irradiation reactions. 2-Methyl-1-(*m*-hydroxybenzyl)-1-pyrrolinium perchlorate was inert under the acetone-sensitized reaction conditions. Control irradiations with Pyrex filtered light, in which CH_3CN was employed as solvent, led to no conversion of the salts. Product yields and distributions were determined by using the same procedures described for direct irradiation reactions.

Preparation of 2-Methyl-1-(*m*-(d_3-methyl)benzyl)-1-pyrrolinium Perchlorate (63-d_3). This substance was prepared following the procedure used for the preparation of the protio analogue: ^{1}H NMR (acetone-d_6) 2.22 (p, 2 H, H-4), 2.35 (p, residual CD_2H), 2.72 (s, 3 H, 2-CH_3), 3.40 (t, 2 H, H-3), 4.11 (t, 2 H, H-5), 5.11 (s, 2 H, $ArCH_2$), 7.24-7.33 (m, 4 H).

Irradiation of 2-Methyl-1-(*m*-(d_3-methyl)benzyl)-1-pyrrolinium Perchlorate (63-d_3). Irradiation of the d_3-pyrrolinium perchlorate **63-d_3** in CH_3CN and 0.2% H_2O-CH_3CN (for direct irradiation) or in acetone (for sensitized irradiation) and workup were carried out as described previously for the protio analogue. This afforded a mixture of 3'-(trideuteriomethyl)-(**67-d_3**)- and 5'-(trideuteriomethyl)-5-methyl-3,4-benzopyrrolizidine (**66-d_3**) each of which was shown by ^{1}H NMR to have completely (ca. 97%) retained the d_3 label.

Acknowledgment. The general financial support provided by the National Science Foundation (Grant CHE-08240) and the National Institutes of Health is gratefully acknowledged. Purchase of the 400-MHz NMR spectrometer used in these studies was aided by an NSF grant (DMB-20157).

Supplementary Material Available: Experimental procedures for the preparation of benzyl chlorides, benzyl alcohols, and ortho and meta substituted benzyl iodide (6 pages). Ordering information is given on any current masthead page.

Intermediates in the Ene Reactions of Singlet Oxygen and *N*-Phenyl-1,2,4-triazoline-3,5-dione with Olefins

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Contribution from the Department of Chemistry, University of Crete, 71110 Iraklion, Crete, Greece, and Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024. *Received November 2, 1989*

Abstract: The reaction between singlet oxygen and *cis*- and *trans*-2-butene-*1,1,1*-d_3 has been studied. The product isotope effects (k_H/k_D) were found to be 1.38 and 1.25, respectively. Similarly, *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD) reacts readily with these substrates and shows isotope effects that are larger (5.36, 1.29) but in the same direction. 2-Methyl-1-propene-3,3,3-d_3 is unreactive with singlet oxygen but reacts easily with PTAD with a product isotope effect of 1.25. The intermolecular (kinetic) and intramolecular (product) isotope effects on the reactions of singlet oxygen with *cis*-1,4-diphenyl-2-butene were found to be 1.07 and 1.50, respectively. cis-Butene is 18 times more reactive with singlet oxygen than the trans isomer. Ene reactions for both singlet oxygen and PTAD probably proceed through the reversible formation of an intermediate with structural requirements similar to a perepoxide or aziridinium imide, respectively.

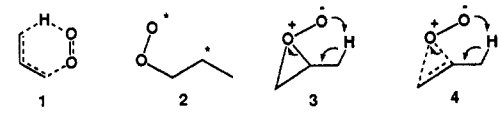
Although the mechanism of the ene reaction of singlet oxygen with olefins has been studied for many years by many research groups, it is still the subject of controversy.[1-6] At least four mechanisms have been proposed for this reaction: (1) a concerted reaction in which the characteristic bond shifts take place through a cyclic transition state (**1**), (2) formation of a zwitterionic or diradical intermediate in which the C-O bond forms first (**2**), (3) formation of a perepoxide intermediate (**3**), and (4) formation of an exciplex (**4**) with a geometry similar to that of **3**. These possibilities are shown in Scheme I.

The concerted mechanism was generally accepted for many years because neither the rate nor the product distribution of ene reactions is sensitive to solvent, many attempts to trap intermediates had been unsuccessful, and there is little evidence for the Markovnikov directivity which would be anticipated for intermediates of type **2**.[7-9]

A diradical mechanism for the reactions of singlet oxygen with many types of substrates was suggested by Goddard and Harding on the basis of GVB calculations.[10] However, this intermediate has not found much support because it would not be expected to give the observed high stereoselectivity if it had sufficient lifetime to rotate around the former double bond.

Evidence for dipolar intermediates in reactions of singlet oxygen has come mainly from substrates in which the cation would be expected to be stabilized by oxygen or by conjugation with a double bond or aromatic system. For example, Jefford demonstrated solvent incorporation in [2 + 2] reactions in the methoxynorbornene system.[11] Jefford has also trapped zwitterionic intermediates by addition to carbonyls in similar systems.[12,13]

Scheme I. Proposed Mechanisms for the Ene Reaction of Singlet Oxygen (* = radical or charge)



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[‡] University of California, Los Angeles.

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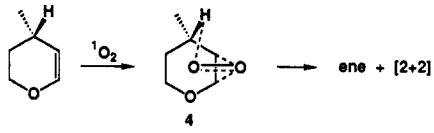
Methanol adducts are also formed in indenes, hindered dienes, and other conjugated systems, although their formation has also been interpreted as resulting from reactions of a perepoxide.[14-16] In addition, Schuster suggested that some rearrangements in acylated enol esters were explicable on the basis of zwitterionic intermediates.[17]

Perepoxide intermediate **3** was first suggested by Sharp.[18] Kearns isolated trapping products consistent with a perepoxide (or, as mentioned above, a zwitterionic) intermediate.[15,19,20] Frimer and Bartlett, in a careful study of isotope effects in some dihydropyrans, proposed either a perepoxide or a charge-transfer complex of similar geometry, **4**, which could yield both ene and [2 + 2] products.[21] Fukui has suggested a geometry for complexes of singlet oxygen with alkenes that does not differ much from that expected for a perepoxide.[22]



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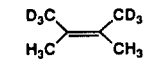
Some of the same intermediates have also been suggested for the [2 + 2] addition of singlet oxygen to electron-rich olefins to produce dioxetanes. It is not certain whether these two reactions proceed through similar transition states, but the pathway to [2 + 2] addition seems to be more polar than the ene route, since the former reaction is favored by polar solvents in cases where the two reactions compete.[21] Recent evidence suggests that even the [2 + 4] reaction with dienes can go through a zwitterionic intermediate.[23]

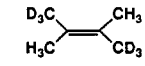
The results of theoretical calculations for this reaction are contradictory. Semiempirical MINDO/3 calculations by Dewar and Thiel suggested that addition of singlet oxygen to propene to form a perepoxide is 16 kcal/mol exothermic.[24] Similar conclusions resulted from orbital correlation diagrams[3] and CNDO/2-CI calculations.[22] In contrast, GVB-CI calculations by Harding and Goddard favor diradical intermediate **2**[10] and place the perepoxide at least 8 kcal/mol above the known activation enthalpies. However this view has been challenged by Hotokka and co-workers on the basis of CASSCF calculations.[25] On the other hand STO-3G and unrestricted MINDO/3 (UM3) calculations by Yamaguchi and Houk concluded that a concerted process was preferred, excluding both perepoxide and biradical mechanisms.[26]

Recent experimental results persistently suggest the formation of an intermediate. The main question is its structure. There is now substantial evidence that the intermediate is a perepoxide or something with similar geometry. The key experiments were those of Stephenson et al., who found a strong stereochemical dependence of the hydrogen isotope effects of the reaction of singlet oxygen with (*Z*)- and (*E*)-2,3-bis(trideuteriomethyl)-2-butene.[27]

Isotope effects similar to those in the *E* isomer were also found with the *gem*-bis(trideuteriomethyl)isomer, where the CH_3 and CD_3 groups are also *Z*.



(*Z*)-5 : k_H/k_D= 1.04-1.09



(*E*)-5 : k_H/k_D= 1.38-1.41

Similar experiments by Green and co-workers with triazolinediones and deuterated tetramethylethylenes gave isotope effects in the same direction as with singlet oxygen, but larger.[28] Green suggested an aziridinium imide intermediate in this reaction, analogous to the perepoxide.

Intra- and intermolecular effects in the ene reaction of singlet oxygen with olefins have never been measured in the same system with the same techniques. Earlier work by Nickon et al. was interpreted on the basis of a concerted mechanism.[29] Kopecky found low intermolecular kinetic isotope effects (k_H/k_D = 1.08, 1.13) for *Z* and *E* d_0- versus d_6-dimethylstilbenes,[30] and more recently, Gollnick compared d_0- versus d_{12}-2,3-dimethylbutene and found a value of 1.11.[9]

Orfanopoulos, Grdina, and Stephenson also showed that there is a strong directing effect in the ene reaction toward attack at the more crowded side in an alkyl-substituted olefin.[31] Similar effects were reported independently by Schulte-Elte et al.[32-34] This unexpected regioselectivity was shown earlier to hold in enol ethers as well, where oxygen adds on the same side as the alkoxy group.[35,36] The ene reaction of singlet oxygen with α,β-unsaturated carbonyl[37-39] and carboxyl compounds[40,41] and related systems[42,43] shows strong stereoselectivity for abstraction of the hydrogen geminal to the functional group. In addition, the ene reaction is stereospecific: optically active di- and trisubstituted olefins gave products in which the transferred hydrogen came only from the side of the alkene on which the C–O bond was formed.[44] This result requires that there be no rotation about the original double bond in the intermediate. However, recent experiments with dienes suggest that this restriction does not apply when the intermediate can give an allylically stabilized cation, and isomerization can occur.[23]

Schuster et al. demonstrated that trans olefins show distinctly lower normalized (negative) entropies of activation for the ene reaction than cis and suggested that a reversible exciplex may be formed, followed by an allylic hydrogen–oxygen interaction in the rate-limiting step.[45] Gorman found that the reactions of singlet

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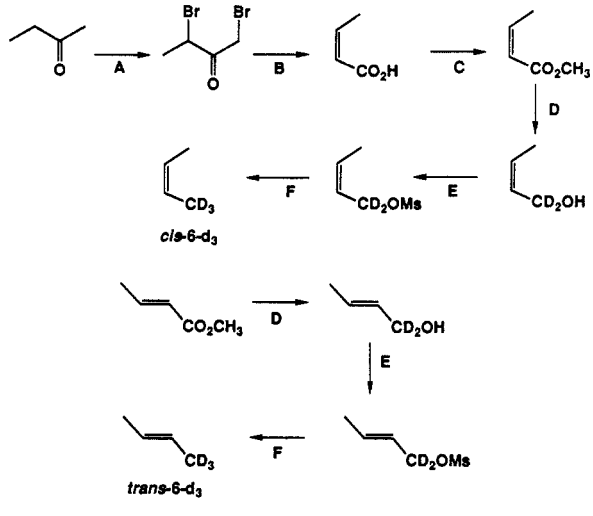
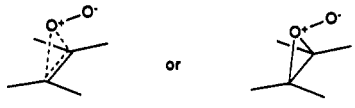
Scheme II. Synthesis of Butenes-d_3



oxygen with a variety of substrates have negative activation enthalpies and concluded that a reversibly formed exciplex is intermediate.[46,47] As pointed out by Gorman, none of the experiments clearly distinguish between formation of a perepoxide or a geometrically similar exciplex. All are consistent with an intermediate with geometry equivalent to that below.



We now report in detail the photooxygenation of the disubstituted olefins, *cis*- and *trans*-2-butenes and 1,4-diphenyl-*cis*-butene.[48] These alkenes are less reactive than most of the substrates studied previously and provide an additional test of the proposed perepoxide intermediate. If the perepoxide or the kinetically equivalent exciplex is *irreversibly* formed in the rate-determining step with a second, faster, product-determining step, there should be no (or only a small secondary) intermolecular kinetic isotope effect, but a significant intramolecular (product) isotope effect. *cis*-Alkenes might be expected to have an intramolecular (product) isotope effect comparable to that in (*E*)-2,3-bis(trideuteriomethyl)-2-butene (*E*-**5**) but *trans*-alkenes should have no such isotope effect. The results of these experiments provide strong evidence for an intermediate in the singlet oxygen ene reaction with the geometry shown above and suggest that its formation may be reversible. Reactions of these substrates with triazolinediones lead to a similar interpretation.[49]

Results

Butene-d_3 Isomers. *cis*- and *trans*-**6**-d_3 were synthesized from butanone and methyl crotonate, respectively, as shown in Scheme II.

Singlet oxygen was found to react readily with *cis*-**6**-d_3 at −80 °C in Freon-11 with mesoporphyrin IX dimethyl ester as sensitizer. The reaction was followed by gas chromatography, and the allylic hydroperoxide was the only observed product.

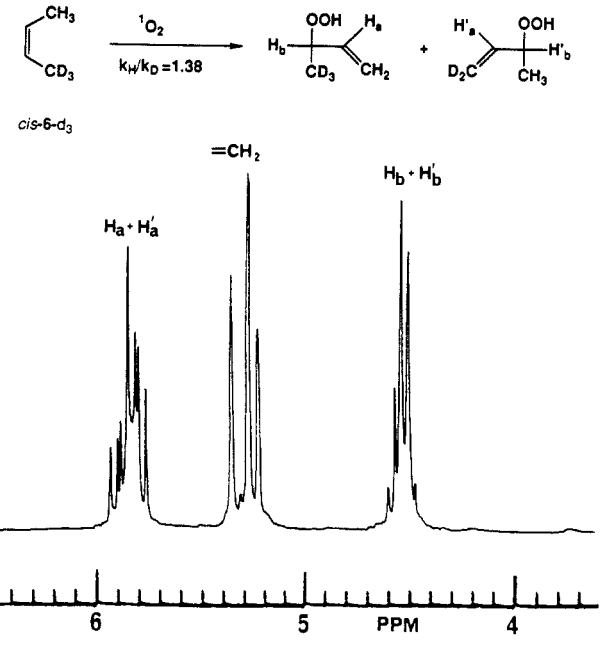
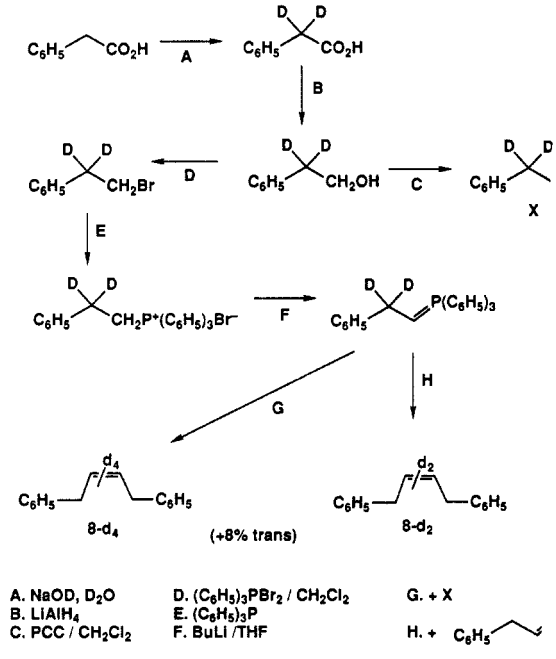
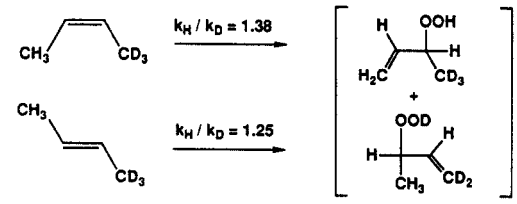


Figure 1. ^1H NMR (200 MHz) of the photooxygenation products of *cis*-**6**-d_3 in $CDCl_3$.

Scheme III. Synthesis of Deuterated 1,4-Diphenyl-*cis*-butenes



The product isotope effects (k_H/k_D) from the cis- or trans-trideuterated butenes were determined by integration of the vinyl and allylic hydrogens between 4 and 6 ppm; the NMR spectrum is shown in Figure 1. Both 200- and 500-MHz spectra were used for this purpose; only the 200-MHz spectra are shown.



Although 2-methyl-1-propene is reported[8] to react 7 times faster with singlet oxygen than *trans*-butene, 2-methyl-1-propene-*3,3,3*-d_3 (**7**) is unreactive under our conditions.

1,4-Diphenyl-*cis*-butenes. Butenes are too volatile to permit determination of the intermolecular isotope effect, and we synthesized 1,4-diphenyl-*cis*-butene-*1,1*-d_2 (**8**-d_2) and 1,4-diphenyl-

(46) Gorman, A. A.; Gould, I. R.; Hamblett, I. *J. Am. Chem. Soc.* **1982**, *104*, 7098–7104.
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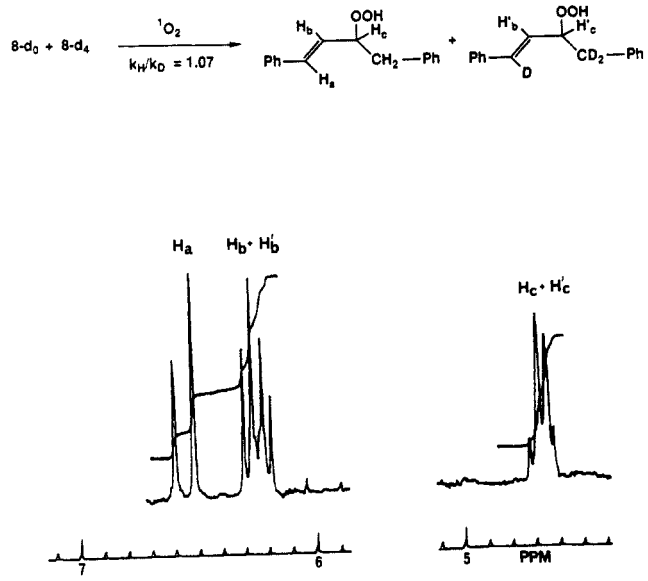


Figure 2. ^{1}H NMR (200 MHz) of the reaction mixture (54% conversion) of a 1:1 mixture of **8**-d_0 and **8**-d_4 with singlet oxygen in acetone-d_6.

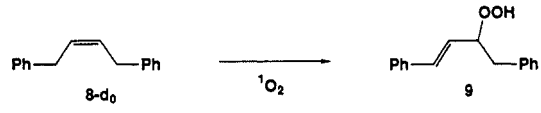
Table I. Isotope Effects for the Ene Reaction of 1,4-Diphenyl-*cis*-2-butene[a] with Singlet Oxygen

reaction type	substrate	conversion, %	k_H/k_D
intermolecular	**8**-d_0/**8**-d_4	38	1.04 ± 0.04
		54	1.09 ± 0.04
		64	1.08 ± 0.05
intramolecular	**8**-d_2	80	1.50 ± 0.04

[a] 92% cis, 8% trans; the trans isomer is much less reactive than the cis. No isomerization of the *Z* isomer was observed.

cis-butene-*1,1,4,4*-d_4 (**8**-d_4) (Scheme III) for this purpose.

A mixture of equal amounts of **8**-d_0 and **8**-d_4 with meso-porphyrin IX in acetone-d_6 reacts smoothly on irradiation with a 650-W tungsten–halogen lamp at 0 °C. The trans allylic hydroperoxide **9** is the only product.



The reaction of the deuterated substrates was interrupted at various conversions, and the product ratios were determined by ^{1}H NMR integration of the vinyl and allylic hydrogen peaks (Figure 2). A very small isotope effect (average k_H/k_D = 1.07) was found in the intermolecular competition between **8**-d_0 and **8**-d_4. In contrast, there is a significant product isotope effect (average k_H/k_D = 1.50) in the intramolecular reaction with **8**-d_2, where methylene groups in the cis configuration compete. The isotope effects are summarized in Table I.

Relative Rates. The relative rates of photooxygenation of *cis*- and *trans*-2-butenes were measured in a competition experiment. The relative rates of disappearance of the two olefins are plotted in Figure 3; the cis isomer reacts 17.7 times faster than the trans.

Reaction of PTAD and Butene-d_3. *N*-Phenyl-1,2,4-triazoline-3,5-dione (PTAD) reacts quantitatively with *cis*- and *trans*-**6**-d_3 and with 2-methyl-1-propene-*3,3,3*-d_3 (**7**) in CH_2Cl_2 at −5 °C. The intramolecular isotope effects were measured by ^{1}H NMR integration of the product mixtures. As shown in Scheme IV, *cis*-**6**-d_3 gives a large isotope effect, k_H/k_D = 5.36. The same isotope effect within experimental error was measured at −40 °C. *trans*-**6**-d_3 and 2-methyl-1-propene-d_3 (**7**) show smaller but significant isotope effects, 1.29 and 1.25, respectively. The NMR spectra of the ene adducts of PTAD with the butenes are shown in Figure 4.

Discussion

Intramolecular Isotope Effects of Butene-d_3 Isomers with $^1O_2$ and PTAD. Isotope effect measurements are a powerful tool for

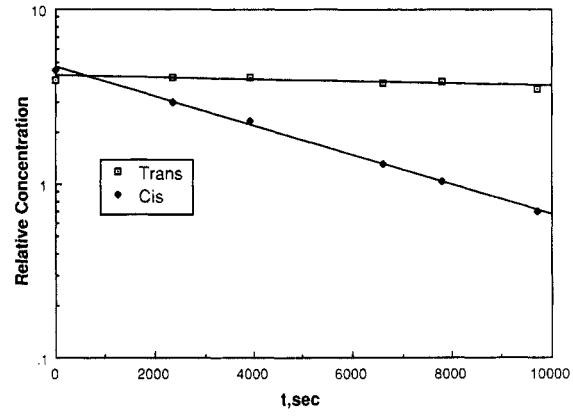


Figure 3. Relative rates of photooxygenation of isomeric 2-butenes. A mixture of 0.76 M (129 mg, 2.3 mmol) *trans*-2-butene and 0.75 M (126 mg, 2.25 mmol) *cis*-2-butene in Freon 11 was irradiated at −80 °C. The decrease of the butenes was measured by GLC analysis on a capillary column at 30 °C (acetone-d_6 internal standard).

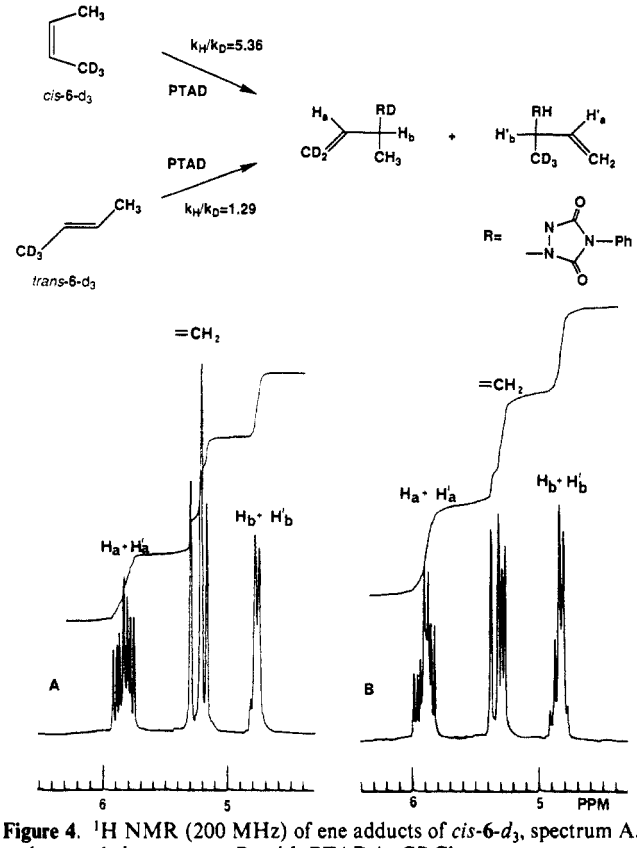
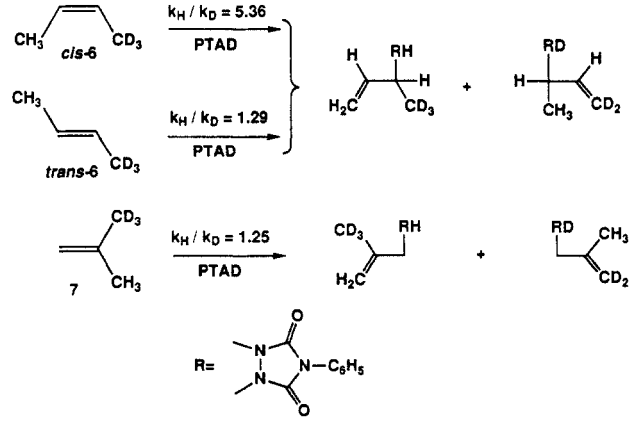


Figure 4. ^{1}H NMR (200 MHz) of ene adducts of *cis*-**6**-d_3, spectrum A, and *trans*-**6**-d_3, spectrum B, with PTAD in $CDCl_3$.

Scheme IV. Isotope Effects for the Reactions of Butene Isomers with PTAD



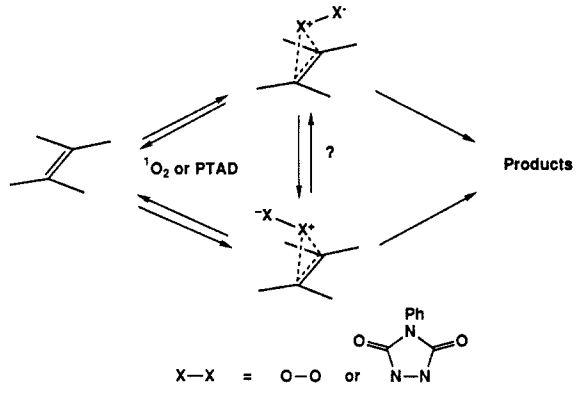


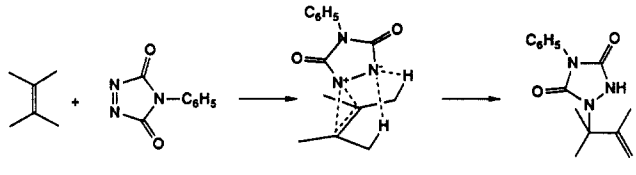
Figure 5. Proposed mechanism for *cis*- and *trans*-butene-d_3 (**6**) reactions.

distinguishing between concerted and stepwise reaction pathways.[5,28,50,51] Large intermolecular primary deuterium isotope effects provide strong evidence for hydrogen abstraction in the rate-determining step of the reaction. However, high *intra*molecular (product) and simultaneous low *inter*molecular (i.e., competition, kinetic) isotope effects are evidence for an intermediate, with an isotope effect on the second (product-determining) but not the first (rate-determining) step.

The reaction of $^1O_2$ with trideuterated butenes gives a substantial product (intramolecular) isotope effect with both isomers.[48] *cis*-Butene-*1,1,1*-d_3 has k_H/k_D = 1.38, close to that observed[27] with the more electron rich (*E*)-2,3-bis(trideuteriomethyl)-2-butene (*E*-**5**) (1,4-cis-competition), whereas the trans isomer shows an unexpectedly large isotope effect, 1.25, much larger than that observed with (*Z*)-2,3-bis(trideuteriomethyl)-2-butene (*Z*-**5**) (1.07, trans competition). Only the ene adduct was detected during the photooxygenation of either butene, and there was no isomerization of starting material or formation of any byproducts.

The isotope effects (k_H/k_D) on the reaction of the butene-d_3 isomers with PTAD are similar to those found with singlet oxygen, but larger (Scheme IV). The isotope effect for the cis compound (5.36) is much larger than that with (*E*)-2,3-bis(trideuteriomethyl)-2-butene[28] (*E*-**5**) (3.8), and is one of the largest ever observed for an ene reaction. In *trans*-**6** and -**7** where CH and CD bonds have trans or gem relationships, the isotope effect is 1.29 and 1.25, respectively. Although the effect in trans and gem compounds is much smaller than that in the *Z* isomer, it is significant, and much larger than that observed with (*Z*)-2,3-bis-(trideuteriomethyl)-2-butene (*Z*-**5**) (1.1).[28] Thus PTAD behaves similarly to singlet oxygen in that cis-related methyl and deuteriomethyl groups give a large isotope effect and trans and gem groups produce a smaller but nontrivial effect.

In a concerted reaction mechanism, one would expect similar isotope effects for *cis*-**6**-d_3, *trans*-**6**-d_3 and **7**. These results provide strong evidence for an intermediate in both reactions with structural requirements similar to the aziridinium imide proposed by Green[28] for the PTAD reaction, or the perepoxide for the singlet oxygen reaction. An aziridinium imide adduct of adamantylideneadamantane is stable at low temperatures and has been recently characterized by Nelsen.[52] This intermediate, shown below, resembles the perepoxide in that it should be able to discriminate between hydrogen and deuterium only when they are on the same side of the double bond.



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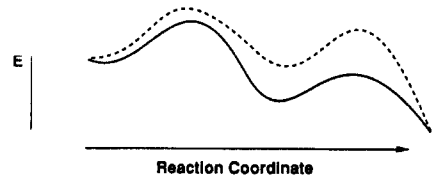
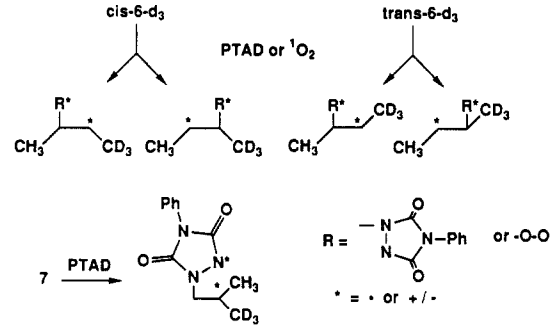


Figure 6. Proposed energy diagram of the reaction of $^1O_2$ with butenes (dashed line) and tetramethylethylenes (solid line). The well is deeper for the tetramethylethylenes, so that reversion is less important.

Equally importantly, these results eliminate diradicals and dipolar species from consideration. Such intermediates expected from the three key labeled butenes (*cis*-**6**-d_3, *trans*-**6**-d_3, and **7**) are shown below. Since no isomerization of the starting olefin was observed, if there is an open intermediate, it cannot return to starting material. Such intermediates should give rather similar and small β (secondary) isotope effects from *cis*-**6**-d_3 and *trans*-**6**-d_3, in contrast to experimental results. Similarly, the diradical formed from **7** should be expected to have a substantial primary isotope effect, which is not observed, since the stereochemistry of the intermediate permits C–H and C–D competition.



The substantial isotope effect observed for *trans*-**6**-d_3, 1.25 with singlet oxygen and 1.29 with PTAD (and 1.25 with isobutylene **7**), could be the result either of partial reversion of the intermediate to the starting materials, or inversion to the isomeric intermediate, since the corresponding hydrogens cannot compete directly in an intermediate of this geometry. If an aziridinium imide or a loose complex with similar configurational structure is formed irreversibly, there should be a significant isotope effect when H and D are cis and able to compete, but none with trans or geminal (**7**) olefins, where the isotopes are on opposite sides of the double bond. However, if either isomerization or reversibility operates to a significant extent, an isotope effect is expected even for opposite methyl groups. The most likely candidate is reversible formation of a perepoxide or aziridinium intermediate, or an exciplex with similar structural requirements, both with singlet oxygen and PTAD (Figure 5).

Although the trans isotope effects for (*Z*)-tetramethylethylene-d_6 (**5**) with $^1O_2$ and PTAD are smaller than with the butenes, they are also not zero. Thus an interconversion process is likely for this olefin as well. The magnitude of the effect should be dependent on the relative contribution of the direct reaction and the isomerization or reversal. Both processes should be more efficient with the butenes than with the more electron-rich olefins, where the bonding should be stronger. A larger trans isotope effect would therefore be expected for the butenes than tetramethylethylenes, as observed.

Beak has carefully analyzed the kinetics of such processes and derived conditions where reversible formation of intermediates can give various isotope effects.[50] One possible energy diagram for the reaction of butenes and tetramethylethylenes, shown in Figure 6, is analogous to one proposed by Houk.[53] In both cases, the intermediate is lower in energy than starting material, consistent with the near zero or negative activation enthalpies. However, the stabilization of the intermediate is less in the less

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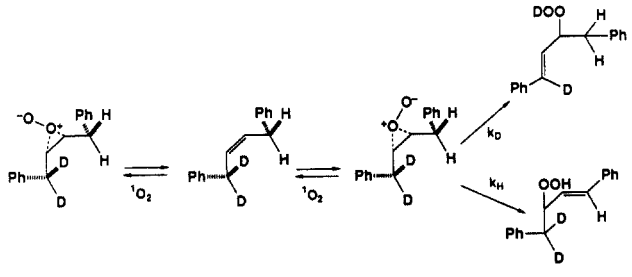
electron-rich alkenes, and the intermediate well is therefore shallower, leading to a lower barrier for reversion.

The fact that the isotope effect for the reaction with PTAD is the same within experimental error at −40 °C as at 5 °C implies a negligible activation enthalpy for the isotope effect. According to Kwart, a combination of a large isotope effect and small temperature dependence is characteristic of a nonlinear transition state, consistent with the model suggested above.[54] However this view has been challenged by McLennan and Gill on the basis of theoretical calculations.[55]

Intra- and Intermolecular Isotope Effects of 1,4-Diphenyl-(*Z*)-2-butene with $^1O_2$. As shown in Table I, a very small intermolecular (kinetic) isotope effect (average $k_H/k_D = 1.07$) was found for the competition between **8**-d_0 and **8**-d_4. This effect is in the range of intermolecular kinetic isotope effects previously reported for tetramethylethylene and other alkenes and interpreted as supporting a concerted mechanism.[9,30] In contrast, there is a significant intramolecular (product) isotope effect (average $k_H/k_D = 1.50$) in the reaction using **8**-d_2, where methylene groups in the cis configuration compete. The magnitude of this effect is similar to those previously reported from tetramethylethylene-d_6, (*E*)-**5**, and other alkenes in which hydrogen and deuterium compete in a cis relationship.[27]

A small kinetic isotope effect and a substantial product isotope effect strongly suggest rate-determining formation of an intermediate without cleavage of a C–H bond. Formation of a perepoxide or an exciplex with similar structural requirements accommodates the present and previous data and is consistent with the discussion above, in which it is suggested that the intermediate is formed reversibly.



Cis disubstituted olefins are invariably more reactive than their trans counterparts.[8,45] In this case, *cis*-butene is 17.7 times more reactive than the trans isomer (Figure 3). This is consistent with Stephenson's mechanism where the more crowded side of the olefin is more reactive, the so-called "cis effect". An alternative explanation has been suggested by Houk based on changes in alkyl group conformational barriers caused by cis substituents.[53] Recent results of Clennan are also consistent with these views.[56]

Finally, in spite of the remarkable similarities between the reactions of singlet oxygen and PTAD noted here and elsewhere,[57] Adam has noted major differences in stereoselectivities of the reaction with allylsilanes,[58] and major differences are found in the reactions with dienes as well.[23,59]

Experimental Section

Nuclear magnetic resonance (NMR) spectra were determined on Bruker WP-200-MHz and AM-500-MHz spectrometers. Deuteration percentage was measured by ^1H NMR integration of the appropriate hydrogen peaks. Calibration experiments showed a 2.0–2.5% integration error on the Bruker AM-500-MHz instrument. All spectra were taken in deuteriochloroform, except as noted. Chemical shift values are reported in δ (ppm) relative to internal tetramethylsilane. Nitromethane was external standard.

Reactions were routinely followed by vapor phase chromatographic (VPC) analysis on a 50-ft OV-100 capillary column in a HP-5880-A model gas chromatograph. Solvents were freshly distilled from sodium metal. Methyl crotonate, methyl methacrylate, lithium aluminum deuteride, mesoporphyrin IX dimethyl ester, and Freon-11 were obtained from Aldrich Chemical Co. PTAD was prepared from 4-phenylurazole by literature methods.[60]

Because of the volatility of the butene-d_3 isomers, samples were kept in a trap with a Rotaflo gas-tight valve. The samples were transferred from the trap to the photooxygenation cell or to an NMR tube by a Teflon tube. The temperature of the receiver was kept below 0 °C, and the weight of the trap before and after the transfer was taken and the amount of the sample was accurately measured.

***trans*-2-Buten-1-ol-*1,1*-d_2.** Reduction of methyl crotonate with lithium aluminum deuteride–aluminum chloride mixture[61,62] gave the title alcohol. To a stirred, ice-cooled suspension of 1.68 g (40 mmol, 160 mequiv) of lithium aluminum deuteride in 180 mL absolute ether was added in small portions 1.77 g (13.3 mmol, 40 mequiv) aluminum chloride. After the hydride mixture was stirred at room temperature for $^1/_2$ h and cooled at ice-bath temperature, 5 g (50 mmol) of methyl crotonate in 30 mL of ether was added dropwise. After acid workup, 3 g (80%) of the alcohol was obtained: ^1H NMR δ 1.7 (d, CH_3), 2.1 (bs, OH), 5.6–5.8 (m, 2 H).

***trans*-2-Butenyl-*1,1*-d_2 Mesylate (Standard Mesylation Procedure).**[63] To 0.6 g (8.1 mmol) of the above alcohol in 15 mL of ice-cooled, stirred CH_2Cl_2 was added triethylamine (0.86 g, 1.2 mL 8.6 mmol), followed by methanesulfonyl chloride (0.59 g, 0.64 mL, 8.4 mmol) in 3 mL of CH_2Cl_2. A precipitate formed immediately. After 2 h the solution was filtered, diluted with CH_2Cl_2, and washed with iced 5% HCl, iced 5% $NaHCO_3$, and saturated NaCl. The solution was dried with $MgSO_4$ and concentrated by flash evaporation to give a crude quantitative yield of the mesylate: ^1H NMR δ 1.8 (d, CH_3), 3.0 (s, SCH_3), 5.7–6.3 (m, 2 H).

***trans*-2-Butene-*1,1,1*-d_3.** To a stirred, ice-cooled suspension of 0.29 g (4.5 mmol) of lithium aluminum deuteride in 10 mL of diglyme was added 1.4 g (9.2 mmol) of mesylate in 2 mL of diglyme dropwise. A constant flow of nitrogen was passed through the reaction flask into a Teflon tube connected with a trap with a Rotaflo gas tight valve, which was cooled to −70 °C. After the addition of the mesylate, the temperature was increased slowly to 100 °C for 1 h. The desired olefin collected in the trap in 62% yield. VPC assay showed the sample to contain only the *E* isomer: ^1H NMR δ 1.6 (m, CH_3), 5.2–5.5 (m, 2 H).

1,3-Dibromobutanone.[64] 2-Butanone (72 g, 1 mol) was mixed with 48% hydrobromic acid (100 mL/mol ketone) and chilled with ice–water. Bromine (102 mL, 2 mol) was added dropwise, followed by addition of 300 mL of water. The heavier organic layer was separated and distilled. The fraction boiling between 64 and 65 °C (2.3 mmHg) gave 100 g (43%) of pure 1,3-dibromobutanone: ^1H NMR δ 1.8 (d, CH_3), 4.1 (d, 1 H, CHH'Br, $J_{H,H'} = 12$ Hz), 4.4 (d, 1 H, CHH'Br, $J_{H,H'} = 12$ Hz) 4.9 (q, 1 H, CHBr); δ $(CD_3)_2CO$, 1.9 (d, CH_3), 4.6 (s, 2 H, CH_2Br), 5.2 (q, 1 H, CHBr).

***cis*-2-Butenoic Acid.** The procedure of Rappe was followed.[65] To a molar solution of potassium bicarbonate in 1 L water was added 1,3-dibromobutanone-2 (48 g, 0.2 mol). The mixture was vigorously stirred for 2 h followed by extraction (2 × 100 mL) with ether. The water layer was acidified with dilute hydrochloric acid and again extracted with 6 × 100 mL portions of ether. The organic layer was dried over $MgSO_4$ followed by ether evaporation (bath temperature below 10 °C) to give 8.6 g (0.1 mol, 50%) *cis*-butenoic acid. ^1H NMR assay showed the sample to be >97% cis. This compound was refrigerated until further use: ^1H NMR δ 2.1 (d, d, CH_3, $J_1 = 8$ Hz, $J_2 = 2$ Hz) 5.8 (d, q, 1 H, = CHCOOH, $J_1 = 11$ Hz, $J_2 = 2$ Hz), 6.1–6.7 (m, 1 H).

***cis*-Methyl 2-Butenoate.** The standard esterification procedure with diazomethane (free from ethanol) was used.[66] The reaction was carried out in the hood behind a safety shield, with use of the Aldrich Minidiazald apparatus with clear-fit joints. In the distilling flask, connected with a downward condenser (cooled by isopropanol–dry ice mixture) and a dropping funnel, were placed 5 g of potassium hydroxide in 8 mL of water, 28 mL of carbitol (diethylene glycol monoethyl ether), and 8 mL of water. The condenser was connected to a 250-mL receiving flask containing a solution of 3 g (35 mmol) of *cis*-butenoic acid in 80 mL of

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absolute ether and cooled in an ice–salt bath. The stirred mixture in the distilling flask was warmed on a water bath at 70–75 °C, followed by dropwise addition of 18 g (80 mmol) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide in 100 mL of absolute ether during 15 min. The condensed ethereal solution of diazomethane reacted with the *cis*-butenoic acid in the receiving flask to give 3.5 g (35 mmol) of crude *cis*-methyl butenoate. VPC indicated the sample to be only the cis isomer contaminated by ~15% nonolefinic byproducts: ^{1}H NMR δ 2.15 (d, d, CH_3, J_1 = 6 Hz, J_2 = 1.5 Hz), 3.7 (s, OCH_3), 5.8 (d, q, 1 H, =C*H*CO_2Me, J_1 = 11 Hz, J_2 = 1.5 Hz), 6.0–6.6 (m, 1 H, CH_3C*H*=).

***cis*-2-Butenol-*1,1*-d_2.** To a stirred, ice-cooled suspension of 1.34 g (32 mmol, 128 mequiv) of lithium aluminum deuteride in 160 mL of absolute ether was added in small portions 1.41 g (10.6 mmol, 32 mequiv) of aluminum chloride. After the hydride mixture was stirred at room temperature $^1/_2$ h and cooled at ice-bath temperature, a solution of 3.5 g (35 mmol) of *cis*-methyl 2-butenoate in 15 mL of ether was added dropwise. The reaction mixture was stirred for an additional 2 h at room temperature followed by acid workup to give 1.5 g (62%) of the desired alcohol. VPC assay showed the sample to be pure Z isomer: ^{1}H NMR δ 1.6–1.8 (m, CH_3), 2.0 (s, broad, OH), 5.4–5.8 (m, 2 H).

***cis*-Butenyl-*1,1*-d_2 Mesylate.** To 0.74 g (10 mmol) of *cis*-butenol-*1,1*-d_2 in 18 mL of ice-salt cooled, stirred CH_2Cl_2 was added 1.06 g (1.4 mL, 10.5 mmol) of triethylamine, followed by dropwise addition of 1.2 g (0.84 mL, 10.5 mmol) of methanesulfonyl chloride in 4 mL of CH_2Cl_2. Immediate precipitate formation was observed. The reaction flask was kept overnight at 3–8 °C (refrigerator). After filtration of the salts, the solution was diluted with CH_2Cl_2 and washed with iced 5% HCl, iced 5% $NaHCO_3$, and a saturated solution of NaCl. The solution was dried over $MgSO_4$ and concentrated by flash evaporation to give 1.24 g (8.15 mmol), 82% yield of the title mesylate: ^{1}H NMR δ 1.8 (d, broad, CH_3), 3.0 (s, SCH_3), 5.5–6.2 (m, 2 H).

***cis*-2-Butene-*1,1,1*-d_3.** To a stirred, ice-cooled suspension of 0.18 g (4 mmol) of lithium aluminum deuteride in 10 mL of dry diglyme was added dropwise 1.24 g (8.15 mmol) of *cis*-butenyl mesylate-*1,1*-d_2 in 3 mL of diglyme. After the addition of the mesylate, the temperature was increased slowly to 100 °C for 1 h. The desired olefin (237 mg, 4 mmol) was obtained in 50% yield and collected in a cooled trap equipped with a Rotaflo valve. VPC assay showed the sample to be 99% *Z* isomer and 1% *E*: ^{1}H NMR δ 1.4–1.6 (m, CH_3), 5.2–5.6 (m, 2 H).

2-Methyl-2-propenol-*1,1*-d_2. Reduction of methyl methacrylate with lithium aluminum deuteride–aluminum chloride mixture[61,62] gave the title alcohol. To a stirred, ice-cooled suspension of 1.90 g (45 mmol, 180 mequiv) of lithium aluminum deuteride in 200 mL of absolute ether was added in small portions 2 g (15 mmol, 45 mequiv) of aluminum chloride. After the hydride mixture was stirred at room temperature for $^1/_2$ h and cooling at ice-bath temperature, 5 g (50 mmol) of methyl methacrylate in 35 mL of ether was added dropwise. After acid workup, 3.4 g (92%) of the title alcohol was obtained: ^{1}H NMR δ 1.75 (m, CH_3), 2.0 (s, broad, OH) 4.8–5.1 (m, 2 H, =CH_2).

2-Methyl-2-propenyl-*1,1*-d_2 mesylate. To 0.74 g (10 mmol) of the above alcohol in 18 mL of ice-cooled, stirred CH_2Cl_2 was added (1.06 g, 1.5 mL, 10.5 mmol) triethylamine, followed by the dropwise addition of 1.2 g (0.84 mL, 10.5 mmol) of methanesulfonyl chloride in 4 mL of CH_2Cl_2. The reaction flask was kept overnight at 3–8 °C (refrigerator). After filtration of the salts, the solution was diluted with CH_2Cl_2 and washed with iced 5% HCl, iced 5% $NaHCO_3$, and saturated NaCl. The solution was dried with $MgSO_4$ and concentrated by flash evaporation to give 1.08 g (7.1 mmol, 71% yield) of the title mesylate: ^{1}H NMR δ 1.8 (m, CH_3), 3.0 (s, SCH_3), 5.0–5.2 (m, 2 H).

2-Methyl-1-propene-*3,3,3*-d_3. To a stirred, ice-cooled suspension of 0.14 g (3.4 mmol) of lithium aluminum deuteride in 8 mL of dry diglyme was added dropwise 1.04 g (6.84 mmol) of 2-methyl-2-butenyl-*1,1*-d_2 mesylate in 3 mL of diglyme. After the addition of the mesylate, the temperature was increased slowly to 100 °C for 1 h. The desired olefin (212 mg, 3.6 mmol) was obtained in 52% yield: ^{1}H NMR δ 1.72 (d, 3 H, *J* = 1 Hz), 4.66 (m, 2 H).

Phenylacetic-*2,2*-d_2 Acid. In a high-pressure bottle were placed 6.8 g (50 mmol) of phenylacetic acid and 20 mL of a 3.5 M solution of NaOD in D_2O. The stirred mixture was warmed at 100 °C for 24 h. After cooling to room temperature, the reaction mixture was acidified with 4 N hydrochloric acid. The product was extracted with dichloromethane and dried with $MgSO_4$. The solution was concentrated by flash evaporation to give a quantitative yield of phenylacetic acid with 90% deuterium incorporation in benzylic position. This procedure was repeated to give 98% deuterated product: ^{1}H NMR δ 7.3 (m, 5 H).

2-Phenylethanol-*2,2*-d_2. To a stirred ice-cooled suspension of 1.36 g (35.8 mmol) of lithium aluminum hydride in 50 mL of tetrahydrofuran was added dropwise 5 g (36 mmol) of phenylacetic-*2,2*-d_2 acid in 80 mL of tetrahydrofuran. The hydride mixture was stirred at room temperature overnight, followed by standard alkaline workup to give after distillation (75–76 °C, 2.5 mmHg) 3.4 g (80%) of the alcohol with >97% deuteration at the benzylic position: ^{1}H NMR δ 3.8 (br s, 2 H), 7.1–7.3 (m, 5 H).

2-Phenylethyl-*2,2*-d_2 Bromide. To a stirred ice-cooled solution of 3.15 g (12 mmol) of triphenylphosphine in 15 mL of CH_2Cl_2 was added dropwise a solution of 1.92 g (0.62 mL, 12 mmol) of bromine in 5 mL of CH_2Cl_2. A white precipitate formed immediately. After the reaction mixture was stirred at room temperature for $^1/_2$ h and cooled at ice bath temperature, a solution of 1.2 g (10 mmol) of 2-phenylethanol-*2,2*-d_2 in 5 mL of CH_2Cl_2 was added dropwise. The reaction mixture was stirred for an additional hour at room temperature and concentrated by flash evaporation. The residue was washed several times with hexane followed by flash evaporation of the solvent to give 1.74 g (93%) of the desired product. NMR analysis showed 97% deuteration at the benzylic position: ^{1}H NMR δ 3.6 (s, 2 H), 7.15–7.4 (m, 5 H).

(2,2-Dideuterio-2-phenylethyl)triphenylphosphonium Bromide. In a high-pressure bottle, 1.70 g (9.09 mmol) of 2-phenylethylbromide-2,2-d_2 and 2.62 g (10 mmol) of triphenylphosphine were stirred neat at 100 °C for 24 h. The salt was allowed to cool to a glassy solid. NMR analysis showed 97% deuteration at the benzylic position: ^{1}H NMR δ ($(CD_3)_2$CO) 4.3 (d, 2 H), 7.1–8.2 (m, 20 H).

Phenylacetaldehyde-*2,2*-d_2. The title aldehyde was prepared by Corey's method.[67] To 1.6 g (7.5 mmol) of pyridinium chlorochromate in 10 mL of CH_2Cl_2 was added 0.62 g (5 mmol) of 2-phenylethanol-*2,2*-d_2 in 10 mL of CH_2Cl_2. The reaction was monitored by VPC and yielded 0.38 g (64%) of the product. NMR analysis showed 96% deuterium incorporation at the benzylic position: ^{1}H NMR δ 7.10–7.45 (m, 5 H), 9.75 (s, 1 H).

***cis*-1,4-Diphenyl-2-butene-*1,1,4,4*-d_4.** To 1.4 g (3.1 mmol) of (2,2-dideuterio-2-phenylethyl)triphenylphosphonium bromide in 10 mL of tetrahydrofuran was added dropwise 1.56 g (3.1 mmol) of 1.98 M butyllithium. After the reaction mixture was refluxed for 3 h and cooled to room temperature, a solution of 0.36 g (2.9 mmol) of phenylacetaldehyde-*2,2*-d_2 in 2 mL of tetrahydrofuran was added dropwise. After 5 h of stirring, the solution was concentrated by distillation, and the olefin was extracted with several portions of hexane. The product was purified by flash column chromatography to yield 0.31 g (50%) of the olefin. VPC analysis showed the formation of the *Z* isomer in 92% isomeric purity. NMR analysis showed 92% deuterium incorporation in the benzylic positions: ^{1}H NMR δ ($(CD_3)CO$) 5.65 (s, 2 H), 7.0–7.4 (m, 10 H); MS calcd for $C_{16}H_{12}D_4$: 212.1503, found 212.1499.

1,4-Diphenyl-*cis*-2-butene-*1,1*-d_2. The olefin was prepared by Wittig coupling of phenylacetaldehyde with the corresponding d_2-ylide, similarly to the procedure used for the **8**-d_4 olefin. The cis isomer was formed in 92% isomeric purity and had >96% deuterium incorporation at the benzylic position: ^{1}H NMR δ 3.5 (d, 2 H) 5.7 (m, 2 H), 7.1–7.3 (m, 10 H); MS calcd for $C_{16}H_{14}D_2$ 210.1377, found 210.1356.

Photooxygenation. General Procedure. The photooxygenation of *trans*-**6**-d_3, *cis*-**6**-d_3, and a mixture of *cis*-**6**-d_0/*trans*-**6**-d_0 was carried out at −80 °C, in a Pyrex cell inside a temperature-controlled cell described previously[68] with a Varian-Eimac 300-W xenon lamp as the light source. A 10^{-4} M mesoporphyrin IX dimethyl ester in Freon 11 was the sensitizer. Photooxygenation of **8**-d_0/**8**-d_4 and of **8**-d_2 was performed in a NMR tube, in acetone-d_6, at 0 °C with a tungsten–halogen lamp. Photooxygenations were routinely followed by vapor-phase chromatographic (VPC) analyses on a capillary column. Removal of the solvent by distillation, where appropriate, was followed by ^{1}H NMR analysis of the reaction mixture.

Photooxygenation of *trans*-2-Butene-*1,1,1*-d_3. A 0.88 M solution of *trans*-**6**-d_3 (130 mg, 2.2 mmol in Freon 11) was irradiated at −80 °C. The reaction was monitored by VPC (30 °C). The only product detected during the reaction was the ene adduct of $^1O_2$ with the olefin. After 13 h of irradiation, 20% conversion was observed.

Photooxygenation of *cis*-2-Butene-*1,1,1*-d_3. A 0.80 M solution of *cis*-**6**-d_3 (140 mg, 2.37 mmol, 99% pure isomer in Freon 11) was irradiated at −80 °C. VPC analysis (30 °C) showed no isomerization of starting material or formation of any byproducts. The ene product was 97% of the reaction mixture after 5 h of irradiation.

Relative Rates of Photooxygenation of *cis*- and *trans*-2-Butene. A solution of 0.76 M (129 mg, 2.3 mmol) *trans*-2-butene and 0.75 M (126 mg, 2.25 mmol) *cis*-2-butene in Freon 11 was irradiated at −80 °C. The decrease of the starting materials was observed periodically by VPC on a 50-ft OV-100 capillary column at 30 °C; acetone-d_6 was the internal standard.

Ene Adducts from PTAD and *cis*- and *trans*-6-d_3 and Isobutylene-d_3 (7). *N*-Phenyl-1,2,4-triazoline-3,5-dione reacts quantitatively with *cis*-**6**-d_3 and *trans*-**6**-d_3, as well as with 2-methyl-1-propene-*3,3,3*-d_3 (**7**) in

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CH_2Cl_2 at -5 °C (-40 °C for *cis*-**6**-d_3). The butenes were in 30–50% excess, and the end of the reaction was indicated by complete decolorization of the reaction mixture (within a few minutes to 1 h). The ^1H NMR spectra of PTAD ene adducts with *cis*-**6**-d_3 and *trans*-**6**-d_3 are shown in Figure 4. MS calcd for *cis*-**6**-d_3-PTAD, $C_{12}H_{10}D_3N_3O_2$, 234.1196, found 234.1190. MS calcd for *trans*-**6**-d_3-PTAD, $C_{12}H_{10}D_3N_3O_2$, 234.1196, found 234.1197. Isobutylene-d_3-PTAD ene isomeric adducts: ^1H NMR δ 1.65 (s, CH_3), 4.05 (s, CH_2), 4.85 (d, J = 2 Hz, $=CH_2$), 7.45 (m, Ph); MS calcd for $C_{12}H_{10}D_3N_3O_2$: 234.1196, found 234.1208.

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Self-Assembly of a Threaded Molecular Loop

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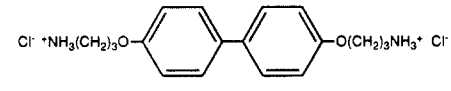
Abstract: An efficient (71% yield) synthesis of a threaded molecular loop is described. The synthetic approach is notable in that it is a template-directed self-assembly process in aqueous solution. The structure of the threaded molecular loop is unprecedented since it is held intact solely by noncovalent interactions. The high yield, mild conditions, and convergent nature of the assembly process suggest that a variety of highly organized supramolecular entities can be efficiently prepared from appropriately designed subunits via noncovalent forces.

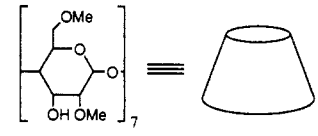
Noncovalent attractive forces are commonly employed in biological systems to drive the assembly of highly organized supramolecular entities (e.g., membranes, ribosomes, and multicomponent enzyme complexes) from relatively simple subunits.[1] In addition, the self-assembly phenomenon is proposed to have been an essential component in the molecular events that comprised protobiogenesis.[2] It is apparent that a process that plays such a fundamentally important role in biology must offer several synthetic advantages. These include (1) a reduction in structural errors in the final product by rejection of defective subunits during self-assembly, (2) synthetic economy by virtue of the convergent nature of the assembly process, and (3) facile formation of the stable end product, facilitated by rapidly established noncovalent interactions. Clearly, such attractive features should prove useful in the synthesis of artificial biologically relevant assemblies as well. Indeed, we have recently achieved an efficient template-driven self-assembly of a prototype for a heme-dependent protein mimic.[3] In addition, the advantages of the multicomponent assembly process should be useful in the construction of compounds that have no counterpart in nature. In the present paper, we describe the self-assembly of a threaded molecular loop.[4]

The diammonium salt **1** was synthesized from biphenyldiol by alkylation of the hydroxyl moieties with *N*-(3-bromopropyl)-phthalimide (71.5%) and subsequent hydrazinolysis (83.0%). The



1

resultant free diamine was dissolved in trifluoroethanol and, upon addition of concentrated hydrochloric acid, precipitated out of solution as the desired diammonium salt in quantitative yield. In spite of its doubly charged character, compound **1** is only sparingly soluble in aqueous solution. However, upon addition of 1.5 equiv of heptakis(2,6-*O*-methyl)-β-cyclodextrin (Me-CD, **2**),[5,6] the diammonium salt was rendered freely water soluble. The radical change in solubility signals the likely formation of an inclusion complex (**3**; since primary ammonium ions tend to be well solvated, we suspect that it is the free amine of **1** that threads the cavity of Me-CD). ^1H NMR (300 MHz, D_2O as solvent) confirmed the formation of **3**, since compound **1** induces upfield chemical shifts for the Me-CD C_3 (18 Hz) and C_5 (102 Hz) protons. Such chemical shifts are a generally recognized manifestation of cyclodextrin-based inclusion compound formation.[7]



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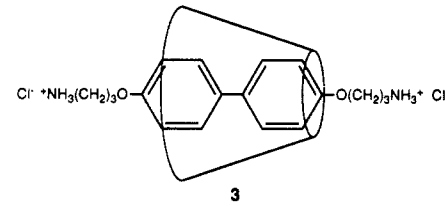

3

Species **3** (a threaded molecular loop) was sequestered at pH 7.0 by the addition of an aqueous solution of sodium tetraphenylboron (4.0 equiv). The resultant precipitate, which formed instantaneously, proved to be species **4**. The structure of this complex bears resemblance to the class of compounds known as rotaxanes, threaded molecular loops whose structural integrity is maintained by the presence of steric impediments. The structural assignment of **4** is based on the following considerations: (1) ^1H and ^{13}C NMR of the complex are consistent with a compound that contains the requisite number of components in the proper ratios [tetraphenylboron (two subunits), Me-CD (one subunit), and compound **1** (one subunit)]. (2) Fast atom bom-

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