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On the Origin of Geminal Regioselectivity in the Ene Reaction of Singlet Oxygen with Substituted Alkenes

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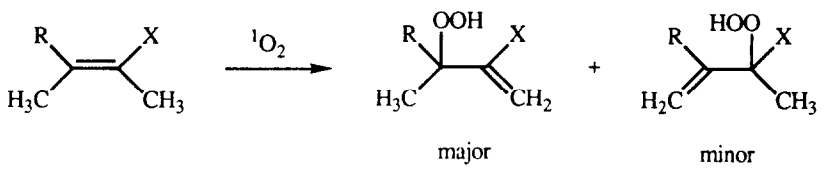
Abstract: *The geminal regioselectivity observed in the ene reaction between singlet oxygen and alkenes with anion-stabilizing groups is rationalized on the basis of a perepoxide intermediate, in which in analogy to the nucleophilic attack on protonated epoxides, the perepoxide is opened preferentially at the C-O bond weakened by the substituent.*

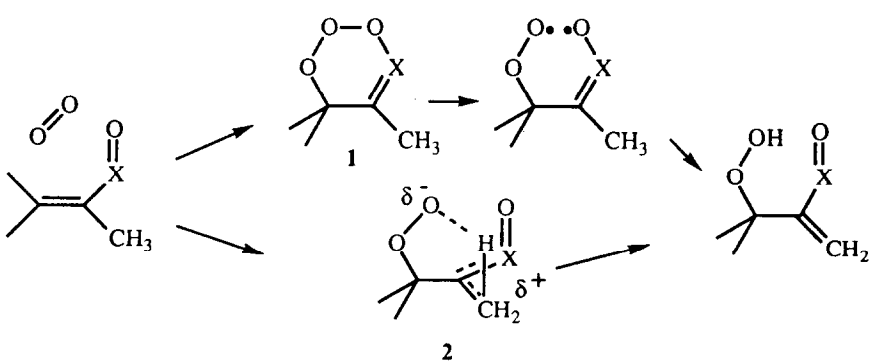
The ene reaction of singlet oxygen ($^1O_2$) with alkenes, which bear anion-stabilizing groups, has received considerable mechanistic interest[1]. It has been documented that hydrogen abstraction occurs regioselectively at the alkyl group geminal to functional groups such as aldehyde,[1a] keto,[1b,c] acid[1d], ester,[1e] amide,[1a], aldimine,[1f,g] oxazoline,[1h] cyano,[1a] and sulfoxide[1i] substituents (eq 1). Additionally, this geminal regioselectivity was observed also for vinyl silanes[2] and vinyl stannanes.[3]



(1)

X = CHO , CO_2H , CO_2R , $CONR_2$, CH=NtBu , CN ,  , SOPh , SiR_3 , SnR_3

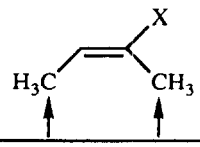
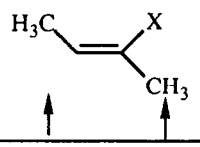
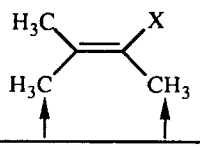
Several explanations have been offered to account for this geminal preference. Thus, for the reaction of $^1O_2$ with unsaturated carbonyl substrates and derivatives,[1b] a [4+2] cycloadduct **1** (eq 2) was proposed,



(2)

cognizant of the fact that enones which are able to adopt the *s-cis* conformation are reactive. Homolysis and hydrogen atom abstraction at the geminal site leads to the observed ene product. A similar mechansim was proposed for unsaturated sulfoxides.[1i] Recently, this mechanism was shown to be unlikely;[1c] on one hand certain enones fixed in the *s-trans* conformation also react with $^1O_2$ *gem*-selectively to the ene product, and on the other hand, asymmetric induction expected for the [4+2] cycloaddition to chiral oxazolines[1h] was not observed. An alternative mechanism has been proposed[1c], in which the dipolar intermediate **2** is responsible for the geminal hydrogen atom abstraction. However, accumulation of a partial or even full positive charge α to the carbonyl group, as in the dipolar intermediate **2** (eq 2), is questionable. Steric effects[2c] may contribute in the control of regioselectivity, but cannot be the sole origin since goups definitely smaller than t-butyl induce higher selectivity (Table).

Table. Geminal Regioselectivities in the Ene Reaction of $^1O_2$ with Functionalized Olefins

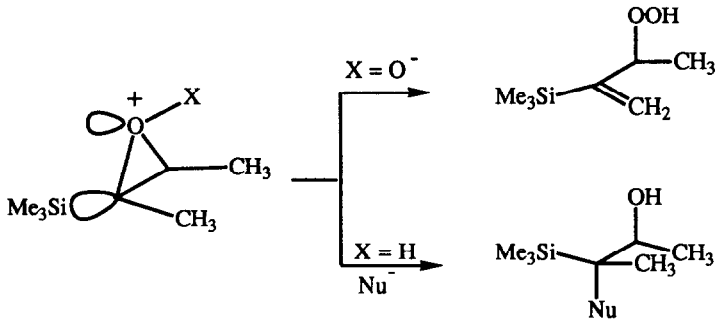




X							ref.
COOMe	<3[a]	>97	14	86	12	88	1c
COOH	-	100					1d
CHO	-	100					1a
CHNR	-	100					1f,g
SOPh	-	46[b]	no rct		-	80[b]	1i
$SiMe_3$	3	97	24	76	-	100[c]	d
$SnMe_3$	11	89	42	58	7	93	3
tBu	34	66					2c
Ph	10	90	36	64	26	74	2c

[a] Percent hydrogen abstraction; [b] isolated yield; [c] from ref. 2c; [d] this work, photooxygenation of mixtures with different *E/Z* ratios of the vinyl silane (Ref. 9) in $CDCl_3$ with tetraphenylporphine as sensitizer at -5 °C, extrapolated to pure isomers.

The geminal selectivity, found in the $^1O_2$ ene reaction of vinyl silanes, has been mechanistically rationalized on the basis of a perepoxide intermediate, as supported by MO calculations.[2a] Experimental evidence for the occurrence of such species has been documented in the ene reaction of simple alkenes and unsaturated esters with $^1O_2$.[4] In a silyl-substituted perepoxide an antibonding interaction between the lone pair at the proximal oxygen and the occupied orbital of the C-Si σ bond, which lies sufficiently high in energy, leads to a weakening of the C-O bond α to silicon (eq 3). Consequently, this bond is preferentially broken, to afford after H transfer the observed ene product. Replacement of the distal oxygen in the perepoxide by a proton leads to a protonated epoxide, which according to MO calculations[2a] possesses a weaker C-O bond α to the silyl substituent, so that nucleophilic ring-opening proceeds regioselectively at this site[5] and, therefore, matches the geminal regioselectivities of the $^1O_2$ ene reaction.

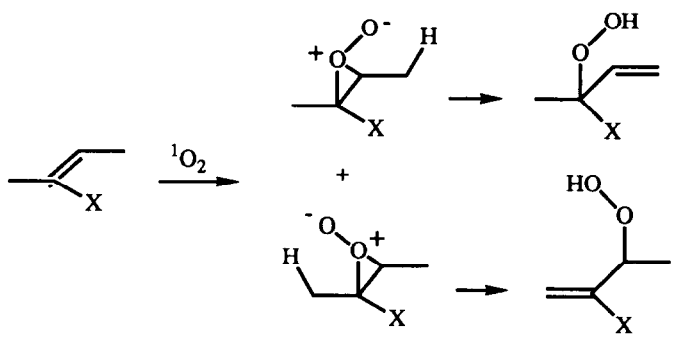
We propose that this mechanism has general validity and applies as well to the $^1O_2$ ene reaction with unsaturated carbonyl compounds and sulfoxides. Consequently, the decisive intermediate is a perepoxide in which the proximate C-O bond is weakened by interaction with the C=O, C=N or S=O groups. The propensity



(3)

of carbonyl groups to destabilize the neighboring C-O bond in epoxides is experimentally well documented in that nucleophilic ring-opening of a ketone or ester-substituted epoxide proceeds regioselectively at the α position,[6] completely analogous to the silylated epoxides. Indeed, recent MO calculation carried out on protonated epoxides[7] confirmed that the C-O bond next to a formyl or aldimino group is the longer and the weaker, in agreement with the displayed reactivity. The same bond elongation is also predicted to be induced by alkenyl and aryl C=C double bonds,[7] which implies that a phenyl group should also display geminal regioselectivity. The Table shows that this is the case,[8] a fact that has not been previously recognized.[1] The origin of this bond elongantion by C=O and C=C bonds may be attributed to the withdrawl of electron desity from the epoxide bonds to the π* orbital, analogous to the model proposed for acceptor-substituted cyclopropanes,[10] which show the same bond elongation phenomenon.[11]

This model applies rigorously only to alkenes with *cis* alkyl groups at the β position with respect to the interacting functionality. For such stereoisomers the *cis* effect[12] operates, which dictates the preferred perepoxide intermediate and regioselectivity is subsequently controlled by breaking of the weaker C-O bond, namely geminal to the functional group. For alkenes with *trans* alkyl groups, the geminal regioselectivity is generally lower (cf. Table). Here two possible perepoxide intermediates may intervene (eq 4) and necessarily a mixture of



(4)

regioisomers results, whose composition is a function of which regioisomer of the perepoxide is of lower energy and not which C-O bond in the perepoxide is weaker. *A priori* it is difficult to assess which perepoxide is preferred, but steric factors seem to be more important for the *Z* alkenes, as has been shown for a series of vinyl stannanes.[3]

In the case of alkenes with three alkyl groups, also two perepoxides are possible, but in accord with the *cis* effect,[12] the perepoxide in which the terminal oxygen atom points to the dialkyl-substituted side will dominate and high geminal regioselectivity as for the *E* alkenes should be observed. While this is the case for the silyl and stannyl derivatives, the ester- and phenyl-substituted alkenes show decreased geminal selectivity (cf. Table).

Again, steric interaction with the *cis* alkyl group may cause rotation of the functional group out of the olefin plane and thus decrease orbital overlap between the epoxide C-O bond and the conjugating ester or phenyl groups. However, the interaction imposed on the spherically symmetric silyl and stannyl group should not be affected by rotation around the C-Si σ-bond.

In conclusion, the geminal regioselectivity of the $^1O_2$ ene reaction with acceptor-substituted olefins can be attributed to a weakening of the proximal C-O bond in the perepoxide intermediate by the substituent. This chemical fate of perepoxides is analogous to the nucleophilic ring-opening of protonated epoxides.

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