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Solvent-Dependent Changes in the Ene Reaction of RTAD with Alkenes: The Cyclopropyl Group as a Mechanistic Probe

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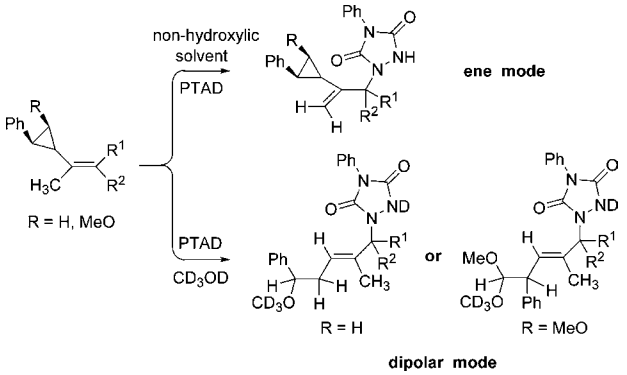
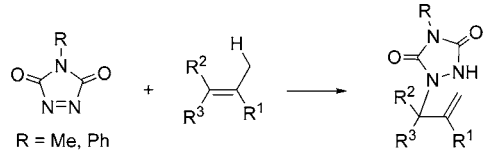
ABSTRACT



The vinylcyclopropyl moiety was used as an efficient probe to test mechanistic possibilities of the triazolinedione−alkene ene reaction. In non-hydroxylic solvents, this reaction afforded only the ene adducts via a closed three-membered aziridinium imide (AI) intermediate, whereas in hydroxylic solvents a dipolar intermediate is favored and trapped by the cyclopropyl moiety to form the corresponding cyclopropyl-rearranged solvent-trapped adducts.

Triazolinedione RTAD (MTAD for R = methyl or PTAD for R = phenyl), one of the most reactive electrophiles, is known to react with conjugated dienes and olefins to give Diels−Alder and ene or [2 + 2] adducts, respectively.[1] The ene reactions of RTADs have attracted considerable mechanistic and theoretical attention due to their synthetic applications[2] and their unusual mechanistic features that exhibit similarities to the ene reactions of singlet oxygen ($^1O_2$)[3] and nitrosoarene (ArNO).[4] Regarding the ene reaction of RTAD with simple alkenes (eq 1), a number of experimental studies



(1)

(kinetic isotope effects,[5,6,7] solvent trapping experiments)[7,8] and to a lesser extent computational work[9] has established a stepwise mechanism, with the formation of an aziridinium imide (AI) intermediate (Figure 1) in the first, rate-determin-

(1) For a recent review regarding the triazolinedione ene reaction, see: Vougioukalakis, G. C.; Orfanopoulos, M. *Synlett*. **2005**, 713−731.

(2) For some recent examples, see: (a) Adam, W.; Degen, H. G.; Krebs, O.; Saha-Möller, C. R. *J. Am. Chem. Soc.* **2002**, *124*, 12938−12939. (b) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628−5629. (c) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *Org. Lett.* **2003**, *5*, 1999−2001.

(3) (a) Smonou, I.; Khan, S.; Foote, C. S.; Elemes, Y.; Mavridis, I. M.; Pantidou, A.; Orfanopoulos, M. *J. Am. Chem. Soc.* **1995**, *117*, 7081−7087. (b) Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595−1615.

(4) (a) Seymour, C. A.; Greene, F. D. *J. Org. Chem.* **1982**, *47*, 5226−5227. (b) Adam, W.; Krebs, O.; Orfanopoulos, M.; Stratakis, M.; Vougioukalakis, G. C. *J. Org. Chem.* **2003**, *68*, 2420−2425.

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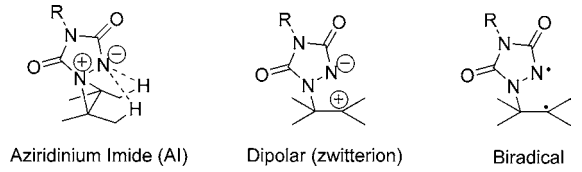
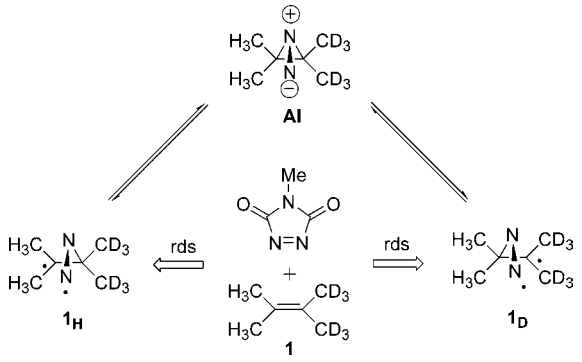


Figure 1. Proposed intermediates for the RTAD ene reaction.

ing step of the reaction. Support in favor of this mechanism was also offered by the direct spectroscopic observation of an AI intermediate.[10]

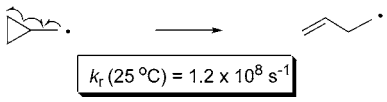
The AI was later on challenged by Singleton and Hang on the basis of experimental and theoretically predicted kinetic isotope effects, as well as transition-state energy profiles.[11] In that work, a mechanism involving a biradical intermediate (Figure 1) was proposed, while the AI was characterized as an "innocent bystander". Since, due to energy factors, rotation in the biradical intermediate was found to be restricted, all of the previously mentioned experimental results may also be rationalized by this "aziridinium imide-like biradical intermediate". Furthermore, to rationalize the large primary isotope effects found earlier for *gem*-tetramethylethylene-d_6,[5] **1** (Scheme 1), and *cis*-2-butene-

Scheme 1. Proposed Biradical Mechanism



d_3,[6] a fast equilibration of biradical intermediates $\mathbf{1_H}$ and $\mathbf{1_D}$ via the AI intermediate was proposed. Nevertheless, the biradical mechanism was later on called into question on the basis of stereoisotopic and product studies.[12,13]

This controversy in the literature prompted us to further investigate the mechanism of the RTAD alkene ene reaction, to ascertain the possible involvement of an open biradical intermediate, by using the phenyl cyclopropyl group as a mechanistic probe. This probe has been used in the past as a trap for other radical intermediates, since it involves the rapid cyclopropylcarbinyl to homoallylcarbinyl radical rearrangement (eq 2).[14]

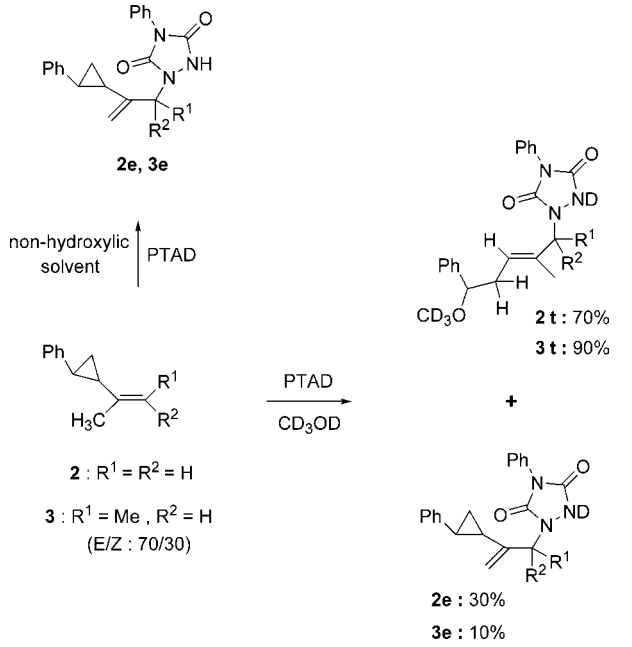


(2)

Kim and O'Shea have also recently reported a study on the reaction of tetracyclopropylethylene with MTAD, in an effort to test the biradical mechanism proposed by Singleton.[15] However, instead of trapping any intermediate, they only isolated a novel mesoionic product that upon heating rearranged to the corresponding diazetidine.

In the present work, to test mechanistic possibilities of this classical ene reaction, cyclopropyl-substituted olefins **2**

Scheme 2. PTAD Addition to Olefins **2** and **3** in Nonhydroxylic Solvents and CD_3OD



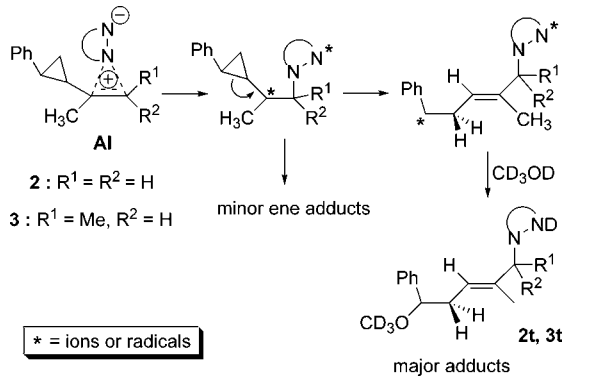
(5) Seymour, A.; Greene, F. D. *J. Am. Chem. Soc.* **1980**, *102*, 6384−6385.
(6) Orfanopoulos, M.; Smonou, I.; Foote, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 3607−3614.
(7) Smonou, I.; Khan, S.; Foote, C. S.; Elemes, Y.; Mavridis, I. M.; Pantidou, A.; Orfanopoulos, M. *J. Am. Chem. Soc.* **1995**, *117*, 7081−7087.
(8) Smonou, I.; Orfanopoulos, M.; Foote C. S. *Tetrahedron Lett.* **1988**, *29*, 2769−2772.
(9) Chen. J. S.; Houk, K. N.; Foote, C. S. *J. Am. Chem. Soc.* **1997**, *119*, 9852−9855.
(10) (a) Nelsen, S. F.; Kapp, D. L.*J. Am. Chem. Soc.* **1985,** *107*, 5548−5549. (b) Squillacote, M.; Mooney, M.; De Felipis, J. *J. Am. Chem. Soc.* **1990,** *112*, 5364−5365. (c) Poon, T. H. W.; Park, S.; Elemes, Y.; Foote, C. S. *J. Am. Chem. Soc.* **1995,** *117*, 10468−10473.
(11) Singleton, D. A.; Hang, C. *J. Am. Chem. Soc.* **1999**, *121*, 11885−11893.
(12) Vassilikogiannakis, G.; Stratakis, M.; Orfanopoulos, M. *Org. Lett.* **2000**, *2*, 2245−2248.
(13) Stratakis, M.; Hatzimarinaki, M.; Froudakis, G. E.; Orfanopoulos, M. *J. Org. Chem.* **2001,** *66*, 3682−3687.
(14) (a) Shimizu, N.; Nishida, S. *J. Chem. Soc., Chem. Commun.* **1972**, 389−390. (b) Rudolph, A.; Weedon, A. *Can. J. Chem.* **1990**, *68*, 1590−1596. (c) Adam, W.; Curci, R.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Gasparrini, F.; Kluge, R.; Paredes, R.; Schulz, M.; Smerz, A. K.; Veloza, L. A.; Weinkötz, S.; Winde, R. *Chem. Eur. J.* **1997**, *3*, 105−109. (d) Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varik, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915−10921.
(15) Kim, D. K.; O'Shea, K. E. *J. Am. Chem. Soc.* **2003**, *126*, 7000−7001.

and **3** (Scheme 2) were prepared. When the reactions of **2** and **3** with PTAD were carried out in $CDCl_3$, CH_2Cl_2, acetone, acetonitrile, and DMSO at ambient temperature, they exclusively afforded the ene adducts **2e** and **3e** respectively (Scheme 2), bearing an intact cyclopropyl group. These results provide strong evidence that in non-hydroxylic solvents the ene reaction proceeds via the established, closed AI intermediate, leading exclusively to the formation of the ene products **2e** and **3e**. Had the biradical intermediate, with a lifetime greater than 10^{-11} s (rate of phenyl-substituted cyclopropyl ring opening: 3×10^{11} s^{-1}),[14d] been formed, the characteristic ring-opened products would have been detected.

When the reaction was carried out in methanol-d_4, apart from the ene adducts **2e** and **3e**, which were formed in a relatively small percentage, rearranged methanol-trapping derivatives **2t** and **3t** were mainly isolated (Scheme 2). When ethanol was used as the solvent analogous ethanol-trapping adducts were isolated. The trans stereochemistry of the newly formed double bonds in **2t** and **3t** was assigned by nuclear Overhauser effect difference experiments (DNOE).

The proposed mechanism that could account for the formation of these ring-opened trapping products is shown in Scheme 3: The initially formed tertiary carbocation or

Scheme 3. Proposed Mechanism for the Formation of the Rearranged Trapping Derivatives

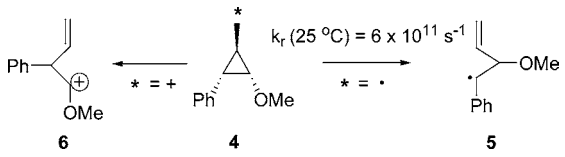


radical undergoes ring opening to the more stable, benzylic cation or radical intermediate, which is subsequently been trapped by one molecule of methanol-d_4.

Although the cyclopropyl rearranged and methanol-trapped products unambiguously indicate the formation of an open intermediate, this probe is unfortunately insufficient to discriminate between radical or carbocation intermediates.[16] It has been previously shown that radicals as well as the corresponding carbocation intermediates may be trapped equally effectively.[17]

To shed more light to this mechanistic problem, and be able to distinguish between biradical and dipolar intermediate, a second-generation hypersensitive probe, developed by Newcomb and co-workers,[17,18] was used. For example, cyclopropylcarbinyl probe **4** (Scheme 4), containing both a

Scheme 4. Mechanistic Probe Capable of Distinguishing between a Radical and a Cation on the Cyclopropylcarbinyl Carbon



phenyl and a methoxy group, not only maintains the hypersensitive radical reactivity, but also permits high discrimination between radical and cationic intermediates. Consequently, in ring openings of this cyclopropyl carbinyl system, the phenyl group stabilizes an incipient radical more effectively than the methoxy group and conversely, the alkoxy group favors an incipient carbocation.

Indeed, cyclopropylcarbinyl radical **4** (Scheme 4) rearranges with high regioselectivity, 170:1 at ambient temperature, to the benzylic radical **5**, while, cyclopropylcarbinyl cation **4** opens with even higher selectivity, >1000:1, to oxonium ion **6**.[17,18]

The efficiency of this useful mechanistic probe to distinguish between radical and dipolar intermediates has already been demonstrated.[17,18] Moreover, thionocarbonate **7** and mesylate **8** (Figure 2) were tested under radical (Barton−

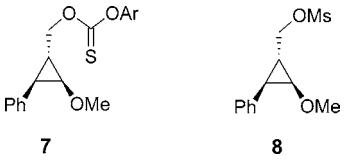


Figure 2. Substrates utilized to study the cation and radical trapping ability of the cyclopropylcarbinyl moiety containing both a phenyl and a methoxy group.

McCombie deoxygenation) and cationic reaction conditions, respectively. The exclusive formation of the benzylic radical or oxonium cationic intermediate respectively led to two distinctive products.

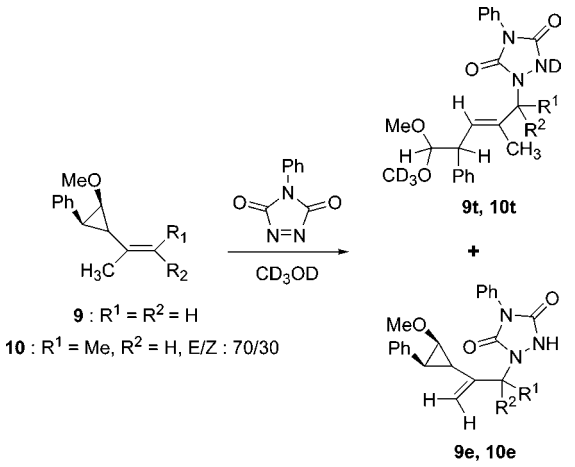
To test the biradical/dipolar intermediacy in the present system, alkenes **9** and **10** (Scheme 5) were prepared and their reactions with PTAD were performed in methanol and ethanol. Similarly to the PTAD addition toward **2** and **3** in methanol-d_4, the ene adducts **9e** and **10e** were formed in a relatively small percentage, while the only rearranged

(16) (a) Pasto, D. J. *Tetrahedron Lett.* **1973**, 713−716. (b) Sarel, S.; Felzestein, A.; Yovell, J. *Tetrahedron Lett.* **1976**, 451−452. (c) Shimizu, N.; Fujioka, T.; Ishizuka, S.; Tsuji, T.; Nishida, S. *J. Am. Chem. Soc.* **1977**, *99*, 5972−5977.

(17) Le Tadic-Biadatti, M.-H.; Newcomb, M. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1467−1473.

(18) (a) Newcomb, M.; Chestney, D. L. *J. Am. Chem. Soc.* **1994**, *116*, 9753−9754. (b) Newcomb, M.; Le Tadic-Biadatti, M.-H.; Chestney, D. L.; Roberts, E. S.; Hollenberg, P. F. *J. Am. Chem. Soc.* **1995**, *117*, 12085−12091.

Scheme 5. PTAD Addition to Olefins **9** and **10** in CD_3OD

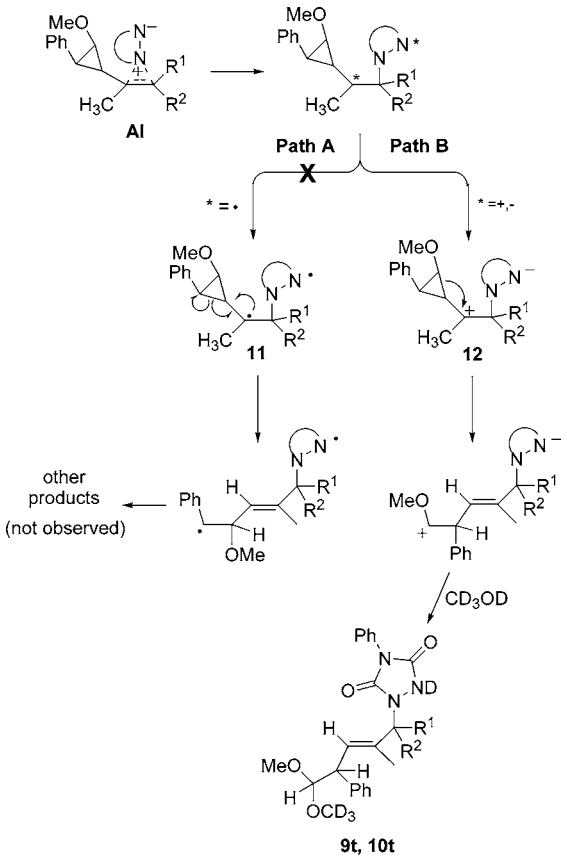


trapping products detected were **9t** and **10t** (Scheme 5). When ethanol was used as the solvent, analogous ethanol-trapping adducts were again isolated. These results strongly support the formation of a dipolar and not a biradical intermediate. In this case, the dipolar intermediate may or may not be precended by an AI intermediate.

According to our previous discussion, out of the two possible mechanistic pathways (Scheme 6), biradical (path A) or dipolar (path B), only path B occurs, leading to cyclopropyl carbinyl cation **12**. Subsequent regiospecific cyclopropyl ring opening from the side of the methoxy substituent afforded the rearranged methanol adducts **9t** and **10t**. In light of these results, it is difficult to argue for the previously proposed biradical intermediate.[11] In that case, path A would be favored, and products other than **9t** and **10t** would have been detected.

In conclusion, we have shown for the first time that the mechanism of the RTAD ene reaction depends on the nature of the solvent. Whereas in non-hydroxylic solvents it proceeds via the well established aziridinium imide (AI) intermediate, leading only to ene adducts, the cyclopropyl rearranged products formed in hydroxylic solvents strongly support a dipolar and not a biradical mechanism.

Scheme 6. Possible Trapping Products from the Addition of PTAD to Alkenes **9** and **10** in CD_3OD



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Supporting Information Available: Detailed experimental procedures and ^1H and DNOE NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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