found. Because the stereoelectronic effects on the two carbons of the double bond of phorone-d_6 are unequal, it is reasonable to assume a nonsymmetrical **TS$_{AI}$**.

To probe this reaction mechanism further and obtain information on the stereoselectivity of the electron-deficient enone moiety, the (*Z*)-mesityl oxide-d_3, **7-*d*$_3$**, was prepared in 96% isomeric purity, by the reaction of $(CD_3)_2CuLi$ with the proper phosphate ester.[26]

The reaction of MTAD with **7-*d*$_3$** was performed in $CDCl_3$ and C_6D_6 at 25 °C. It showed a remarkable 93% *syn* preference (corrected for 100% geometrical purity of **7-*d*$_3$**) for ene adducts formation (Scheme 6).

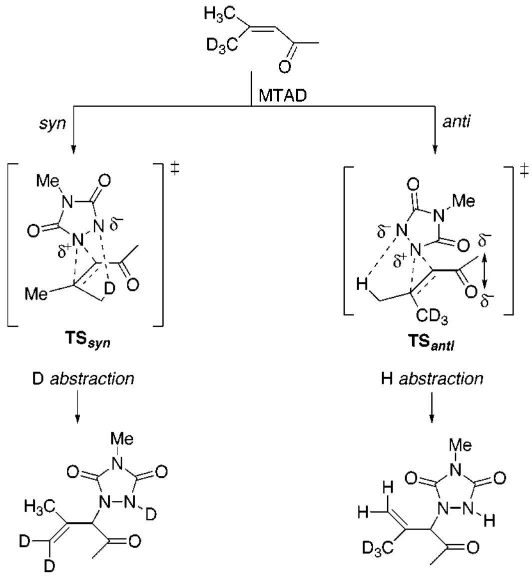
Scheme 6. *Syn* Selectivity in the Ene Reaction of MTAD to (*Z*)-Mesityl Oxide-d_3



7-*d*$_3$ **8-*syn*** (93%) **8-*anti*** (7%)

The *syn* stereoselectivity can be rationalized by examining the possible transition states leading to the major **8-*syn*** and minor **8-*anti*** ene products. In the *syn*-transition state **TS$_{syn}$** and the *anti*-transition state **TS$_{anti}$** the bond of the allylic hydrogen or deuterium that is being abstracted must be perpendicular to the alkene plane. A parallel approach[5,27] of the MTAD to the enone double bond will minimize electrostatic repulsions developed between the negatively charged nitrogen of MTAD and the carbonyl moiety of the enone, as well as between the C=O carbonyl group of MTAD and the C=O group of enone. Such interactions are developing during a perpendicular approach. Subsequently, the MTAD moiety moved enough to interact with each of the two methyls but was not perpendicular to the former double bond. In the *anti*-transition state **TS$_{anti}$** leading to the minor *anti*-product, the electrostatic repulsions between the carbonyl groups of the enophile and the enone are expected to be stronger than those in the *syn*-transition state, leading to the major ene product, where the electrostatic interactions between the negatively charged nitrogen and the carbonyl group of the enone are smaller.

Scheme 7. Possible Mechanisms of MTAD Addition to Phorone-d_6



8-*syn* (major) **8-*anti*** (minor)

In conclusion, the ene reaction of MTAD with dienone **5-*d*$_6$** gave a substantial inverse β-secondary isotope effect and with mesityl oxide displayed *syn*-selectivity. The results were rationalized by a stepwise mechanism involving the formation of an aziridinium imide intermediate in the rate-determining step. An open biradical or dipolar intermediate fails to rationalize the present results. However, as we pointed out elsewhere,[6] the stability of an AI intermediate and in some extreme cases its equilibration with its open dipolar intermediate depends on the particular olefin substrates. Therefore, the mechanistic information derived from this study may not be applicable to other substrates.

Acknowledgment. M.O. thanks professor K. C. Nicolaou for his generous hospitality during his sabbatical stay at The Scripps Research Institute (2000).

Supporting Information Available: ^{1}H NMR spectra for compounds **5-d$_6$**, **6$_H$** and **6$_D$**, **7-d$_3$**, **8$_{syn}$** and **8$_{anti}$**. HRMS for **6$_H$**. This material is available free of charge via the Internet at http://pubs.acs.org

OL000109B

---

[22] Vassilikogiannakis, G.; Orfanopoulos, M. *J. Org. Chem.* **1999**, *64*, 3392−3394.

[23] Hatzimarinaki, M.; Vassilikogiannakis, G.; Orfanopoulos, M. Manuscript in preparation.

[24] Koening, T.; Walf, R. *J. Am. Chem. Soc.* **1967**, *89*, 2948−2952.

[25] For an extensive discussion see: Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev.* **1993**, *93*, 3−22.

[26] Sum, F. W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431−1440.

[27] Adam, W.; Schwarm, M. *J. Org. Chem.* **1988**, *53*, 3129−3130.