

0040-4039(95)00742-3

## Anti "cis Effect" Selectivity in the Reaction of Singlet Oxygen with Trisubstituted Alkenes

## Manolis Stratakis and Michael Orfanopoulos\*

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

**Abstract:** In the reaction of singlet oxygen with certain trisubstituted alkenes, a strong preference for regioselectivity favoring hydrogen abstraction on that side of the olefin with one substituent has been recognized. These results are rationalized in terms of non bonded interactions and the lack of oxygen interaction with two allylic hydrogens in the same side of the double bond.

The *ene* reaction of singlet oxygen with non functionalized olefins exhibits a fascinating regio- and stereoselectivity (scheme I). In the reaction with di- and trisubstituted alkenes<sup>1</sup> the allylic hydrogens next to a bulky alkyl group are more reactive (eq. 1). For olefins with a bulky alkyl group at the vinylic or allylic position a remarkable geminal selectivity is observed<sup>2</sup> (eq. 2). The repulsive non bonded interactions seem to play the major role in the regioselectivity of these reactions.<sup>3</sup> In an earlier work, the side selectivity of <sup>1</sup>O<sub>2</sub> with trisubstituted alkenes<sup>4</sup> and enol ethers<sup>5</sup> had been recognized (eq. 3). Hydrogen abstraction in this case occurs on the more crowded side of the double bond (*cis effect*).



Scheme I

The "cis effect" selectivity has attracted the mechanistic interest of many organic chemists. Bartlett and Frimer,<sup>6</sup> in order to rationalize this effect, proposed a "hydrogen bond" type of interaction between the <sup>1</sup>O<sub>2</sub> and the allylic hydrogens of the olefin. Stephenson<sup>7</sup> suggested that the interaction between the LUMO of the oxygen and the "pseudo butadiene like" HOMO of the olefin stabilizes the transition state, thus leading to the formation of the proper perepoxide intermediate. Houk and coworkers,<sup>8</sup> based on STO-3G semiempirical calculations, rationalized the syn selectivity in trialkyl substituted alkenes in terms of barriers to rotation of the methyl groups. The lower the calculated rotational barrier to rotation, the higher the reactivity. For cycloalkenes, Schulte-Elte and Rautenstrauch<sup>9</sup> suggested that regioselectivity of the ene reaction is related to the conformation parameters of the reaction of <sup>1</sup>O<sub>2</sub> with *cis* alkenes and found that the activation entropy ( $\Delta S^{=}$ ) is more negative than in the reaction with the corresponding *trans* or *geminal* alkyl substituted alkenes and suggested that in the reaction limiting step there is some type of "positive interaction" between the oxygen and two allylic hydrogens of *cis* olefins.

In this communication we report results from a series of acyclic trisubstituted alkenes which show "anti cis effect" selectivity and discuss the possibilities under which trisubstituted alkenes may show similar selectivity. This type of selectivity has not been previously recognized and may shed some light on the factors controlling product formation. These results are summarized below.<sup>11</sup>



Numbers indicate percent of hydrogen abstraction in the reaction of  ${}^{1}\text{O}_{2}$  with the olefins.<sup>a</sup> For substrate 1, the ratio 75/25 was measured by stereospecifically labelling the *cis* or *trans* methyl group with CD<sub>3</sub>. (ref. 3)

Unlike the syn selectivity,<sup>4,7</sup> where the hydrogen abstraction occurs at the more substituted side of the olefin (alkenes 4, 5 and 7, ref.4b), photooxygenation of trisubstituted alkenes 1-3 impressively illustrates a strong preference for hydrogen abstraction on the less substituted side of the double bond.

Examination of the possible transition states leading to the major and minor product provides new insight into the "anti cis effect" selectivity. In  $TS_{II}$ , leading to the minor (endo) ene product, the nonbonded interactions involving the large *tert*-butyl group and the incoming oxygen are expected to be stronger than those in  $TS_{I}$ , where this steric interaction is absent.



Scheme II

Furthermore, unlike the "cis effect" where two allylic C-H units are available on the same side of the double bond, there is only one allylic C-H unit ( $TS_I$  and  $TS_{II}$ ) on each side of the double bond for "positive interaction" of the incoming oxygen, favoring equally the two transition states  $TS_I$  and  $TS_{II}$ . This observation indicates that non bonded interactions in  $TS_I$  and  $TS_{II}$  play the major role in the observed *anti cis* selectivity. Therefore, the product ratio 75/25 represents the ratio of the perepoxide intermediates PE<sub>I</sub> versus PE<sub>II</sub>, which is consistent with the fact that formation of PE<sub>II</sub> is less favorable due to steric repulsions.

The most dramatic *anti* selectivity is demonstrated in olefin 3, where only the *trans* methyl hydrogens react. This can be attributed to the fact that in  $TS_{III}$ , apart from the 1, 3 nonbonded interactions of the *tert*-butyl group with the oxygen, the *cis* configuration of the newly forming double bond places the methyl groups *cis* to each other, thus increasing its free energy of activation compared to  $TS_{IV}$ , where these nonbonded interactions are absent. Consequently,  $TS_{IV}$  leads exclusively to hydrogen abstraction from the methyl group to produce stereospecifically the "*anti cis effect*" ene product.



It is instructive to note here that the *anti* selectivity increases as the disubstituted side of the double bond becomes more crowded. This is illustrated with the trisubstituted alkenes 5,  $6^{14}$  and 3. Alkene 5 shows the normal "*cis effect*" selectivity where only the 10% of the *anti* ene adduct is formed. However, as the size of the *cis* alkyl substituent increases from methyl in 5, to isopropyl in 6 and *tert*-butyl in 3, the *anti* selectivity increases from 10% to 42% to >95% respectively. The same trend is also noted in substrate 8. A substantial deviation from "*cis effect*" selectivity is observed by replacing one methyl group in 7, to a tert-butyl group in 8. The totally unreactive methylenic hydrogens in 7 (*cis effect*) become reactive in 8, producing the exo ene adduct in a 38% yield.



In conclusion, we have shown that the *anti* selectivity for hydrogen abstraction of the ene reaction of trisubstituted olefins is related 1) to the degree of crowdedness of the more substituted side of the olefin, 2) to the non bonded interactions in the new double bond formation and 3) to the lack of interaction of oxygen with two allylic hydrogens.

Acknowledgments. We thank professor G. J. Karabatsos for valuable comments. The financial support of M & S. Hourdakis SA. and NATO grant No CRG 931419 are also acknowledged.

## **References and notes**

- a) Orfanopoulos, M.; Stratakis, M.; Elemes, Y. Tetrahedron Lett. 1989, 30, 6903-06. b) Thomas A. F.; Pawlak, W. Helv. Chim. Acta 1971, 54. 1822-45.
- a) Orfanopoulos, M.; Stratakis, M.; Elemes, Y. J. Am. Chem. Soc. 1990, 112, 6417-19. b).Stratakis, M.; Orfanopoulos, M. Synth. Comm. 1993, 23, 425-30. c) Clennan, E. L.; Chen, X.; Koola, J. J. J. Am. Chem. Soc. 1990, 112, 5193-99. d) Adam, W., Richter, M.J. Tetrahedron Lett. 1993, 34, 8423-26.
- 3. Orfanopoulos, M.; Stratakis, M.; Elemes, Y.; Jensen, F. J. Am. Chem. Soc. 1991, 113, 3180-81.
- a) Schulte-Elte, K. H.; Muller, B. L.; Rautenstrauch, V. Helv. Chim. Acta 1978, 61, 2777-83
  b) Orfanopoulos, M.; Grdina, M. B.; Stephenson, L. M. J. Am. Chem. Soc. 1979, 101, 275-76.
- a) Rousseau, G.; Leperchec, P. Conia, J. M. Tetrahedron Lett. 1977, 18, 2517. b) Ledral, D.; Foote, C. S. Tetrahedron Lett. 1978, 19, 3227.
- a) Frimer, A.A.; Bartlett, P. D.; Boshung, A. F.; Jewett, J. D. J. Am. Chem. Soc. 1977, 99, 7977.
  b) Bartlett, P.D; Frimer, A. A. Heterocycles 1978, 11, 419.
- a) Stephenson, L. M. Tetrahedron Lett. 1980, 21, 1005-08, b) Stephenson, L. M.; Grdina, M. B.; Orfanopoulos, M. Acc. Chem. Res. 1980, 13, 419-425.
- 8. Houk, K. N.; Williams, J. C.; Mitchell, P. A.; Yamaguchi, K. J. Am. Chem. Soc. 1981, 103, 949-51.
- 9. Schulte-Elte, K. H.; Rautenstrauch, V. J. Am. Chem. Soc. 1980, 102, 1738-40.
- a) Hurst, J. R.; McDonald, J. D.; Schuster, G. B. J. Am. Chem. Soc. 1982, 104, 2065-67. b) Hurst, J. R.; Wilson, S. L.; Schuster, G. B. Tetrahedron 1985, 41, 2191-97.
- 11. The synthesis of olefins 1-3 and 8 was accomplished as follows. The synthesis of olefins 1-E and 1-Z (CD<sub>3</sub>) is in reference 3. Olefin 2 was synthesized according to the literature<sup>12</sup>, by reacting 2-butyne, t-butyl chloride and ZnCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>. The resulting E-vinylic chloride was reduced stereospecifically to the alkene with Na in liquid NH<sub>3</sub>. The Z/E ratio was found to be 93/7. {<sup>1</sup>H NMR [acetone-d6]: 5.21 (q, 1H J = 7.2 Hz), 1.71 (d, 3H J = 7.2 Hz), 1.66 (s, 3H), 1.13 (s, 9H)}. Olefin 3 was prepared in 80% geometric purity by coupling the ylide from triphenyl phosphine and 2-bromo butane with pivalaldehyde. {<sup>1</sup>H NMR [acetone-d6]: 5.11 (s, 1H), 2.12 (q, 2H J=8.4 Hz), 1.63 (d, 3H J= 1.2 Hz), 1.08 (s, 9H), 0.98 (t, 3H J=8.4 Hz)}. The E isomer 8, was prepared surprisingly in 95% geometrical purity by reacting<sup>13</sup> the dianion of 2-methyl butyric acid with pivalaldehyde, subsequent lactonization of the resulting hydroxy acid and finally pyrolysis of the α-lactone. {<sup>1</sup>H NMR [acetone-d6]: 5.11 (s, 1H), 1.95 (q, 2H J = 7.6 Hz), 1.71 (d, 3H J = 1.2 Hz), 1.08 (s, 3H), 0.95 (t, 3H J = 7.6 Hz)}.
- 12. Marcuzzi, F.; Melloni, G. J. Chem. Soc. Perk. Trans. II 1976, 1517.
- 13. Adam, W.; Baeza, J.; Liu, J. C. J. Am. Chem. Soc. 1972, 94, 2000-06.
- 14. Olefin 6 was prepared in more than 97% geometric purity by stereospecific coupling of the stabilized ylide from methyl 2-bromo butyrate and PPh3 with isobutyraldehyde to form the α,β- unsaturated methyl ester followed by reduction of the ester group to form the allylic alcohol with LiAlH4/AlCl3 and finally reaction of the allylic alcohol mesylate with LiAlH4 in diglyme. {<sup>1</sup>H NMR [acetone-d6] : 4.90 (d, 1H J = 9.6 Hz), 2.50 (m, 1H), 2.03 (q, 2H J = 8 Hz), 1.62 (d, 3H J = 1.6 Hz), 0.93 (t, 3H J = 6.2 Hz), 0.88 (d, 6H J = 7.2 Hz)}.

(Received in UK 24 February 1995; revised 19 April 1995; accepted 21 April 1995)