

Georgios Vassilikogiannakis, Manolis Stratakis, Gerasimos J. Karabatsos and Michael Orfanopoulos\*

Department of Chemistry, University of Crete, Iraklion 71409, Greece  
Received February 12, 1996

Dedicated to the memory of Professor Nicholas Alexandrou

Secondary isotope effect measurements of methanol adducts from the reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with 2,5-dimethyl-2,4-hexadiene, support the formation of an aziridinium imide intermediate rather than an open dipolar intermediate in the rate determining step.

*J. Heterocyclic Chem.*, **33**, 993 (1996).

4-Phenyl-1,2,4-triazoline-3,5-dione is a powerful electrophile. With alkenes and dienes it gives a variety of cycloadditions ([4+2], [2+2]) and ene reactions. Deuterium isotope effects [1] and stereochemical studies [2] have shown that the ene reaction proceeds *via* the irreversible formation of an aziridinium imide intermediate. Only with the less reactive *trans* disubstituted alkenes [1b] the product forming step competes with aziridinium imide formation. The existence of the aziridinium imide intermediate was established from low temperature nmr studies in the reactions of adamandylidenoadamantane [3], *trans*-cycloheptene [4] and *trans*-cyclooctene [5].

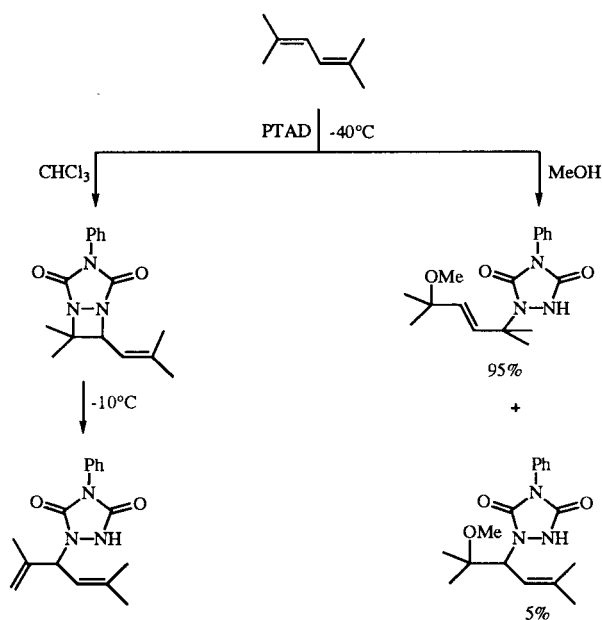
In methanol, the reaction of triazolinedione with dienes gives methoxy adducts [6]. The methoxy adducts are formed at low temperature, whereas the ene products are formed at high temperature [7]. This result is consonant with the expectation that the entropy of activation for the reaction with methanol is substantially more negative than that of the competing ene reaction.

Furthermore, the stereochemistry of the methoxy adducts [8] and secondary isotope effects [9] with *gem*-tetramethylethylene- $d_6$  supported the stereospecific capture of the aziridinium imide by methanol (Scheme 1).

Extensive studies of the addition of 4-phenyl-1,2,4-triazoline-3,5-dione to isomeric 2,4-hexadienes [6] and *tert*-butoxy butadienes [10], revealed that the [4+2] adducts are formed from a non-concerted mechanism. For example, (*Z,Z*)-2,4-hexadiene gives two Diels-Alder adducts with the major product having the "wrong" stereochemistry.

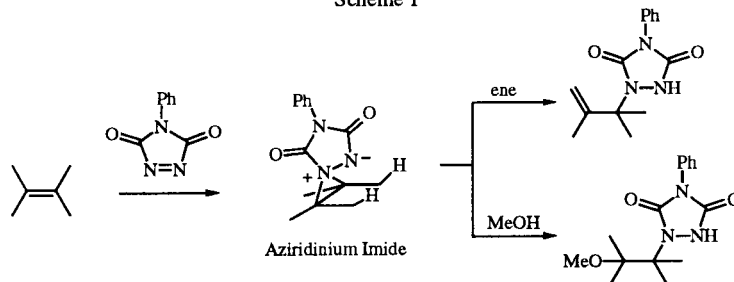
With 2,5-dimethyl-2,4-hexadiene, no Diels-Alder adducts were formed, presumably due to steric interac-

Scheme 2



tions. At -40° a labile 1,2-diazetidone is formed as the only product. Upon warming the sample to room temperature, the diazetidine completely rearranges to the ene product, along with some other unidentified products (Scheme 2). However, when methanol is the solvent, at -40° the only reaction products are the 1,2- and 1,4-methoxy adducts

Scheme 1



(5/95 ratio). It was proposed [6] that the reactions of 2,4-hexadienes and 2,5-dimethyl-2,4-hexadiene with 4-phenyl-1,2,4-triazoline-3,5-dione proceed through an aziridinium imide, which subsequently opens to a 1,4-zwitterionic intermediate. Possibly the 2,5-dimethyl-2,4-hexadiene reaction involves only the 1,4-zwitterionic intermediate.

The above results prompted us to study the isotope effects of the reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with 2-methyl-1',1',1'-d<sub>3</sub>-5-methyl-2,4-hexadiene-1,1,1-d<sub>3</sub> [11] in order to establish the formation and identity of the intermediate in the rate determining step. The reaction proceeded smoothly at -15° and gave the expected 1,4- and 1,2-trapping products. Fractional crystallization at low temperature afforded only the 1,4-adducts [12] (compounds **2a** and **2b**, Scheme 3).

The  $k_H$  is proportional to the rate of formation of adduct **2a**, where the new C-N bond is formed next to the geminal -CH<sub>3</sub> methyls, and the methoxy group is next to the geminal -CD<sub>3</sub> methyls. The  $k_D$  is proportional to the rate of formation of adduct **2b**, where the methoxy group is next to the geminal -CH<sub>3</sub> methyls. By integrating the single peaks that resonate at 1.61 ppm (6H next to urazole

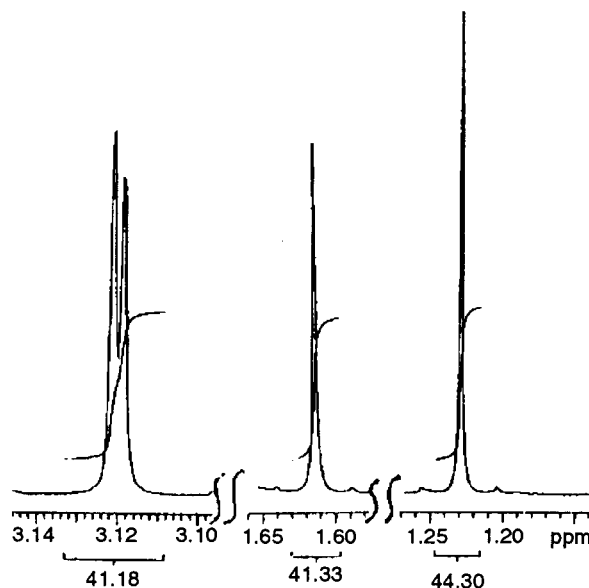


Figure 1. <sup>1</sup>H nmr spectrum of the 1,4-adducts, **2a** and **2b**.

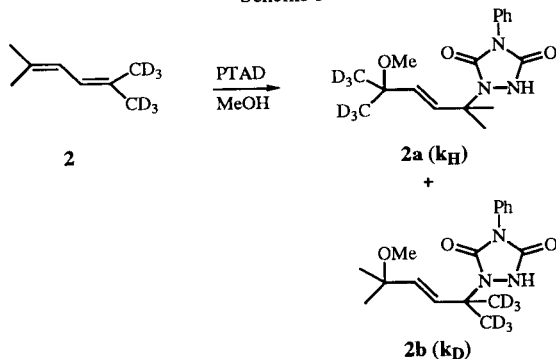
methoxy peaks at 3.12 ppm (methoxy next to the geminal CD<sub>3</sub> methyls) and at 3.11 ppm (methoxy next to the geminal CH<sub>3</sub> methyls).

The observed small secondary isotope effect excludes the formation of a zwitterionic intermediate in the rate determining step. In such a case (rate determining formation of a dipolar intermediate), a substantial secondary  $k_H/k_D$  would be expected, ( $k_H/k_D \sim 0.7-0.8$ ) because of conjugative effects (see intermediates Z<sub>I</sub> and Z<sub>II</sub>, Scheme 4). In the analogous addition of tetracyanoethylene [13] with 2-methyl-1',1',1'-d<sub>3</sub>-5-methyl-2,4-hexadiene-1,1,1-d<sub>3</sub> in methanol to form the 1,4-methoxy adduct, a significant reverse isotope effect  $k_H/k_D = 0.72 \pm 0.04$  was measured. In that case a dipolar intermediate formed in the rate determining step was proposed.

Our present results are consonant with either a synchronous addition of 4-phenyl-1,2,4-triazoline-3,5-dione and methanol to the diene, which is quite unlikely, or with the irreversible formation of a noncarbocationic intermediate in the rate limiting step. Taking into account the relevant work by Foote and Jensen, we propose the formation of an aziridinium imide intermediate as the first step. This intermediate collapses to the products in a single step or through the prior fast formation of the open zwitterionic intermediate. This open zwitterion can collapse to 1,2-diazetidene, which was observed by Foote and Jensen at -40°, or can be captured by the solvent, to give the methoxy adducts. The small inverse isotope effect observed can be attributed to steric interactions involving 4-phenyl-1,2,4-triazoline-3,5-dione with either the d<sub>6</sub> or the d<sub>0</sub> side of the molecule.

In conclusion, the reaction of 2,5-dimethyl-2,4-hexadiene with 4-phenyl-1,2,4-triazoline-3,5-dione proceeds

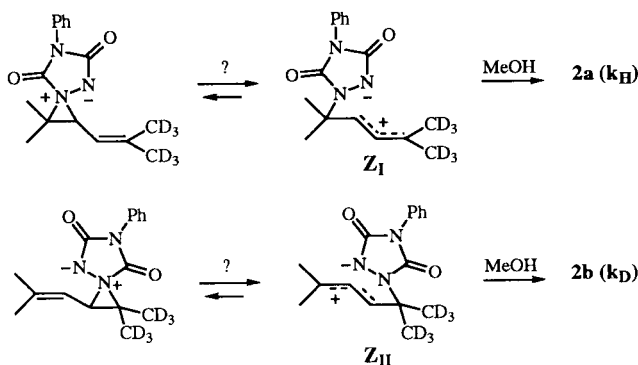
Scheme 3



ring in **2a**) and at 1.23 ppm (6H next to methoxy group in **2b**), an intramolecular secondary isotope effect  $k_H/k_D = 0.93 \pm 0.04$  was found (Figure 1).

This slightly inverse secondary isotope effect can also be assessed by the almost equivalent intensity of the two

Scheme 4



through the formation of an aziridinium imide in the rate determining step, which rearranges in a fast step to the 1,2-diazeditine, probably *via* the zwitterionic intermediate. In methanol, the reaction gives preferentially the 1,4-methanol adducts.

## REFERENCES AND NOTES

[1a] C.-C. Cheng, C. A. Seymour, M. A. Petti, F. D. Greene and J. F. Blount, *J. Org. Chem.*, **49**, 2910 (1984); [b] I. Smonou, M. Orfanopoulos and C. S. Foote, *Tetrahedron Letters*, **29**, 2769 (1988).

[2a] Y. Elemen, M. Stratakis and M. Orfanopoulos, *Tetrahedron Letters*, **30**, 6903 (1989); [b] M. Orfanopoulos, Y. Elemen and M. Stratakis, *Tetrahedron Letters*, **31**, 5775 (1990); [c] E. L. Clennan, J. J. Koola, and K. A. Oolman, *Tetrahedron Letters*, **31**, 6759 (1990); [d] M. Orfanopoulos, M. Stratakis, Y. Elemen and F. Jensen, *J. Am. Chem. Soc.*, **113**, 3180 (1991).

[3] S. F. Nelsen and D. L. Kapp, *J. Am. Chem. Soc.*, **107**, 5548

(1985).

[4] M. Squillacote, M. Mooney and J. De Felippis, *J. Am. Chem. Soc.*, **112**, 5364 (1990).

[5] T. H. W. Poon, S. H. Park, Y. Elemen and C. S. Foote, *J. Am. Chem. Soc.*, **117**, 10468 (1995).

[6] F. Jensen and C. S. Foote, *J. Am. Chem. Soc.*, **109**, 6376 (1987).

[7] Y. Elemen and M. Orfanopoulos, *Tetrahedron Letters*, **32**, 2667 (1991).

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

[9] Y. Elemen and M. Orfanopoulos, in preparation.

[10] E. L. Clennan and A. D. Earlywine, *J. Am. Chem. Soc.*, **109**, 7104 (1987).

[11] 2-Methyl-1',1',1'-d<sub>3</sub>-5-methyl-2,4-hexadiene-1,1,1-d<sub>3</sub>, was prepared by Wittig coupling of triphenyl phosphoranylidene 3-methyl-2-butene with acetone-d<sub>6</sub> in ether, <sup>1</sup>H nmr (deuteriochloroform): 5.96 (s, 2H), 1.78 (s, 3H), 1.72, (s, 3H); hrms for **2**: Calcd. for C<sub>8</sub>H<sub>8</sub>D<sub>6</sub>: 116.1472. Found 116.1458.

[12] hrms for **2a** and **2b**: Calcd. for C<sub>17</sub>H<sub>17</sub>D<sub>6</sub>N<sub>3</sub>O<sub>3</sub>: 323.2116. Found 323.2104.

[13] G. Vassilikogiannakis and M. Orfanopoulos, *Tetrahedron Letters*, in press.