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Reaction Profile of the Photooxygenation of Trisubstituted Alkenes

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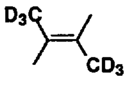
Abstract: Photooxygenation of a series of isotopically-labeled trimethylethylenes shows that formation of the perepoxide intermediate is rate-determining.

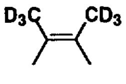
The mechanism of the ene reaction of singlet oxygen with alkenes has attracted the interest of many organic chemists in the past two decades, primarily because of its unusual regio-and stereoselectivity.[1] The synthetic applications[2] of the initially formed allylic hydroperoxides are also remarkable. Isotope effect measurements in the series of the isomeric tetramethylethylenes-d_6 (TME-d_6) have shown that the reaction proceeds through a perepoxide intermediate.[3] A value of k_H/k_D=1.4 was measured for TME-*trans* and TME-*gem*, where the competing methyls are in a *cis* configuration. In contrast, for TME-*cis*, since there is no isotopic competition on the same side of the double bond, only a very small isotope effect was observed. These results established that the rate-determining step in the ene photooxygenation of tetrasubstituted alkenes is the formation of the perepoxide intermediate.[3]

TME-trans



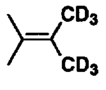
$k_H/k_D = 1.4$

TME-cis



$k_H/k_D = 1.06$

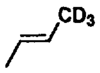
TME-gem



$k_H/k_D = 1.4$

Similar experiments[4] on the reaction of $^1O_2$ with the disubstituted *cis*- and *trans*-2-butenes-1,1,1-d_3 showed that in the case of the less reactive *trans* -disubstituted alkenes, hydrogen abstraction is competitive with the formation of the perepoxide intermediate (i.e. k_H/k_D *trans* is smaller than k_H/k_D *cis*).

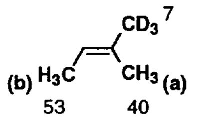
$k_H/k_D = 1.4$



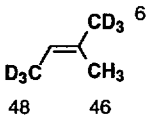
$k_H/k_D = 1.25$

Although the reaction profile of tetrasubstituted and disubstituted alkenes has been well established, there is no detailed study concerning the reaction mechanism of the moderately reactive trisubstituted alkenes. In this communication, we report in detail the regioselectivity of the singlet oxygen ene reaction of various isotopically labeled isomeric trimethylethylenes, and provide evidence that the formation of the perepoxide is the rate determining step. The results are summarized in Table 1.

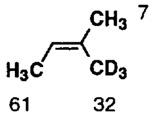
Table 1. Stereoselectivity in the Ene Reaction of $^1O_2$ with Trimethylethylenes **1-6**



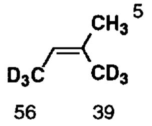
$\mathbf{1}^a$



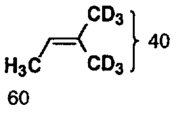
$\mathbf{2}^b$



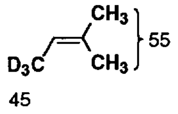
$\mathbf{3}^b$



$\mathbf{4}^b$



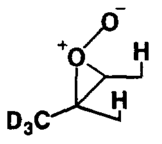
$\mathbf{5}^a$



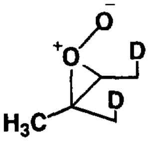
$\mathbf{6}^a$

Reaction products were determined by ^1H NMR integration of the appropriate signals on a Brucker 360-MHz spectrometer. The error was ±5%. Numbers next to the methyl groups indicate percent of hydrogen abstraction. [a]Reference 3. [b]This work.

Substrates **1-6**[5] react smoothly with singlet oxygen generated by irradiation of tetraphenylporphyrin in $CDCl_3$ with an ILS Technology Cermax 300-W Xenon lamp under an oxygen atmosphere. The ene products were determined by ^1H NMR integration of the appropriate signals. In Table 1, the reactivity of the remote methyl group (*cis* to hydrogen) is small regardless of isotopic substitution ($-CH_3$ or $-CD_3$), and varies from 5 to 7 % (substrates **1-4**). This result is consistent with the well known "*cis* effect" selectivity in $^1O_2$ reaction with trisubstituted alkenes.[1a] It also indicates that methyl groups in the *trans*-relationship do not compete for isotopic H or D abstraction, as in TME-*cis*. Large changes in product distribution are observed only on the more crowded side of the olefin, where the competing methyl groups are *cis* to each other. For example, when either of the methyl groups (b) or (a) in alkene **1** (Table 1), is replaced by a $-CD_3$ to produce compounds **2** and **3** respectively, the reactivity of the *cis* methyl groups changes substantially, while the reactivity of the *trans* methyl group remains unaffected. Furthermore, replacement of both (a) and (b) methyl groups in **1** by CD_3 to produce compound **4** again gives a similar product distribution. In this case, the intermediate perepoxides PE_1 and PE_2, which lie on the most crowded side of the double bond, do not compete for H and D abstraction. Thus, the relative reactivity of the *cis* methyl groups in **1** and **4** is very similar, 53 : 40 vs. 56 : 39, regardless of isotopic substitution. These results, i.e. intramolecular competition for H and D only between *cis* groups, require the formation of the perepoxide intermediate to be the rate determining step.



PE_1



PE_2

By using the isotope effect $k_H/k_D = 1.4$ for *cis* competition (from TME), and averaging the reactivity of the remote methyl group to 6%, it is possible to predict successfully the ene product distribution from on replacement of $-CH_3$ by $-CD_3$ (and vice versa). For example, in going from **1** to **2** and **5**, the competition between the two *cis* methyl groups is affected by a factor of 58 % : 42 % ($k_H/k_D = 1.4$). Based on the inherent reactivities of the three positions in **1** (Table 1), the new product distribution for the photooxygenation of compounds **2**-**6** can be predicted quantitatively. This is done by applying the following equation:

% inherent reactivity of (a) x (0.58) x (A) + % inherent reactivity of (b) x (0.42) x (A) = 94% **Eq. 1**

where (A) is a normalizing factor. The results are summarized in Table 2, where there is good agreement between the predicted and observed results.

Table 2. Predicted and Observed Product Distribution from the Photooxygenation of **2**-**6**.

Alkene	Methyl group	[a](A)	% Predicted	% Found
2	(a)	2.06	47.8	46
	(b)	"	45.8	48
3	(a)	1.98	33.2	32
	(b)	"	60.8	61
4	(a)	2.02	40.4	39
	(b)	"	53.5	56
5	(a)	1.98	33.2	34
	(b)	"	60.8	60
6	(a)	2.06	47.8	49
	(b)	"	45.8	45

[a] Normalization factor calculated by solving Equation 1.

In conclusion, in the photooxygenation of deuterium labeled trisubstituted alkenes, we determined: (1) *syn* regioselectivity is 93 - 95 %; (2) the reactivity of the remote methyl group is unaffected by isotopic substitution; and (3) $k_H/k_D = 1.4$ for $-CH_3$ and $-CD_3$ groups in the *cis* configuration. These results support the formation of the perepoxide intermediate as the rate determining step. This report completes a comprehensive study of the general reaction profile of the ene reaction, from the very reactive tetrasubstituted to the less reactive disubstituted olefins. The tetrasubstituted and trisubstituted alkenes share a rate-determining second (product-determining) step, whereas in the Disubstituted alkenes, because the first step is slower, both steps play a part in determining the rate.

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4. Orfanopoulos, M.; Smonou, I.; Foote, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 3607-3614.
5. Olefins **3** and **4** were prepared by coupling the stabilized ylide methyl (triphenylphosphoranylidene) propionate-3,3,3-d_3 with acetaldehyde-d_4 acetaldehyde to give the (E) esters. The (E) esters were reduced to the olefins in two steps, first with $AlCl_3/LiAlH_4$ and then with $LiAlH_4$ addition to the allylic alcohol mesylate. Olefin **2** was prepared by first coupling the stabilized ylide methyl(triphenylphosphoranylidene)propionate-3,3,3-d_3 with acetaldehyde-d_4. and then reducing to the (E) ester in two steps as in the cases of **3** and **4**.

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