Reactions of Singlet Oxygen and *N*-Methyltriazolinediones with *β,β*-Dimethylstyrene. Exceptional Syn Selectivity in the Ene Products

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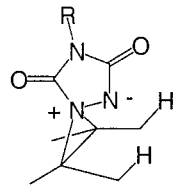
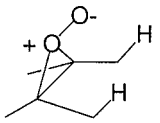
The ene reactions of singlet oxygen ($^1O_2$) and triazolinediones (RTAD, R = methyl or phenyl, usually) with alkenes are closely related mechanistically and exhibit a fascinating variety of regio- and stereoselectivities. Both reactions appear to proceed via intermediates; the singlet oxygen reaction via a "perepoxide" [1] and the RTAD reaction via an aziridinium imide (AI).[2] In the reaction of $^1O_2$ with trisubstituted alkenes[3] and enol ethers,[4] the more reactive side of the olefin is the more substituted one ("cis effect"), but there is very little Markovnikov selectivity. These results have been rationalized[5] by postulating an attractive interaction of singlet oxygen with allylic hydrogens on the more substituted side of the double bond. On the other hand, phenyl- and methyltriazolinedione (PTAD and MTAD) exhibit strong Markovnikov selectivity, giving products with the nitrogen exclusively on the less substituted carbon.[6]



Aziridinium imide



Perepoxide

In the reaction of $^1O_2$ and RTAD with cis-disubstituted alkenes, the major ene products arise from allylic hydrogen abstraction next to the bulkiest group.[7] Also, geminal selectivity[8] with respect to a bulky alkyl substituent at allylic or vinylic position is observed. These selectivities were rationalized in terms of nonbonded interactions in the product-forming transition states.[9] Furthermore, coordination of $^1O_2$ to hydroxyl[10] and amino[11] groups, or electronic repulsions with several other functionalities[12] in the allylic positions, can lead not only to highly threo or erythro diastereoselective ene reactions but also can control the regioselectivity.[13]

In this paper, we report an unprecedentedly high "cis effect" selectivity in the ene products from singlet oxygen and MTAD addition to *β,β*-dimethylstyrene (**1**). It was reported[12] several years ago that sensitized photooxygenation of **1** in several solvents affords a variable mixture of ene product (**1b**), benzaldehyde, and two diastereomeric diendoperoxides **1d** and **1e** in 68/32 ratio; diendoperoxides arise from initial [4 + 2] addition of $^1O_2$ to **1**, followed by a second addition of $^1O_2$ to the newly formed diene endoperoxide **1c**, (Scheme 1).

To distinguish the syn/anti stereosectivity of the ene products produced from the two geminal methyls, the *anti*-methyl group was specifically labeled (>99% geometrical purity) by a literature procedure.[15] The ene adducts can be separated from the reaction mixture by column chromatography using benzene as eluent. Examination of the syn/anti stereoselectivity of the ene products of **2** in different solvents revealed that there is a strong selectivity for attack on the methyl syn to the phenyl group. The magnitude of this selectivity depends on solvent polarity. On increasing the dielectric constant of the solvent, a substantial increase in the amount of hydrogen abstraction in the *syn*-methyl group occurs. For instance, the ratio of syn/anti ene products increases by a factor of 3.4 on going from CCl_4 to methanol (Table 1).

The intermolecular isotope effect upon competition of **1** with the deuterated olefin **3** in chloroform is negligible ($(k_H/k_D)_{total} = 1.00 \pm 0.02$), which means that formation of perepoxide is irreversible, as in other trisubstituted

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Scheme 1

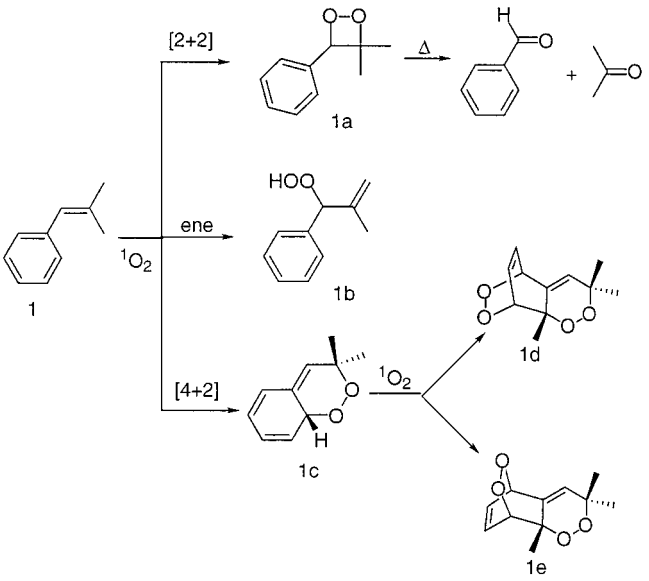
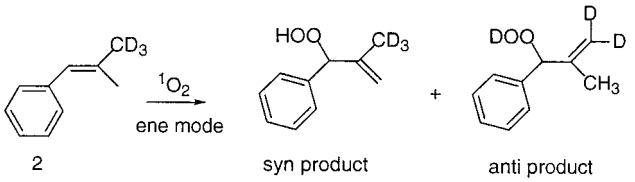


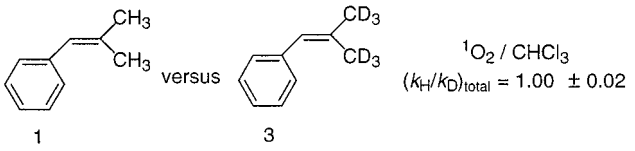
Table 1. Stereoselectivity of the Photooxygenation of 2 in a Variety of Solvents



solvent	sensitizer[a]	syn/anti selectivity
CCl_4	TPP	56/44
C_6H_6	TPP	57/43
$CHCl_3$	MB	63/37
CH_3CN	MB	71/29
CH_3OH	MB	82/18

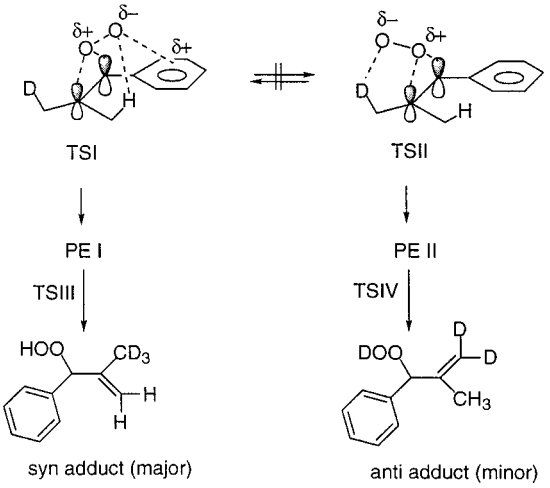
[a] TPP, tetraphenylporphine; MB, methylene blue.

alkenes.[16] It also requires a very early transition state, where rehybridization is negligible.



A possible mechanism that accounts for the observed results is depicted in Scheme 2. The incoming oxygen oriented toward the more substituted side of the olefin in TS_I interacts only with one allylic hydrogen, but this transition state affords the major product. In TS_{II}, which leads to the anti ene product (D-abstraction), oxygen also interacts only with one allylic hydrogen. Thus the extra stabilization for the preferential formation of the more hindered TS_I must arise from interaction of singlet oxygen with the phenyl group. In TS_I, the benzylic carbon is slightly electron-deficient and is stabilized by electron donation from the phenyl. Interaction of the negatively charged oxygen of the perepoxide with the partially positive phenyl results in stabilization of the syn transition state. On increasing the polarity of the

Scheme 2



solvent, this stabilization becomes more significant because the transition state becomes more polar.

We propose that an analogous interaction between the negatively charged oxygen of the perepoxide and the methoxy group (made electron deficient by its electron donation to the adjacent perepoxidic carbon) can also explain the "cis effect" behavior observed previously in the photooxygenation of trisubstituted enol ethers.[4]

Addition of *N*-methyl-1,2,4-triazoline-3,5-dione (MTAD) to **2** in CH_2Cl_2 at −78 °C or in $CDCl_3$ at rt affords the ene product exclusively, and with greater than 99% syn selectivity. No [2 + 2] or [4 + 2] adducts were observed, which would be expected to derive from a zwitterionic intermediate where the positive charge is stabilized by the phenyl. Zwitterionic intermediates have been proposed in the addition of PTAD to conjugated dienes[17] and substituted indenes.[18] Also, when the addition was carried out in 1/1 $MeOH/CH_2Cl_2$ at −78 °C, or in methanol-d_4 at rt, no methanol adducts (which are formed in many ene reactions with RTAD)[19] could be identified by ^1H NMR. Again, only the ene product was observed, with >99% syn selectivity.

In contrast to the singlet oxygen reaction, kinetic competition of **1** versus **3** gave a significant inverse intermolecular isotope effect $(k_H/k_D)_{total} = 0.76 \pm 0.02$ in $CHCl_3$, and 0.72 ± 0.02 in methanol ($k_H/k_D = 0.96$ per H atom), clearly revealing that formation of the AI is irreversible and that the transition state is much later than in the singlet oxygen reaction. The inverse isotope effect is caused by the change in hybridization of the olefinic carbons from sp^2 to sp^3 during the rate-determining step for formation of the intermediate, which favors deuterium over hydrogen; the transition state in AI formation is rather loose.[20]

These results are consistent with the formation of a syn AI intermediate between MTAD and **2** in the rate-determining step, with interaction of the incoming electrophile with the phenyl ring. Subsequent decomposition of the intermediate produces the ene products with the

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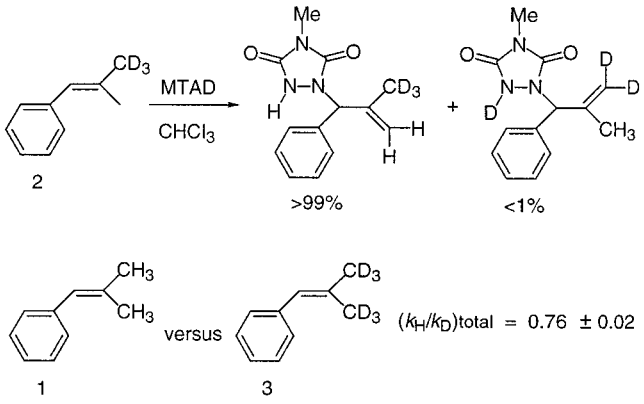

observed stereochemistry. The positive charge developed on the benzylic carbon during AI formation is much more substantial than that developed during perepoxide formation because of the later transition state, thus the phenyl−AI interaction is much more important. This interaction probably stabilizes the ene pathway, making it more energetically favorable[21] compared to the zwitterionic pathway.

In conclusion, we have shown for the first time that the phenyl ring of styrene substrates can dictate the syn/anti stereochemistry in their ene reactions with singlet oxygen and triazolinediones. We propose that a favorable interaction of the enophiles with the phenyl directs the orientation of perepoxide or the AI.

Experimental Section

All NMR spectra were taken in $CDCl_3$.

***β,β*-Dimethylstyrene (1).** This compound was synthesized by Wittig coupling of isopropylidene-triphenylphosphorane (from the phosphonium salt of 2-iodopropane) with benzaldehyde in 40% yield. Purification was accomplished by flash column chromatography (hexane/ether = 5/1). ^{1}H NMR: 7.12−7.36 (m, 5H), 6.27 (s, 1H), 1.90 (d, J = 1.3 Hz, 3H), 1.86 (d, J = 1.3 Hz, 3H).

Photooxygenation of 1. A solution of 100 mg of **1** in 10 mL of CCl_4 containing 10 mg of 2,6-di-*tert*-butylphenol as free radical scavenger was irradiated (TPP, 1×10^{-4} M as sensitizer) for 1.5 h at 0 °C. A filter was used to cut off wavelengths below 588 nm. The same procedure was followed in several other solvents (see Table 1). The products were fractionated on silica gel (benzene as eluent) and identified by NMR, according to their published spectroscopic data.[14a]

***N*-Methyl-1,2,4-triazoline-3,5-dione (MTAD) Addition to 1.** Solid MTAD was added to a solution of **1** in several solvents affording the ene product as the only product. ^{1}H NMR: 7.28−7.67 (m, 5H), 5.72 (s, 1H), 5.17 (s, 1H), 4.91 (s, 1H), 1.75 (s, 3H).

Synthesis of 2. (*E*)-Methyl α-Methylcinnamate. The corresponding acid was prepared according to a literature procedure.[22] In a flame-dried flask were placed 4.23 g of NaH (80% in oil, 150 mmol) and 120 mL of dry DME. The flask was cooled to 0 °C, and then 6 mL of triethyl phosphite (47 mmol) was added slowly dropwise. The solution was stirred for 30 min; then 3.9 mL of 2-chloropropionic acid was added slowly at 0 °C. A vigorous evolution of hydrogen gas was observed. After 1 h, 4.6 mL of benzaldehyde (45 mmol) was added and the mixture was stirred at rt for 5 h more and then quenched with saturated $NaHCO_3$ until alkaline pH was reached. The aqueous layer was acidified and extracted with ether. The crude unsaturated acid (^{1}H NMR: 7.87 (d, J = 1.6 Hz, 1H), 7.3−7.5 (m, 5H), 2.15 (d, J = 1.6 Hz, 3H)) was dissolved in 100 mL of methanol, and ∼100 mg of *p*-TsOH was added. The solution was refluxed for one night and then extracted with ether. The ether layer was washed with saturated $NaHCO_3$ and brine. The ether was removed to afford 3.2 g of ester (40% overall yield). GC and NMR analysis indicated the existence of only one isomer. ^{1}H NMR: 7.70 (d, *J* = 1.4 Hz, 1H), 7.30−7.41 (m, 5H), 3.82 (s, 3H), 2.13 (d, J = 1.4 Hz, 3H).

(*E*)-3-Phenyl-2-methylprop-2-en-1-ol-*1,1-d*$_2$. The α,β-unsaturated ester (3.1 g, 17 mmol) was added dropwise at 0 °C to a solution containing 0.76 g of $LiAlD_4$ (18 mmol) and 0.80 g of anhydrous $AlCl_3$. The $AlCl_3$ had been added in portions to the $LiAlD_4$ at 0 °C over a 15 min period. After 30 min, GC showed the disappearance of the starting material. The solution was quenched with HCl (1 N) and then extracted with ether to afford 2.2 g of allylic alcohol-d_2. ^{1}H NMR: 7.17−7.38 (m, 5H), 6.52 (s, 1H), 1.91 (d, *J* = 1.3 Hz, 3H), 1.62 (br s, 1H).

(*E*)-1-Phenyl-2-methylprop-1-ene-*3,3,3-d*$_3$ (2). The allylic alcohol was transformed to the allylic choride according to a literature procedure.[15] To a slurry of *N*-chlorosuccinimide (2.66 g, 20 mmol) in dry CH_2Cl_2 was added at 0 °C 1.75 mL of dimethyl sulfide. The reaction mixture became cloudy. After 30 min, the solution was cooled to −40 °C, and the allylic alcohol was added dropwise. The solution was stirred at low temperature for 3 h and then warmed at rt for 1 h. The allylic choride-d_2 was isolated by extraction with CH_2Cl_2 (∼2.2 g) and used directly in the next step without further purification. ^{1}H NMR: 7.21−7.38 (M, 5H), 6.59 (s, 1H), 1.99 (d, *J* = 1.4 Hz, 3H).

In a flame-dried flask were added 0.3 g of $LiAlD_4$ and 50 mL dry of THF. A solution of the allylic chloride-d_2 in THF was added dropwise at rt. The reaction mixture was left overnight. At that time, the allylic chloride had completely disappeared. The crude alkene was isolated by flash column chromatography over silica gel using hexane as eluant and finally distilled under vacuum. The geometric purity was > 97% by NMR. ^{1}H NMR: 7.17−7.33 (m, 5H), 6.27 (s, 1H), 1.86 (d, *J* = 1.3 Hz, 3H). ^{13}C NMR: 138.62, 135.16, 128.68, 127.94, 125.71, 125.23, 19.19. HRMS: calcd for $C_{10}D_3H_9$ 135.1127, found 135.1128.

Preparation of 3. Isopropyl-*d*$_7$-triphenylphosphonium Mesylate. The mesylate of 2-propanol-d_8 (SIC, 99.5% D) was prepared in 65% yield, by adding 1 equiv of $MeSO_2Cl$ to 1 equiv of 2-propanol-d_8 in dry CH_2Cl_2 containing 3 equiv of triethylamine at −10 °C. After 2 h of stirring at 0 °C, the mesylate was isolated by extraction with CH_2Cl_2. The organic layer was washed first with cold 1 N HCl then with saturated $NaHCO_3$ and finally with brine. ^{1}H NMR: 3.01 (s, 3H).

The neat mesylate was placed in a sealed tube and was heated with 1.2 equiv of Ph_3P at 120 °C for one night, until the mixture solidified. The solid was washed with hot toluene and then dried under vaccum. ^{1}H NMR: 7.70−7.88 (m, 15H), 3.94 (s, 3H).

1-Phenyl-2-methylprop-1-ene-*3,3,3,2′,2′,2′-d*$_6$ (3). Alkene **2** was prepared by Wittig coupling of the ylide produced by *n*-BuLi addition to the above salt, with benzaldehyde (30% yield). Purification was accomplished by flash column chromatography and then by vacuum distillation. ^{1}H NMR: 7.17−7.33 (m, 5H), 6.27 (s, 1H). No proton absorptions were detected in the region of the allylic methyl absorption (1.85−1.90 ppm). GC-MS: M^+ = 138. In the preparation of **3**, the ylide derived from benzyltriphenylphosphonium chloride was used instead via coupling with acetone-d_6, significant scrambling at the allylic methyls and the olefinic hydrogen was observed.

Intermolecular Kinetic Isotope Effects. Perprotio olefin **1** and deuterated olefin **3** are sufficiently separated on a capillary GC column (HP-5 cross-linked, 5% phenyl methyl silicone) for direct analysis, and the change in the ratio of **1** to **3** was easily monitored at several percentages of reaction progress with $^1O_2$ or MTAD. For the estimation of the kinetic isotope effect, the

(20) Similar inverse intramolecular isotope effect have been measured in the reaction of PTAD with trimethylethylene. Elemes Y.; Orfanopoulos, M., unpublished results.

(21) Preliminary studies have shown that MTAD addition to the *p*-methyl derivative of **1** affords the ene product exclusively. Even with the *p*-methoxy derivative, where the *p*-methoxybenzyl cation is far more stable than the tertiary alkyl, there is a significant amount of ene product (∼20%), along with several other adducts, including [2 + 2] and [4 + 2] products. Stratakis, M.; Hadjimarinaki, M.; Orfanopoulos, M., unpublished results.

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following expression[23] was used:

$$\frac{k_H}{k_D} = \frac{\log[1 - H_r/H_t]}{\log[1 - D_r/D_t]}$$

where H_r and D_r are the amounts of **1** and **3** that reacted, or the amounts of adducts formed by **1** and **3**, and H_t and D_t are the initial amounts of **1** and **3**, respectively.

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