Stepwise Mechanisms in the Ene Reaction of α,β-Unsaturated Esters with *N*-Phenyl-1,2,4-triazoline-3,5-dione and Singlet Oxygen. Intermolecular Primary and Secondary Hydrogen Isotope Effects

Yiannis Elemes and Christopher S. Foote*

Contribution from the Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024-1569. *Received March 6, 1992*

Abstract: Intermolecular primary and secondary isotope effects on the ene reaction of *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD) and singlet oxygen ($^1O_2$) with deuterium-substituted (*E*)-2-methylbuten-2-oic (tiglic) acid methyl esters have been determined. In the case of $^1O_2$, the primary isotope effect is 1.30–1.49 and the α and β secondary isotope effects are near unity, consistent with a stepwise reaction path via a perepoxide intermediate, where the allylic hydrogen-abstraction step is rate determining. On the other hand, the existence of both primary (1.44) and inverse α and β secondary isotope effects (0.91 and 0.77, respectively) in the PTAD reaction is consistent with either a concerted or a stepwise mechanism. Experiments in which both intermolecular primary and secondary isotope effects were measured at the same time suggest that, like singlet oxygen, PTAD reacts in a stepwise manner with the formation of the aziridinium imide intermediate (AI) in the rate-determining-step.

Introduction

The ene[1] reaction of PTAD[2-4] and $^1O_2$[5-7] with alkenes bearing allylic hydrogens has attracted significant attention in recent years and remains an active field from both the synthetic[8-11] and mechanistic[12-15] points of view. In particular, the ene reaction of these two electrophiles appears to be stepwise rather than concerted, although recent theoretical calculations reveal that the two pathways are nearly equal in energy.[16]

Isotope effect measurements on deuterated tetramethylethylenes[17,18] and *cis*- and *trans*-2-butenes[19,20] with the two electrophiles suggest that the reaction proceeds via an intermediate, with the formation of a perepoxide or the analogous aziridinium imide as the rate-determining first step. Aziridinium imide intermediates have been observed and spectroscopically characterized in the [2 + 2] reaction of PTAD with adamantylideneadamantane at −40 °C[21] and in the ene reaction of PTAD with *trans*-cycloheptene at −135 °C[22] and can also be trapped with methanol.[23-25] Similarly, a perepoxide intermediate could be trapped to give the corresponding epoxide when the reaction of singlet oxygen with adamantylideneadamantane was carried out in the presence of $P(OR)_3$[26] and solvent trapping of perepoxides occurs in indenes.[27]

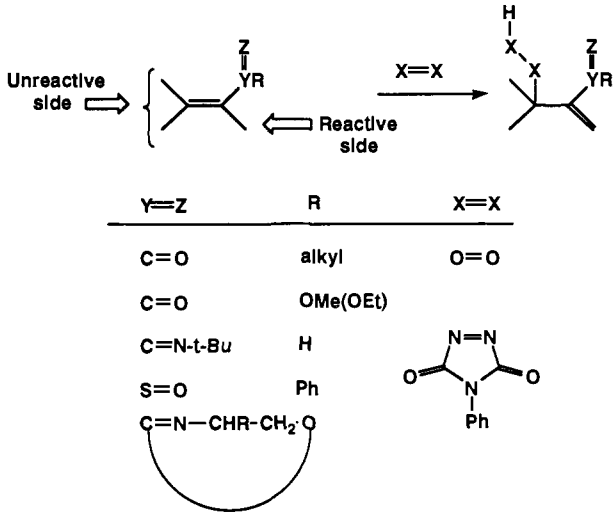
The regiochemistry of the reaction with various alkyl-substituted alkenes[28-30] reveals a high degree of similarity between the two electrophiles toward nonbonded interactions[31] either at the first or the second step. Also, in spite of the significant differences in activation parameters in the two reactions, kinetic studies[17,32] suggest the formation of intermediates with analogous structures during the course of the reactions. Contrary to the above similarities, different reaction pathways have been proposed for the ene reaction of the two electrophiles with silicon-substituted alkenes.[33,34]

The reactions of PTAD and $^1O_2$ with alkenes bearing electron-withdrawing substituents have also attracted considerable interest in the last years. Early work by Ensley and co-workers[35] reported that the reaction of $^1O_2$ with s-cis-α,β-unsaturated ketones

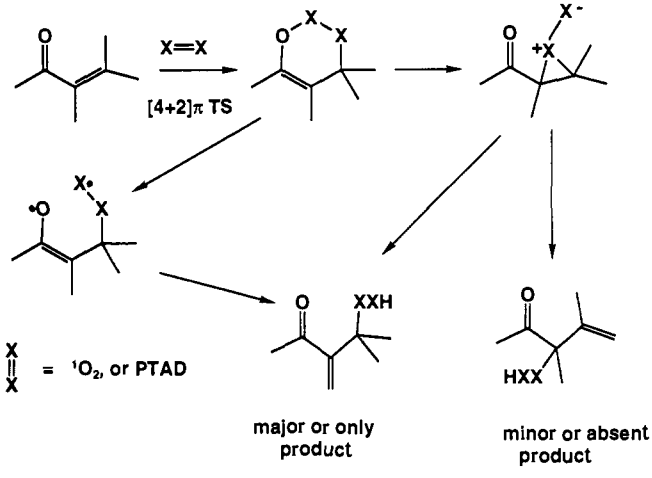
(1) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556–577.
(2) Pirkle, W. H.; Stickler, J. C. *J. Chem. Soc., Chem. Commun.* **1967**, 760–761.
(3) Ohashi, S.; Leong, K. W.; Matyjiaszewski, K.; Butler, G. B. *J. Org. Chem.* **1980**, *45*, 3467–3471.
(4) Ohashi, S.; Butler, G. B. *J. Org. Chem.* **1980**, *45*, 3472–3476.
(5) Matsumoto, M. In *Singlet O₂*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; pp 205–272.
(6) Frimer, A. A.; Stephenson, L. M. In *Singlet O₂*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; pp 68–87.
(7) Gollnick, K.; Kuhn, H. J. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979; pp 287–429.
(8) Corey, E. J.; Snider, B. B. *Tetrahedron Lett.* **1973**, *35*, 3091–3094.
(9) Adam, W.; Griesbeck, A. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1070–1071.
(10) Akasaka, T.; Takeuchi, K.; Misawa, Y.; Ando, W. *Heterocycles* **1989**, *28*, 445–451.
(11) Adam, W.; Nestler, B. *Liebigs Ann. Chem.* **1990**, 1051–1053.
(12) Yamada, S.; Yamano, K.; Shimizu, M. *Tetrahedron Lett.* **1991**, *32*, 2379–2382.
(13) Elemes, Y.; Stratakis, M.; Orfanopoulos, M. *Tetrahedron Lett.* **1989**, *30*, 6903–6906.
(14) Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *Tetrahedron Lett.* **1989**, *30*, 4875–4879.
(15) Clennan, E. L.; Chen, X.; Koola, J. J. *J. Am. Chem. Soc.* **1990**, *112*, 5193–5199.
(16) Davies, A. G.; Schiesser, C. H. *Tetrahedron* **1991**, *47*, 1707–1726.
(17) Cheng, C. C.; Seymour, C. A.; Petti, M. A.; Greene, F. D.; Blount, J. F. J. *J. Org. Chem.* **1984**, *49*, 2910–2916.
(18) Grdina, M. J.; Orfanopoulos, M.; Stephenson, L. M. *J. Am. Chem. Soc.* **1979**, *101*, 3111–3112.
(19) Orfanopoulos, M.; Foote, C. S.; Smonou, I. *Tetrahedron Lett.* **1987**, *28*, 15–18.
(20) Orfanopoulos, M.; Foote, C. S. *Free Radical Res. Commun.* **1987**, *2*, 321–326.
(21) Nelsen, S. F.; Kapp, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 5548–5549.
(22) Squillacote, M.; Mooney, M.; De Felippis, J. *J. Am. Chem. Soc.* **1990**, *112*, 5364–5365.
(23) Jensen, F.; Foote, C. S. *J. Am. Chem. Soc.* **1987**, *109*, 6376–6385.
(24) Elemes, Y.; Orfanopoulos, M. *Tetrahedron Lett.* **1991**, *32*, 2667–2670.
(25) Smonou, I.; Orfanopoulos, M.; Foote, C. S. *Tetrahedron Lett.* **1988**, *29*, 2769–2772.
(26) Stratakis, M.; Orfanopoulos, M.; Foote, C. S. *Tetrahedron Lett.* **1991**, *32*, 863–866.
(27) Hatsui, T.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2655–2658.
(28) Clennan, E. L.; Koola, J. J.; Oolman, K. A. *Tetrahedron Lett.* **1990**, *31*, 6759–6762.
(29) Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6417–6419.
(30) Orfanopoulos, M.; Elemes, Y.; Stratakis, M. *Tetrahedron Lett.* **1990**, *31*, 5775–5778.
(31) Orfanopoulos, M.; Stratakis, M.; Elemes, Y.; Jensen, F. *J. Am. Chem. Soc.* **1991**, *113*, 3180–3181.
(32) Hurst, J. R.; Wilson, S. L.; Schuster, G. B. *Tetrahedron* **1985**, *41*, 2191–2197.
(33) Adam, W.; Schwarm, M. *J. Org. Chem.* **1988**, *53*, 3129–3130.
(34) Dubac, J.; Laporterie, A. *Chem. Rev.* **1987**, *87*, 319–334.
(35) Ensley, H. E.; Carr, R. V. C.; Martin, R. S.; Pierce, T. E. *J. Am. Chem. Soc.* **1980**, *102*, 2836–2838.

0002-7863/92/1514-6044$03.00/0

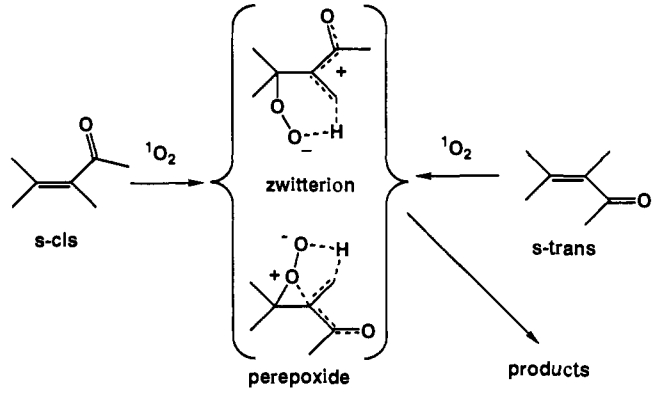
proceeds with high regioselectivity at the methyl group geminal to the substituent, whereas s-trans ketones fail to react. The same geminal (to the substituent) selectivity occurs in the reaction of α,β-unsaturated aldimines,[36] sulfoxides,[37] esters,[11,38] acids, aldehydes, amides, and oxazolines.[39] The scheme below summarizes reactions in these systems.



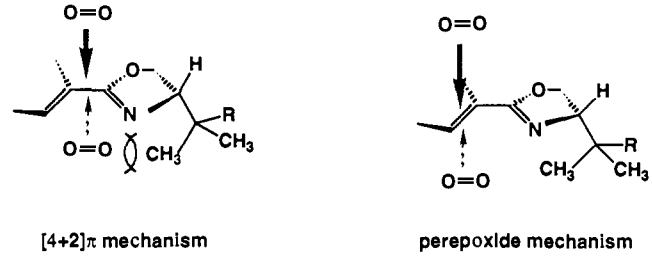
To explain the reactivity difference between s-cis and s-trans ketones and the regioselectivity of the reaction with singlet oxygen, Ensley first proposed a mechanistic scheme in which a trioxene intermediate is formed in a $[4 + 2]\pi$ transition state and then rearranges by breaking the weak O–O bond to give either a biradical or a perepoxide intermediate.[35] Allylic hydrogen abstraction by the biradical intermediate would lead to the major product, whereas the minor or absent product would come from the perepoxide. Similar schemes can be drawn for PTAD.[10,36,37]



Recently Foote and co-workers[40] reported that some *s-trans*-2-cyclopenten-1-ones are reasonably reactive toward singlet oxygen but give the same geminal selectivity observed in the s-cis compounds. They suggested that the geminal selectivity appears to be independent of the relative arrangement of the carbonyl group and alkene moiety and thus cannot derive from a cyclic trioxene. They also proposed that the geminal regioselectivity derives from a zwitterion or a perepoxide intermediate. In this intermediate, the stabilization of a full or partial charge by conjugation with the unsaturated carbonyl group can lead to relatively weak C–H bonds next to the substituent and thus dictates the observed product distribution.



The formation of a perepoxide intermediate has also been supported by a recent paper by Adam and co-workers on the reaction of $^1O_2$ with chiral oxazolines.[41] The lack of product diastereoselectivity was taken as evidence against a $[4 + 2]\pi$ concerted transition state, which might be expected to show significant steric effects from the chiral center, and thus supported the intervention of a perepoxide intermediate relatively distant from the bulky substituent at the chiral center.



Also, solvent effects on the side selectivity in the ene reaction of singlet oxygen with α,β-unsaturated esters suggest the formation of a perepoxide intermediate in the rate-determining step.[42]

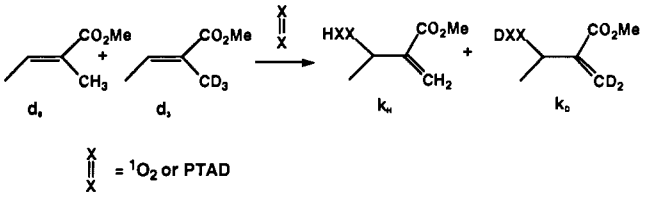
These recent results prompted us to investigate the reaction mechanism of conjugated substrates in order to further establish whether the reaction proceeds via a concerted or multistep pathway. Isotope effect measurements are a powerful tool for distinguishing between stepwise and concerted mechanisms.[43-46] Their use in the ene reaction of PTAD and $^1O_2$[47] and carbonyl electrophiles[44,48] has been recently reviewed.

Results

The basic approach used in this work is to use the primary kinetic isotope effect to establish the rate-determining step of the reaction and to supplement this test with secondary kinetic isotope effect studies to detect possible changes in hybridization at the unreactive side of the substrate during the rate-determining step.

(36) Akasaka, T.; Takeuchi, K.; Ando, W. *Tetrahedron Lett.* **1987**, *28*, 6633–6636.
(37) Akasaka, T.; Misawa, Y.; Goto, M.; Ando, W. *Tetrahedron* **1989**, *45*, 6657–6666.
(38) Orfanopoulos, M.; Foote, C. S. *Tetrahedron Lett.* **1985**, *26*, 5991–5994.
(39) Adam, W.; Griesbeck, A. *Synthesis* **1986**, 1050–1051.
(40) Kwon, B. M.; Kanner, R. C.; Foote, C. S. *Tetrahedron Lett.* **1989**, *30*, 903–906.
(41) Adam, W.; Brunker, H.-G.; Nestler, B. *Tetrahedron Lett.* **1991**, *32*, 1957–1960.
(42) Orfanopoulos, M.; Stratakis, M. *Tetrahedron Lett.* **1991**, *32*, 7321–7324.
(43) Song, Z.; Chrisope, D. R.; Beak, P. *J. Org. Chem.* **1987**, *52*, 3940–3941.
(44) Song, Z.; Beak, P. *J. Am. Chem. Soc.* **1990**, *112*, 8126–8134.
(45) Melander, L.; Saunders, W. H. J. *Reaction Rates of Isotopic Molecules*; Wiley-Interscience: New York, 1980.
(46) Carpenter, B. K. *Determination of Organic Reaction Mechanisms*; Wiley-Interscience: New York, 1984.
(47) Orfanopoulos, M.; Smonou, I.; Foote, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 3607–3614.
(48) Snider, B. B.; Ron, E. *J. Am. Chem. Soc.* **1985**, *107*, 8160–8164.

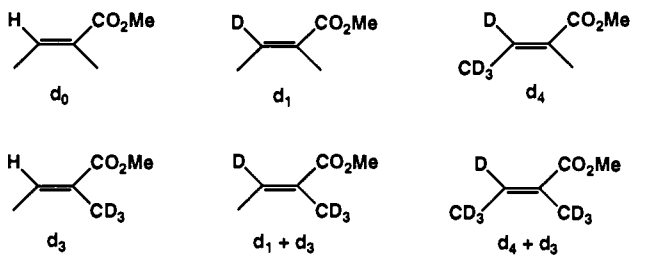
Table I. Effect of Solvent and Temperature on the Primary Kinetic Isotope Effect (d_0/d_3)



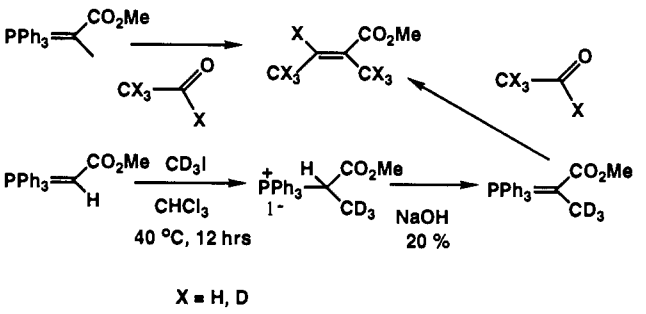
electrophile	solvent	T, °C	k_H/k_D' [c]
PTAD	CD_3CN	24	1.35 ± 0.05
		-20	1.40 ± 0.03
	$CHCl_3$	24	1.44 ± 0.04
$^1O_2$	C_6D_6 [a]	24	1.30 ± 0.06
	$(CD_3)_2CO$ [b]	24	1.48 ± 0.03
		-15	1.49 ± 0.04

[a] Mesoporphyrin IX dimethyl ester as sensitizer. [b] Rose Bengal as sensitizer. [c] k_H/k_D' is the primary isotope effect.

For this purpose, we synthesized the following deuterated E-α,-β-unsaturated esters.



The synthesis of these compounds was carried out by Wittig coupling of the stabilized ylide methyl (triphenylphosphoranylidene)propionate with acetaldehydes, which is known to give the E-esters in high isomeric purity (>97%),[49] as shown in the following scheme,



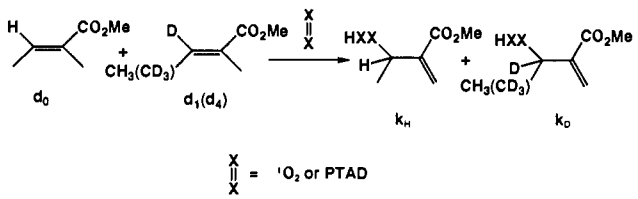
We chose compounds $\mathbf{d_0}$ and $\mathbf{d_3}$ for the primary kinetic isotope effect measurements because the reaction goes regiospecifically with PTAD, attacking the methyl geminal to the ester, as shown by the two single olefinic peaks in the ^1H NMR spectrum of the product. The reaction is also highly regioselective (97%) at the same methyl group with $^1O_2$.[38] Thus these compounds possess a methyl group that is reactive with respect to hydrogen abstraction and a monosubstituted vinylic carbon which undergoes a change of hybridization from sp^2 to sp^3 on going from reactant to product.

For the measurement of the primary kinetic isotope effects in the singlet oxygen reaction, an equimolar mixture of $\mathbf{d_0}$ and $\mathbf{d_3}$ esters was photooxidized in acetone-d_6 or benzene-d_6 in the presence of sensitizer. The progress of the reaction was followed by integration of the appropriate ^1H-NMR hydrogen peaks of the hydroperoxide mixtures. In a similar manner, solid PTAD was added to equimolar solutions of the two esters. After the removal of solvent, the isotope effects were measured by ^1H-NMR integration of the appropriate hydrogen peaks. The primary kinetic isotope effects measured with different solvent polarities and temperatures are listed in Table I.

For both electrophiles, the kinetic primary isotope effects are substantially greater than unity and of the same magnitude within experimental error in polar and nonpolar solvents and at different temperatures.

Compounds $\mathbf{d_1}$ and $\mathbf{d_4}$ in competition with $\mathbf{d_0}$ are ideal substrates for the secondary kinetic isotope effect measurements since the deuteration appears at carbons which are not involved in the hydrogen abstraction step. Photooxidations and PTAD reactions were carried out as described above. The secondary kinetic isotope effects measured for the two electrophiles are listed in Table II.

Table II. Intermolecular Secondary Isotope Effects in the Reaction of PTAD and $^1O_2$ with α,β-Unsaturated Esters



competitive species	isotope effects PTAD [a]	isotope effects $^1O_2$ [b]	k_H/k_D'' [c]
$\mathbf{d_0/d_1}$	0.91 ± 0.02	0.98 ± 0.02	$(k_H/k_D)''^{\alpha}$ [d]
$\mathbf{d_1/d_4}$	0.77 ± 0.02	1.05 ± 0.02	$(k_H/k_D)''^{\beta 3}$ [e]
$\mathbf{d_0/d_4}$	0.86 ± 0.02	1.02 ± 0.02	$(k_H/k_D)''^{\alpha}(k_H/k_D)''^{\beta 3}$

[a] In $CHCl_3$ at room temperature. [b] In acetone-d_6 at -15 °C with Rose Bengal as sensitizer. [c] Secondary isotope effect. [d] α secondary isotope effect (one vinylic D). [e] β secondary isotope effect (three allylic D).

Table III. Combination of Primary and Secondary Kinetic Isotope Effects in the Ene Reaction of PTAD and $^1O_2$ with α,β-Unsaturated Esters

entry	competitive species	isotope effects PTAD [a]	isotope effects $^1O_2$ [b]
1	$\mathbf{d_1/d_3}$	1.50 ± 0.02	1.30 ± 0.07
2	$\mathbf{d_4/d_3}$	1.52 ± 0.03	1.34 ± 0.07
3	$\mathbf{d_0/(d_1 + d_3)}$	0.95 ± 0.05	1.33 ± 0.06
4	$\mathbf{d_0/(d_4 + d_3)}$	0.97 ± 0.05	1.35 ± 0.11

[a] In $CHCl_3$ at room temperature. [b] In acetone-d_6 at -15 °C with Rose Bengal as sensitizer.

As seen from Table II, with PTAD, all the isotope effects are substantial and inverse and of the typical magnitude for reactions where substantial $sp^2 \rightarrow sp^3$ rehybridization occurs at the transition state.[50-53] In marked contrast, there is almost no secondary isotope effect with $^1O_2$.

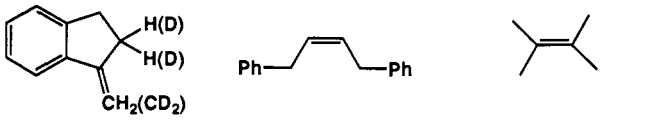
In order to obtain a clearer picture, we carried out some intermolecular competitions where there is a combination of primary and secondary isotope effects. The measurement of the isotope effects was done as described above. The results are listed in Table III.

Table III shows that there is a slightly larger isotope effect with PTAD (in comparison with the $\mathbf{d_0/d_3}$ competition) in the first two entries, where the primary and the secondary isotope effects are in the same direction, whereas with $^1O_2$, the isotope effects measured are of the same magnitude as those in Table I. In the last two entries, where the primary and the secondary isotope effects are in the opposite direction, an inverse isotope effect is observed with PTAD, but with $^1O_2$ there is again no change.

(49) House, H. O.; Rasmussen, G. H. *J. Org. Chem.* **1961**, *26*, 4278.
(50) Gajewski, J. J.; Peterson, K. B.; Kagel, J. R.; Huang, Y. C. J. *J. Am. Chem. Soc.* **1989**, *111*, 9078-9081.
(51) Llewellyn, J. A.; Robertson, R. E.; Scott, J. M. W. *Can. J. Chem.* **1960**, *38*, 222-232.
(52) Dolbier, W. R. J.; Dai, S.-H. *J. Am. Chem. Soc.* **1968**, *90*, 5028-5030.
(53) Shiner, V. J. J.; Buddenbaum, W. E.; Murr, B. L.; Lamaty, G. *J. Am. Chem. Soc.* **1968**, *90*, 418-428.

Discussion

Inspection of Table I reveals that the primary intermolecular isotope effects are substantially greater than unity with both electrophiles and thus require the hydrogen abstraction step to be rate determining. The magnitudes of the effects, although far smaller than the theoretical maximum, are the largest ever measured for the ene reaction of PTAD and $^1O_2$. Despite the large number of isotopic studies, there are few cases where intermolecular primary isotope effects have been measured. In all of these studies, the primary kinetic isotope effects are nearly equal to unity. In particular, almost no overall primary kinetic isotope effect was found in the reaction of $^1O_2$ with *cis*-1,4-diphenylbut-2-ene[54] and tetramethylethylene.[55] There was also no overall kinetic isotope effect in the reaction of PTAD with the geminally-substituted double bond in 1-methyleneindene (shown below), whereas other electrophiles give kinetic isotope effects in the ene reaction with the same substrate.[56] Although the contribution of possible inverse kinetic secondary isotope effects in these competitions was unclear, these results were taken as evidence for the rate-determining formation of perepoxide or aziridinium imide intermediates.



PTAD: $k_H/k_D = 1.02$ $^1O_2$: $k_H/k_D = 1.07$ $^1O_2$: $k_H/k_D = 1.07$

From the results in Table I, the solvent polarity appears to have almost no effect on the magnitude of the primary isotope effect, which suggests there are no highly polar intermediates or transition states along the reaction coordinate. The lack of temperature dependence of the isotope effects is evidence for a small activation enthalpy[19] during the isotopic discrimination step. A similar temperature independence was taken as evidence for a nonlinear transition state by Kwart,[57] but this suggestion has been challenged by McLennan[58] on the basis of theoretical calculations.

Although the primary isotope effects are in the same direction with both electrophiles, the secondary isotope effects are quite different (Table II). In the case of PTAD, substantial inverse α and β secondary isotope effects were measured, which reveal a large change of hybridization (from sp^2 to sp^3) during the rate-determining step of the reaction at the formerly monosubstituted vinylic carbon atom. To our knowledge, these are the first inverse isotope effects ever measured in the ene reaction of PTAD. Furthermore in entry 3 of Table II, a combination of α and β isotope effects are measured at the same time. The observed overall isotope effect is within experimental error of the product of the two independent contributing terms.

In contrast to the case with PTAD, no secondary isotope effect was found with $^1O_2$, which means that there is no change of hybridization at the carbon atoms where the C–O bond forms during the rate-determining step of the reaction.[59] For a concerted mechanism through a $[4 + 2]\pi$ transition state, one would expect an inverse secondary isotope effect with both electrophiles. The lack of any inverse secondary isotope effect with $^1O_2$ clearly speaks against the concerted pathway and, in connection with the substantial primary isotope effect, suggests that singlet oxygen follows a stepwise mechanism with a fast preequilibrium step to give a perepoxide intermediate, followed by a second, rate determining, step in which the allylic hydrogen abstraction takes place. This mechanism is in agreement with earlier and more recent reports. The magnitude of the isotope effects can be visualized in terms of a highly conjugated transition state, with the ester functionality leading to weakened C–H bonds, as proposed by Foote and coworkers.[40] Note that for these esters both the rate- and the product-determining step must be the second step, whereas with simple alkenes the first step is rate determining.[44,47]

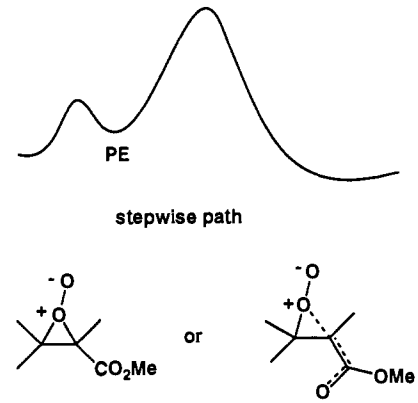


Figure 1. Energy diagram for the reaction of singlet oxygen with α,β-unsaturated esters.

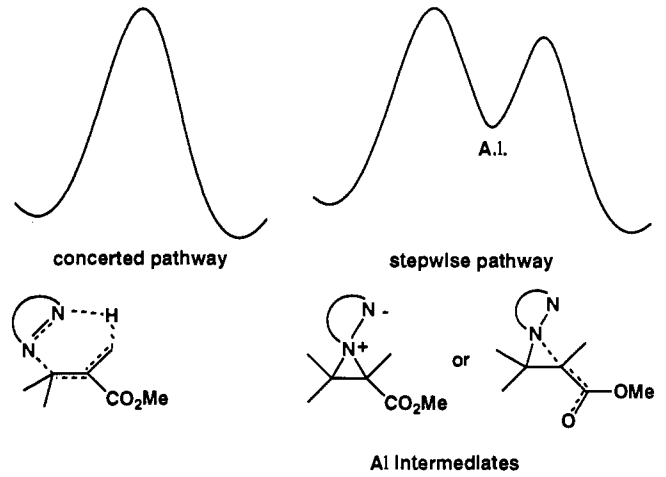
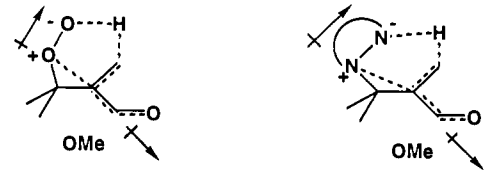


Figure 2. Possible energy diagrams for the ene reaction of PTAD with α,β-unsaturated esters.



The above mechanism could also explain the recently-observed solvent dependence of the side selectivity in the reaction of singlet oxygen with α,β-unsaturated esters,[42] where the dipole moments of the O–O moiety and the ester functionality can control the product distribution during the second step of the reaction in solvents of different polarity.

The observed substantial primary and inverse secondary isotope effects for PTAD are consistent with two very different mechanisms. One is a concerted mechanism, where the change in hybridization at the former vinylic monosubstituted carbon (from

(54) Orfanopoulos, M.; Foote, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 6583–6584.

(55) Gollnick, K.; Hartmann, H.; Paur, H. In *Oxygen And Oxy-radicals In Chemistry And Biology*; Rodgers, M. A. J., Powers, E. L., Eds.; Academic Press: New York, 1981; pp 379–395.

(56) Starflinger, W.; Huss, K.; Kresze, G. *J. Org. Chem.* **1986**, *51*, 37–40.

(57) Kwart, H. *Acc. Chem. Res.* **1982**, *15*, 401–408.

(58) McLennan, D. J.; Gill, P. M. W. *J. Am. Chem. Soc.* **1985**, *107*, 2971–2972.

(59) A referee points out that a change in hybridization would also not be detected if the transition state were too early, as has often been suggested for singlet oxygen reactions. Although this mechanism is not consistent with the significant primary product isotope effects observed in the ene reaction by many authors, it cannot be ruled out completely, since the values are far less than the theoretical maximum. However, such a transition state is inconsistent with recent work on ene reactions of α,β-unsaturated ketones[40] and oxazolines.[41] To our knowledge, no secondary isotope effects have ever been measured in Diels–Alder reactions of singlet oxygen.

Table IV. Comparison of Observed Isotope Effects in the Reaction of PTAD with Those Expected for a Concerted Reaction

entry	competition	k_H/k_D overall: expected for concerted reaction	k_H/k_D overall: measured
1	d_0/d_3	$(k_H/k_D)' \times (k_H/k_D)''^{\beta^3} = A^a$	1.44 ± 0.04
2	d_1/d_3	$A \times 1/(k_H/k_D)''^{\alpha b}$	
		1.44 × 1/0.91 = 1.58	1.50 ± 0.02
3	d_4/d_3	$A \times 1/(k_H/k_D)''^{\beta^3} \times (k_H/k_D)''^{\alpha b}$	
		1.44 × 1/0.86 = 1.67	1.52 ± 0.03
4	$d_0/(d_1 + d_3)$	$A \times (k_H/k_D)''^{\alpha b}$	
		1.44 × 0.91 = 1.31	0.95 ± 0.05
5	$d_0/(d_4 + d_3)$	$A \times (k_H/k_D)''^{\alpha} \times (k_H/k_D)''^{\beta^3 b}$	
		1.44 × 0.86 = 1.24	0.97 ± 0.05

[a] Possible secondary isotope effect contribution from the reactive three β-hydrogens during the formation of the intermediates. [b] Secondary isotope effects from the nonreactive one α-hydrogen and three β-hydrogens during the formation of the intermediates.

sp^2 to sp^3) and the allylic hydrogen abstraction occur in the same step. In this case, one would observe both an inverse secondary (at the monosubstituted carbon) and a primary isotope effect at the reactive methyl group. Alternatively, a stepwise mechanism is possible where an aziridinium imide intermediate (AI, with a structure similar to the perepoxide) is formed in the first, rate-determining step followed by a product-determining hydrogen-abstraction step. In this case, one would expect some isotopic discrimination at the second step if the two steps of the reaction have nearly the same energy barriers,[43,44] as observed in some ene reactions of PTAD and $^1O_2$, where similar arguments have been made.[47] This is the mechanism currently favored for the reaction of simple alkenes.

In order to have a better view of the "timing" of the reaction (especially for the case of PTAD), we performed competition experiments with the compounds listed in Table III. In these compounds, primary and secondary isotopic competitions occur at the same time. In the first two cases (entries 1 and 2) of Table III, both the primary and the secondary isotope effects are in the same direction (i.e. allylic hydrogen abstraction from the hydrogenated reactive methyl group is favored). In the case of a concerted mechanism, one would expect an overall isotope effect nearly equally to the primary divided by the secondary isotope effects. In the last two entries (3 and 4) of Table III, where the two isotope effects are in the opposite direction (the secondary isotope effect favors hydrogen abstraction from the deuterated methyl, but the primary isotope effect favors abstraction from the protiated methyl), one would expect the overall isotope effect for a concerted reaction to be nearly equal to the primary multiplied by the secondary isotope effects. These expected overall isotope effects for a concerted reaction are listed in Table IV. For singlet oxygen, one would expect no change in the overall isotope effect from the above combination since secondary isotope effects do not occur in this case and this is what is measured, as seen from Table III.

While with singlet oxygen the results are as expected and in accord with the proposed mechanism, with PTAD there is a distinct discrepancy between the first two and the last two entries of Table III. Where the two isotope effects are in the same direction (first two entries), a normal overall isotope effect is measured, consistent with the concerted mechanism. On the other hand, in the last two entries (where the isotope effects are in the opposite direction), an inverse overall isotope effect is measured. The observed overall isotope effects in Table IV clearly exclude the concerted mechanism for PTAD and suggest a stepwise one with the formation of the AI intermediate as the rate-determining step followed by a faster hydrogen abstraction step, as suggested above.

Recently Beak and co-workers proposed a mechanistic model which gives a better understanding of small isotope effects in the ene reaction of carbonyl electrophiles in terms of equilibrating intermediates.[43,44] They also extended their model to the isotope effects measured in ene reactions of PTAD and $^1O_2$. According to this model, the intermolecular isotope effect is equal to the secondary isotope effect during the formation of the intermediate at the first step: $(k_H/k_D)_{inter} = (k_{1H}/k_{1D})$ in the case of an equilibrating intermediate in which the first step is rate determining. If we assume that this is the case with the d_0/d_3 competition (i.e. the secondary isotope effect is 1.44 with PTAD), then the expected overall isotope effects of the competitions listed on Table IV would be of the same order as that in a concerted reaction since α and β secondary isotope effects contribute in the first step. From inspection of the results of Table IV, this is clearly not the case.

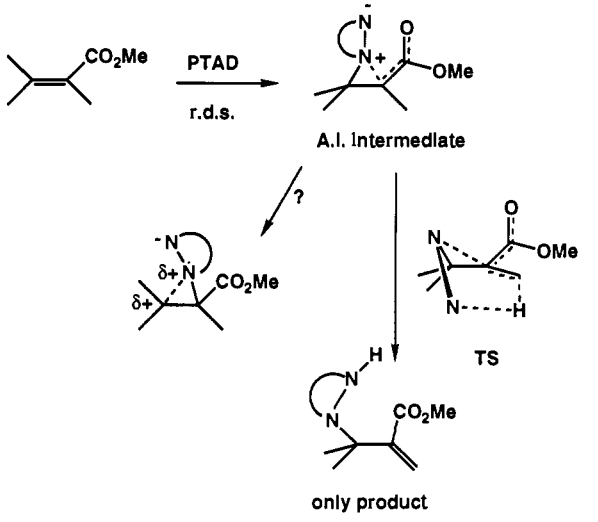
With singlet oxygen, we found in this study that the rate-determining step is hydrogen abstraction, and thus (according to the model) the intermolecular isotope effect is given by

$$(k_H/k_D)_{inter} = (k'_H/k'_D)(k_{1H}/k_{-1H})/(k_{1D}/k_{-1D})$$

Since we observe no interference from the secondary isotope effect (at the nonreactive side of the molecule), the above results for singlet oxygen are also consistent with Beak's proposal, with an equilibrating perepoxide formed at the first (faster) step of the reaction, and the hydrogen abstraction is rate determining.

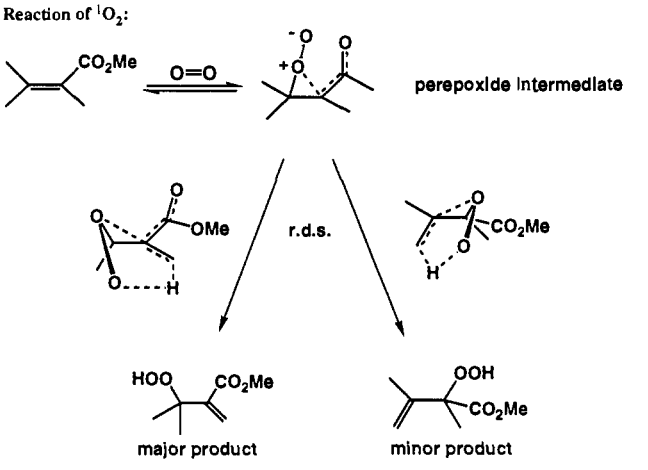
From the above discussed results, we propose the following mechanistic schemes for the ene reaction of PTAD and $^1O_2$ with α,β-unsaturated esters.

Reaction of PTAD:



PTAD reacts with formation of the aziridinium imide (AI) intermediate in the first rate-determining step. The transition state at this step is stabilized by conjugation with the ester group and thus gives rise to the geminal regiospecificity. The second possible path (which is not assisted by conjugative stabilization) lies at higher energy, and none of the minor product is formed. With the same concept, the extended conjugation leads to relatively weak C–H bonds and thus gives rise to the moderate primary isotope effect measured.[60]

Reaction of $^1O_2$:



With singlet oxygen, the preequilibrium first step, although leading to the formation of the perepoxide intermediate, does not allow secondary isotope effects, and thus the extended conjugation in the transition state of the second rate-determining step leads to the observed geminal high regioselectivity and, for the same reasons advanced above, lower isotopic discrimination.

Conclusion

Although these two common electrophiles behave in the same manner in terms of reaction pathways and regioselectivity in most cases, with α,β-unsaturated esters they follow two slightly different stepwise mechanisms with perepoxide and aziridinium imide intermediates; changes in hybridization at the vinylic carbons of the olefin during the reaction give rise to secondary isotope effects with PTAD but not with $^1O_2$. The two mechanisms differ only in the relative energy of the first and second steps. The present study provides an example of the utility of simultaneous primary and secondary kinetic isotope effect measurements for the clarification of ene reaction mechanisms.

It would be extremely interesting to compare these results with similar studies of [2 + 4] reactions of these dienophiles. Such studies have not been reported and are under investigation.

Experimental Section

Nuclear magnetic resonance (NMR) spectra were determined on a Bruker AF-200 spectrometer. Deuteration percentage was measured by integration of the appropriate peaks in the ^1H NMR spectrum. Spectra from the PTAD adducts were taken in deuteriochloroform and for singlet oxygen in acetone-d_6 or benzene-d_6. Chemical shift values are reported in δ (ppm) relative to internal tetramethylsilane. Isomeric purities of the esters were determined in a Hewlett-Packard Model 5890 Series II gas chromatograph.

Chloroform and methylene chloride were freshly distilled from phosphorous pentoxide and kept under 3 Å molecular sieves. Methyl 2-bromopropionate, methyl bromoacetate, triphenylphosphine, trideuteriomethyl iodide, acetaldehyde, acetaldehyde(*d*), acetaldehyde-d_4, rose bengal, mesoporphyrin IX dimethyl ester, and PTAD were obtained from Aldrich Chemical Co. and used without further purification.

1-(Methoxycarbonyl)-2-bromoethyl)triphenylphosphonium Salt. This phosphonium salt was prepared by the method of House.[49] To a 500-mL toluene solution of 200 mmol (52.46 g) of triphenylphosphine were added 200 mmol (22.3 mL) of methyl 2-bromopropionate, and the resulting mixture was stirred overnight at 90 °C. After filtration and washing of the precipitate with 400 mL of warm toluene, the phosphonium salt was isolated in quantitative yield. ^1H NMR δ 1.70 (dd, 3 H, J_1 = 18.39 Hz, J_2 = 7.18 Hz), 3.57 (s, 3 H), 7.03 (m, 1 H), 8.05–7.64 (m, 15 H).

Stabilized Ylide Methyl (Triphenylphosphoranylidene)propionate. The above phosphonium salt was dissolved in 1 L of water and the appropriate amount of 20% NaOH solution was added while the mixture was stirred. After extraction of the aqueous layer with methylene chloride, the organic layer was dried over $MgSO_4$ and the solvent removed by flash evaporation. The pale yellow ylide was isolated in quantitative yield. ^1H NMR δ 1.62 (d, 3 H, J = 13.72 Hz), 3.13 (s, 3 H), 7.87–7.42 (m, 15 H).

Methyl (*E*)-2-Methylbut-2-enoate (d_0). To a solution of 20 mmol (6.97 g) of the above stabilized ylide in 50 mL of dry dichloromethane were added 20 mmol (1.1 mL) of acetaldehyde (in 3 mL of dry dichloromethane). After the solution was stirred overnight at room temperature, removal of the solvent on the rotary evaporator and distillation of the residue afforded the ester in 65% yield (1.48 g). The isomeric purity was determined to be >98% by GC (SE-30, analytical column). ^1H NMR δ 1.79 (d, 3 H, J = 7.00 Hz), 1.84 (s, 3 H), 3.73 (s, 3 H), 6.86 (q, 1 H, J = 6.96 Hz).

Ene Reaction of PTAD with Methyl (*E*)-2-Methylbut-2-enoate (d_0). To a stirred solution of d_0 (0.020 g, 0.18 mmol) in 5 mL of dry chloroform were added 31 mg (0.18 mmol) of solid PTAD in one portion at room temperature. After the decolorization of the solution, the solvent was evaporated and the ^1H NMR spectrum of the oily residue showed the formation of only one ene adduct. ^1H NMR δ 1.54 (d, 3 H, J = 7.11 Hz), 3.82 (s, 3 H), 5.20 (q, 1 H, J = 7.14 Hz), 5.98 (s, 1 H, vinylic), 6.36 (s, 1 H, vinylic), 7.54–7.33 (m, 5 H), 8.18 (s, br, 1 H, N–H). Exact mass for $C_{14}H_{15}O_4N_3$, calculated 289.1063, found 289.1063.

Photooxygenation of Methyl (*E*)-2-Methylbut-2-enoate (d_0). The photooxygenation was carried out in an NMR tube containing a solution of the ester in acetone-d_6 with rose bengal (10^{-4} M) as sensitizer at −15 °C. A tungsten–halogen lamp was used as the light source and a $K_2Cr_2O_7$ solution (0.1 M) as the cutoff filter (<400 nm). A ^1H NMR spectrum was taken right after completion of the reaction (monitored by GC) and showed the formation of two allylic hydroperoxides in 97:3 molar ratio. ^1H NMR (of the major product) δ 1.27 (d, 3 H, J = 6.58 Hz), 3.74 (s, 3 H), 4.86 (q, 1 H, J = 6.35 Hz), 5.92 (s, 1 H, vinylic), 6.27 (s, 1 H, vinylic), 10.90 (s br, 1 H, OO–H).

Methyl (*E*)-2-Methyl-3-deuteriobut-2-enoate (d_1). The same method as above (preparation of d_0) was used. To the solution of 20 mmol (7.73 g) of the stabilized ylide in 40 mL of dry methylene chloride were added 22.2 mmol (1 g) of acetaldehyde-d_4. The resulting ester was isolated in 60% yield (>98% isomeric purity). ^1H NMR δ 1.79 (s, 3 H), 1.83 (s, 3 H), 3.73 (s, 3 H). Exact mass for $C_6H_9DO_2$, calculated 115.0744, found 115.0760.

Methyl (*E*)-2-Methyl-3,4,4,4-tetradeuteriobut-2-enoate (d_4). To a 20.8-mmol (7.25 g) solution of the above stabilized ylide in 40 mL of dry methylene chloride were added 20.8 mmol (1 g) of acetaldehyde-d_4. The corresponding ester was isolated in 55% yield (>97% isomeric purity). ^1H NMR δ 1.83 (s, 3 H), 3.73 (s, 3 H). Exact mass for $C_6H_6D_4O_2$, calculated 118.0933, found 118.0940.

(Methoxycarbonymethyl)triphenylphosphonium Bromide. To a toluene (500 mL) solution of 200 mmol (52.46 g) of triphenylphosphine were added 200 mmol (18.93 mL) of methyl bromoacetate and the mixture was allowed to stir for 12 h at 90 °C. After filtration of the precipitate and washing with 400 mL of warm toluene, the white phosphonium salt was isolated in quantitative yield. ^1H NMR δ 3.60 (s, 3 H), 5.64 (d, 2 H, J = 13.56 Hz), 7.95–7.62 (m, 15 H).

Stabilized Ylide Methyl (Triphenylphosphoranylidene)acetate. The above salt was dissolved in 1 L of water and, with stirring, the appropriate amount of 20% NaOH solution was added. The aqueous solution was extracted with methylene chloride and the organic layer dried over $MgSO_4$. After removal of the solvent the ylide was isolated quantitatively. ^1H NMR δ 2.92 (d, 1 H, J = 21.70 Hz), 3.56 (s, 3 H), 7.70–7.39 (m, 15 H).

(1-(Methoxycarbonyl)-2,2,2-trideuterioethyl)triphenylphosphonium Iodide.[31] To a solution of 80 mmol (26.75 g) of the above stabilized ylide in 200 mL of dry chloroform were added 120 mmol (7.63 mL) of CD_3I (in 20 mL of dry chloroform) through an ice-cooled addition funnel. The solution was stirred for 12 h at 40 °C and, after removal of the solvent by flash evaporation, the phosphonium iodide salt was isolated quantitatively. ^1H NMR δ 3.58 (s, 3 H), 6.50 (d, 1 H, J = 14.83 Hz), 8.00–7.66 (m, 15 H).

Stabilized Ylide d_3 Methyl 2-(Triphenylphosphoranylidene)-3,3,3-trideuteriopropionate. The above phosphonium salt was dissolved in 300 mL of chloroform and to the resulting solution was added the appropriate amount of 20% NaOH solution. After separation, the organic layer was dried over $MgSO_4$ and the solvent removed by flash evaporation. The pale yellow stabilized ylide was isolated in quantitative yield. ^1H NMR δ 3.15 (s, 3 H), 7.87–7.42 (m, 15 H).

Methyl (*E*)-2-(Trideuteriomethyl)but-2-enoate (d_3). To a solution of 20 mmol (7.03 g) of the above stabilized ylide d_3 in 40 mL of dry methylene chloride were added 20 mmol (1.1 mL) of acetaldehyde (in 2 mL of dry methylene chloride) through an ice-cooled addition funnel. The resulting solution was allowed to stir at room temperature for 4 h and, after the removal of the solvent in the rotary evaporator, the ester was isolated by distillation of the residue in 65% yield (1.52 g, isomeric purity, >97%). ^1H NMR δ 1.79 (d, 3 H, J = 7.10 Hz), 3.73 (s, 3 H), 6.86 (q, 1 H, J = 7.12 Hz). Exact mass for $C_6H_7D_3O_2$, calculated 117.0869, found 117.0899.

Methyl (*E*)-2-(Trideuteriomethyl)-3-deuteriobut-2-enoate (d_1 + d_3). To a solution of 22.2 mmol (7.80 g) of the above stabilized ylide d_3 in 40 mL of dry methylene chloride were added 22.2 mmol (1 g) of acetaldehyde(*d*) in 3 mL of dry methylene chloride through an ice-cooled addition funnel. The resulting solution was allowed to stir at room temperature for 4 h. After solvent evaporation, the desired ester was isolated by distillation of the residue in 57% yield (1.50 g, >98% isomeric purity). ^1H NMR δ 1.77 (s, 3 H), 3.72 (s, 3 H). Exact mass for $C_6H_6D_4O_2$, calculated 118.0933, found 119.0922.

Methyl (*E*)-2-(Trideuteriomethyl)-3,4,4,4-tetradeuteriobut-2-enoate (d_4 + d_3). To a solution of 20.8 mmol (7.31 g) of the above stabilized ylide d_3 in 40 mL of dry methylene chloride were added 20.8 mmol (1 g) of acetaldehyde-d_4 in 3 mL of dry methylene chloride through an ice-cooled addition funnel. After the solution was stirred at room temperature for 4 h, the solvent was evaporated and the desired ester isolated

(60) Although this moderate primary isotope effect can be considered to be the product of a primary and a secondary isotope effect at the reactive methyl group (the latter inverse during the formation of the intermediate), it is reasonable to expect that the conjugative ability of the ester group favors the change of hybridization (from sp^2 to sp^3) of the reactive methyl group at the transition state leading to the intermediate.

by distillation of the residue in 50% yield (1.26 g, >98% isomeric purity). ^{1}H NMR δ 3.72 (s, 3 H). Exact mass for $C_6H_3D_7O_2$, calculated 121.1120, found 121.1092.

General Procedure for Intermolecular Isotope Effect Determination with PTAD. To 5-mL equimolar chloroform solutions of deuterated and hydrogenated *E* esters (ca. 10^{-2} M) was added solid PTAD at room temperature at the following three molar ratios: hydrogenated ester: deuterated ester:PTAD, 1:1:0.1, 1:1:0.2, and 1:1:0.4.

After completion of the reaction (decolorization of the red solutions) and removal of the solvent in high vacuum, the oily residues were recrystallized from *n*-hexane/$CHCl_3$. The isotope effects reported were taken as the average of three independent ^{1}H NMR integrations of the appropriate hydrogen peaks and were the same either before or after the recrystallization. Errors are standard deviations.

General Procedure for Intermolecular Isotope Effect Measurements with Singlet Oxygen. The photooxygenations were carried out in an NMR tube at -15 °C. An equimolar solution of the deuterated and hydrogenated esters (10^{-2} M) was dissolved in 1 mL of deuterated solvent. When the solvent was acetone-d_6, a 10^{-4} M solution of rose bengal was used, and in benzene-d_6 a 10^{-4} M solution of mesoporphyrin IX dimethyl ester was used as sensitizer. A tungsten-halogen lamp was used as the light source, with a filter solution to cut off wavelengths <400 nm (0.1 M $K_2Cr_2O_7$). The reaction was monitored three times during the reaction period (until 40-50% overall conversion of the reactant mixture), with ^{1}H NMR integration of the appropriate hydrogen peaks of the product allylic hydroperoxides. The isotope effects are an average of the three runs. Errors are standard deviations.

Acknowledgment. This work was supported by NSF Grant No. CHE89-11916 and NATO Grant No. 01230/88.

The Samarium Grignard Reaction. In Situ Formation and Reactions of Primary and Secondary Alkylsamarium(III) Reagents

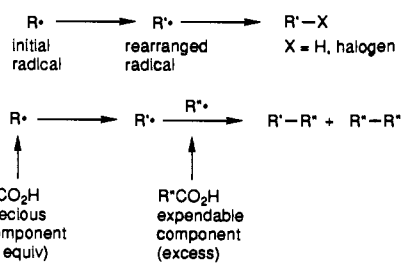
Dennis P. Curran*,[1] and Michael J. Totleben

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. *Received November 27, 1991*

Abstract: This work shows that primary and secondary radicals are rapidly reduced in THF/HMPA to form primary- and secondary-alkylsamarium reagents. The primary- and secondary-radicals can be formed either by direct SmI_2 reduction of primary- and secondary-halides or by a previous rapid radical cyclization. The samarium reagents have moderate stability in solution, and they react with a variety of typical electrophiles, including aldehydes and ketones. The work further shows that organosamarium intermediates can be involved in the traditional samarium Barbier reaction of aldehydes and ketones conducted in THF/HMPA. A new procedure called the "samarium Grignard" method is introduced, and it is suggested that this new procedure will have considerably more scope and generality than the samarium Barbier reaction.

Introduction

One of the most attractive features of radical reactions in synthesis is the ability to conduct them in sequence.[2] Perhaps the most important step in any radical sequence is the final one, which must convert a radical to a nonradical.[2c] Radical reactions are usually terminated by functional group transformations like atom transfer (hydrogen, halogen, see eq 1), fragmentation (to an alkene), or oxidation (to an alkene or lactone). To increase the power of radical reactions, it would be desirable to terminate a single or tandem radical reaction with another carbon-carbon bond forming step. Becking and Schäfer have accomplished this by conducting mixed Kolbe oxidations of a "precious" carboxylic acid with an "expendable" one (eq 2).[3] An excess of the expendable component is used to maximize the yield of the cross-coupled product; however, large amounts of the dimer of the expendable component are also formed.



(2)

The statistical formation of coupled products is the normal result in radical/radical coupling reactions. However, selective, stoichiometric cross-couplings can be effected if one of the radicals is persistent.[4] Thus, we envisioned that a sequence of radical reactions might be terminated by selective cross-coupling with a ketyl (eq 3). To execute such a sequence, we were immediately attracted to the samarium Barbier reaction (eq 4).[5] This reaction was discovered by Kagan in 1980, and during the ensuing decade it has been developed into a powerful synthetic method.[6] Especially useful are Molander's intramolecular reactions, which

(1) Dreyfus Teacher-Scholar, 1986-1991. NIH Research Career Development Awardee, 1987-1992. ICI Pharmaceuticals Awardee, 1990.

(2) (a) Curran, D. P. *Synthesis* **1988**, 417 and 489. (b) Giese, B. Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds; Pergamon Press: Oxford, 1986. (c) Curran, D. P. *Comprehensive Organic Synthesis*; Trost, D. M., Fleming, I., Eds.; Pergamon: Vol. 4, in press.

(3) Becking, L.; Schäfer, H. J. *Tetrahedron Lett.* **1988**, *29*, 2797, and 2801.

(4) Fischer, H. *J. Am. Chem. Soc.* **1986**, *108*, 3925.

(5) (a) Kagan, H. B. *New J. Chem.* **1990**, *14*, 453. (b) Recent review: Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573. (c) For a detailed discussion of possible mechanisms and available evidence, see: Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, *37*, Suppl. 1, 175. (d) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (e) Sasaki, M.; Collin, J.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 6105. (f) Sasaki, M.; Collin, J.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 4847. (g) Collin, J.; Dallemer, F.; Namy, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 7407. (h) Kagan, H. B.; Sasaki, M.; Collin, J. *Pure Appl. Chem.* **1988**, *60*, 1725. (i) Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250*, 227.

(6) (a) Review: Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (b) Review: Soderquist, J. A. *Aldrich. Acta* **1991**, *24*, 15. (c) Molander, G. A.; Etter, J. B. *Synth. Commun.* **1987**, *17*, 901. (d) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453. (e) Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556. (f) Imamoto, T.; Takeyama, T.; Yokoyama, M. *Tetrahedron Lett.* **1984**, *25*, 3225. (g) Imamoto, T.; Takeyama, T.; Koto, H. *Tetrahedron Lett.* **1986**, *27*, 3243. (h) Gupta, A. K.; Cook, J. M.; Weiss, U. *Tetrahedron Lett.* **1988**, *29*, 2535. (i) Lannoye, G.; Cook, J. M. *Tetrahedron Lett.* **1988**, *29*, 171. (j) Zoretic, P.; Yu, B. C.; Caspar, M. L. *Synth. Commun.* **1989**, *19*, 1859. (k) Zhang, Y.; Liu, T.; Lin, R. *Synth. Commun.* **1988**, *18*, 2003. (l) Otsubo, K.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 1487. (m) Moriya, T.; Handa, Y.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1988**, *29*, 6947. (n) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 1195. (o) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3891.

0002-7863/92/1514-6050$03.00/0