Pergamon

Tetrahedron Letters, Vol. 38, No. 36, pp. 6437-6440, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01471-8

An Interplay in the Regioselectivity Induced by Non Bonding Interactions, in the *ene* Reactions of Singlet Oxygen and Triazolinediones with Tetrasubstituted Alkenes

Yiannis Elemes[*a], Manolis Stratakis[*b] and Michael Orfanopoulos[*c]
[a]*Department of Chemistry, University of Ioannina, 45110 Ioannina, Greece.*
[b]*Department of Natural Sciences, University of Cyprus, 1678 Nicosia, Cyprus.*
[c]*Department of Chemistry, University of Crete, 71409 Iraklion, Greece.*

Abstract: The ene reactions of N-phenyl-1,2,4-triazoline-3,5-dione (PTAD) and singlet oxygen ($^1O_2$) with tetrasubstituted alkenes, follow regioselectivity trends governed mainly by 1,3- non bonded interactions (type I) for the case of PTAD, and mainly by the steric hindrance caused during the formation of the new double bond (type II) for the case of $^1O_2$. The results are explained in terms of a "late" product forming transition state of hydrogen abstraction for triazolinediones and an "early" transition state for the analogous singlet oxygen reaction.

The ene reactions of singlet oxygen[1] and triazolinediones[2] with alkenes, has received a considerable mechanistic attention. It was found that both electrophiles react with alkenes forming structurally similar intermediates (aziridinium imide [AI] and perepoxide [PE] respectively), and their ene stereoselectivity occurs at remarkably similar manner. So far, the only substrates that show a significant deviation in product stereoselectivity are the allylsilanes.[3] Recent studies dealing with the regioselectivity revealed the importance of non bonded interactions in the product forming transition states.[4] The non bonded interactions in the possible transition states of the ene reactions that contribute in the stability of the transition states, can be classified into two major types as shown in scheme I : a) Repulsive 1,3-interactions between the bridgeheaded heteroatom of AI or PE intermediates and the bulky allylic or vinylic substituent (Type I), which directs the regioselectivity either adjacent,[4a,b] or geminal[4c-e] to the large substituent, and b) repulsive interactions between the alkyl groups during the formation of the new double bond (Type II) that adopt a cis arrangement. Both types of interactions contribute to the higher energy barrier of the product forming transition states.

We report in this communication a mechanistic comparison in the regioselectivities of the ene reactions of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) and $^1O_2$ with a series of symmetrical tetrasubstituted alkenes **1-4**,[5] which indicates a significant difference in the structure of the product forming transition states, that affects the distribution of the ene products. With a systematic variation of the alkyl group size, we followed the regioselectivity of the reaction balancing between the two types of non bonded interactions described above.

The results are summarized in Table 1. For discussion purposes, comparison of the regioselectivities in the reactions of PTAD and $^1O_2$ was done with the structurally similar disubstituted alkenes **5-8**.

Dedicated to Professor Gerasimos J. Karabatsos, on the occasion of his 65th birthday

Scheme I

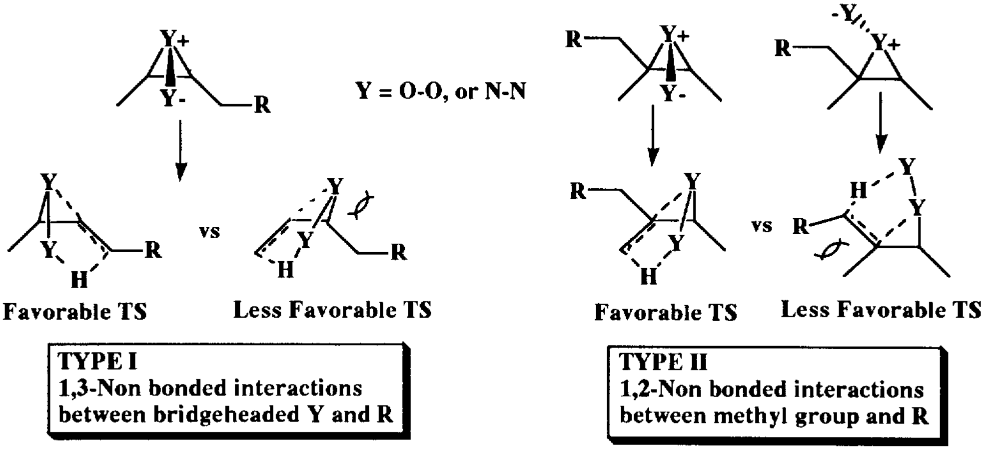
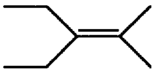
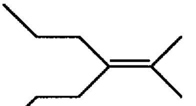
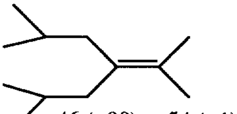
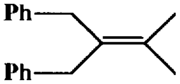
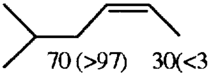
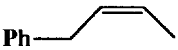


Table 1. Regioselectivity Trends[a] in the Reactions[b] of Singlet Oxygen and PTAD With Symmetrical Tetrasubstituted and *cis* Disubstituted Alkenes.

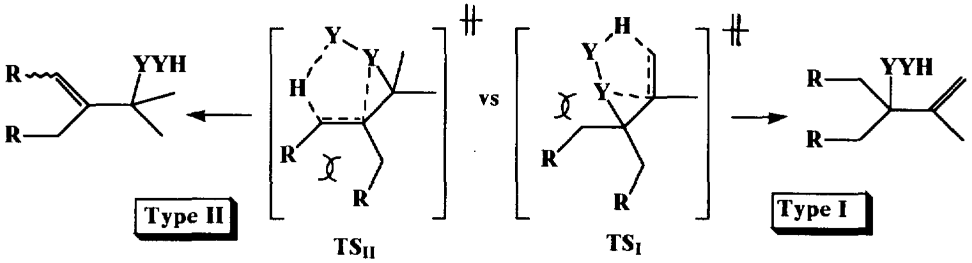
 30 (37) 70 (63) **1**	 5 (70) 95 (30) **2**	 46 (>99) 54 (<1) **3**	 48 (>99) 52 (<1) **4**
 50 (50) 50 (50) **5**	 50 (60) 50 (40) **6**	 70 (>97) 30(<3) **7**	 70 (>97) 30(<3) **8**

[a] Numbers indicate percentages of double bond formation with singlet oxygen and those in parentheses with PTAD. [b] The numbers are not statistically corrected per H-atom in each site of the double bond. In the reaction of $^1O_2$ with alkenes **3** and **4**, the methylenic hydrogen abstraction products, appear as a 50/50 and 60/40 ratio respectively of the stereoisomers whose stereochemistry was not assigned. Also in the addition of PTAD to **3**, the ene products appear as a 80/20 ratio of the stereoisomers.

We start our discussion with the earlier reported[2a,4a] reaction of $^1O_2$ and PTAD with *cis*-2-pentene (**5**) whose methyl and methylene allylic hydrogens are equally reactive for both electrophiles. By adding a methyl and an ethyl group in the unsubstituted side of the double bond of alkene **5** to produce **1**, a preference for hydrogen abstraction from the methyl end of the double bond is observed for both electrophiles. This result indicates that type II interactions between the R substituent (here R = methyl) disfavor transition state TS_{II}

compared to TS$_I$ where these interactions are absent (Scheme II). Also, the 1,3- non bonded interactions (type I) in TS$_I$ are not important since R is too small (methyl). Consequently, TS$_I$ leads predominantly to hydrogen abstraction from the methyl groups of **2** to produce the corresponding ene product.

Scheme II



In compound **2** where the size of the alkyl group R has increased from methyl to ethyl, both types of non bonded interactions are expected to be present in the TS's, however a dichotomy in the regioselectivity is observed revealing a different balance between the two types of repulsions. It is evident that an extra methyl group is enough to add relatively strong type I interactions in AI for the case of PTAD, which clearly predominate over type II interactions affording a 70/30 ratio of the ene products, favoring double bond formation at the propyls site. If we consider the roughly similar ene regioselectivity observed in the reaction of the cis disubstituted analogue **6**, (60/40),[4a] we can conclude that the bulky PTAD is more sensitive to type I interactions than to type II when they coexist in a transition state. On the other hand, the reaction of singlet oxygen with substrate **2**, results a dramatic shift in the regioselectivity, compared to PTAD. The "opposite" ene products was formed in a ratio 5/95, regardless that the regioselectivity observed in the reaction with substrate **6**[6] (free of type I interactions) is absent. This result indicates that for $^1O_2$, type II non bonded interactions predominate over type I.

In substrate **3**, type I interactions increase substantially because of the two geminal isobutyl groups. These groups constibute to a substantial increase of 1,3- non bonded interactions leading to the adduct with exclusive double bond formation next to the isopropyl group, for the case of PTAD. However for $^1O_2$, type I and type II interactions constibute almost equally in the TS's of the reaction, resulting to ene adducts with roughly equal percent (46/54) double bond shift.

Analogous results to substrate **3** are obtained for both electrophiles in the case of the sterically similar geminal diphenyl substituted alkene **4**, indicating that for singlet oxygen only the size of the substituent is important, whereas electronic effects of the phenyl rings are negligible (conjugation of the new double bond with the phenyl).

In conclusion we have shown that the regioselectivity of the ene reactions of PTAD and $^1O_2$ with tetrasubstituted alkenes, depends either on interactions during the formation of the new double bond (type I), or on the 1,3- interactions of the bridgeheaded heteroatom with the bulky alkyl substituents (type II). In the case of PTAD, type I non bonded interactions are predominant. On contrary, type II non bonded interactions, play a very significant role for the $^1O_2$ ene reactions. This interesting dichotomy in regioselectivity can be also expressed in terms of a "late" product forming transition state for PTAD, and a relatively "early" transition state for the singlet oxygen reaction. An "early" transition state for singlet oxygen disfavors the 1,3- non bonded interactions to be developed to a significant degree, while the new double bond has been formed to a less extend (small percentage of allylic C-H bond breaking). Therefore substantial type II interactions develop in the transition state, and are responsible for the observed regioselectivity in the $^1O_2$ ene reactions. On the other hand in a "late" transiton state for PTAD, the pronounced double bond formation favors 1,3- non bonded interactions to be predominant. The above mentioned "early" and "late" transition states, are also consisted with the small isotope effects (k_H/k_D = 1.4) measured with singlet oxygen,[7] and the large isotope effects ($k_H/k_D \sim 5$), measured with PTAD[8] in their ene reactions with tetramethylethylene.

Aknowledgements

This work was supported by M. & S. Hourdakis SA and by NATO grant No CRG 931419.

REFERENCES AND NOTES

1. a) Wasserman, H. H.; Murray, R. W. Singlet Oxygen, Academic Press, New York, 1979. b) Stephenson, L. M.; Grdina, M. B.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, 13, 419-25. c) Frimmer, A. A.; Stephenson, L. M. *Singlet oxygen, reactions, modes and products*, A. A. Frimer Eds. CRC Press. Boca Raton FL. 1985 vol. II, Chapter 3, pp. 68-87. d) Foote, C. S.; Clennan, E. L. in *Active Oxygen in Chemistry*; Foote, C. S.; Valentine, J. S.; Greenberg, A.; Liebman, J. F. Eds; Chapman and Hall, London 1995; pp. 105-140. e) Prein, M.; Adam, W. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 477-94.
2. a) Cheng, C. C.; Seymour, C. A.; Petti, M. A.; Greene, F. D.; Blount, J. F. *J. Org. Chem.* **1984**, 49, 2910-16. b) Elemes, Y.; Foote, C. S. *J. Am. Chem. Soc.* **1992**, 114, 6044-50. c) Squillacote, M.; Mooney, M.; De Felippis, J. *J. Am. Chem. Soc.* **1990**, 112, 5364-65. d) Poon, T. H. W.; Park, S. H.; Elemes, Y.; Foote, C. S. *J. Am. Chem. Soc.* **1995**, 117, 10468-73.
3. Adam, W.; Schwarm, M. *J. Org. Chem.* **1988**, 53, 3129-30.
4. a) Elemes, Y.; Stratakis, M.; Orfanopoulos, M. *Tetrahedron Lett.* **1989**, 30, 6903-06. b) Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *Tetrahedron Lett.* **1989**, 30, 4875-78. c) Clennan, E. L.; Chen, X.; Koola, J. J. *J. Am. Chem. Soc.* **1990**, 112, 5193-99. d) Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *J. Am. Chem. Soc.* **1990**, 112, 6417-19. e) Orfanopoulos, M.; Elemes, Y.; Stratakis, M. *Tetrahedron Lett.* **1990**, 31, 5775-78. f) Orfanopoulos, M.; Stratakis, M.; Elemes, Y.; Jensen, F. *J. Am. Chem. Soc.* **1991**, 113, 3180-81. g) Stratakis, M.; Orfanopoulos, M. *Tetrahedron Lett.* **1995**, 36, 4291-94.
5. Alkene **1** was prepared according to a literature procedure, starting from isobutyric acid and diethyl ketone : Adam, W.; Baeza, J.; Liu J-C. *J. Am. Chem. Soc.* **1972**, 94, 2000-06. Alkenes **2-4** were prepared by mixed Ti(0) coupling of 4 equivalent of acetone with the 1 equivalent of the appropriate ketone : McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, 43, 3255-66.
6. Rautenstrauch, V.; Thommen, W.; Schulte-Elte, K. H. *Helv. Chim. Acta* **1986**, 69, 1638-43.
7. Grdina, B.; Orfanopoulos, M.; Stephenson, L. M. *J. Am. Chem. Soc.* **1979**, 101, 3111-12.
8. Seymour, C. A.; Greene F. D. *J. Am. Chem. Soc.* **1980**, 102, 6384-85.

(*Received in UK* 12 *May* 1997; *accepted* 18 *July* 1997)