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SYNTHETIC AND MECHANISTIC ASPECTS OF 1,3-DIENE PHOTOOXIDATION

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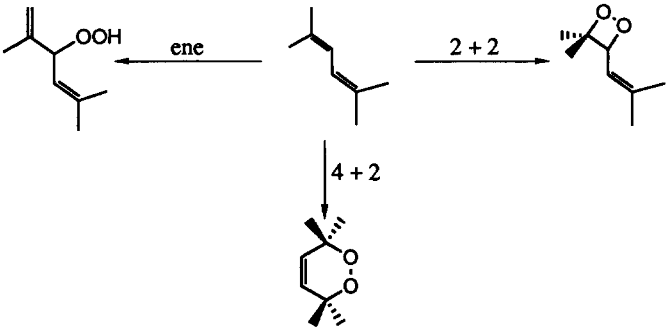
CONTENTS

1. INTRODUCTION

Windaus and Brunken[1] in a very early example of a 1,3-diene photooxidation isolated an endoperoxide from irradiation of ergosteryl acetate in an oxygen saturated alcohol solution containing the dye eosin. This seminal discovery resulted in the examination of the behavior of a large number of dienes under photooxidative conditions, and the isolation of a vast array of endoperoxides.[2] It is now recognized that photosensitized oxidations of dienes can also produce, in addition to endoperoxides,[3] hydroperoxides[4] and dioxetanes.[5] (Figure 1) The ability to functionally modify these initially formed peroxides has provided the synthetic chemist with a powerful tool to incorporate oxygen, in a controlled manner, into a wide variety of substrates.[6]

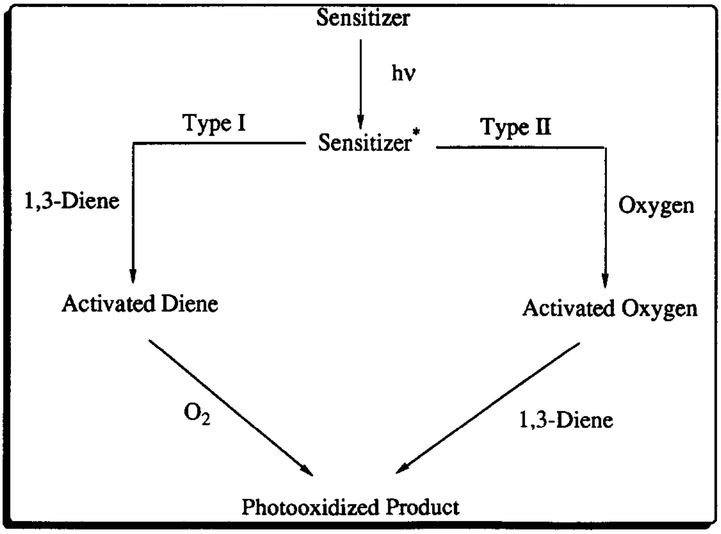
Figure 1.



Concomitant with the synthetic development of 1,3-diene photooxidations, an appreciation of the mechanistic diversity of these reactions has also evolved. Detailed mechanistic studies have revealed both stepwise and concerted pathways for the photooxidative insertion of singlet ($^1\Delta_g$) oxygen into 1,3-dienes.

The photooxidation of a 1,3-diene begins with the absorption of a photon by the sensitizing dye to produce a sensitizer excited state. (Figure 2) The subsequent reaction can be classified as either a Type I or Type II process.[7] These two reaction types differ in the order in which oxygen and the diene appear on the reaction surface. In the Type I process the initial interaction of the excited sensitizer is with the substrate and in the Type II process with oxygen. The activation of the substrate can either occur by hydrogen abstraction or electron transfer, and the activation of oxygen by energy transfer to produce singlet oxygen or by electron transfer to give superoxide.

Figure 2



The contributions of these two pathways to the overall photooxidation process can be adjusted by manipulating the experimental conditions. The Type I process is favored, and the Type II process disfavored by: (1) low concentrations of oxygen, (2) high concentrations of substrate, (3) electron rich substrates, (4) higl temperatures,[8] (5) short lifetimes for singlet oxygen, which can be selected by proper choice of the solvent,[9] and (6) the use of sensitizing dyes which are prone to hydrogen abstraction or are redox active.[10]

The determination of whether a product is formed via a Type I or Type II process is not always straightforward. Several experimental techniques to implicate the involvement of singlet oxygen, however, have been developed and taken together can form a strong case for either Type I or Type II reactivity. These include: (1) Quenching by DABCO or other amines,[11] (2) The observation of an increased rate of reaction in deuterated in comparison to hydrogenated solvents,[9] (3) Identical product distributions as a function of sensitizer or chemical source of singlet oxygen,[12] and (4) Substrate quenching of singlet oxygen emission at

1270 nm.[13]

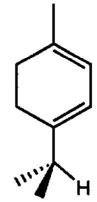
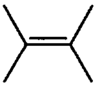
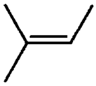
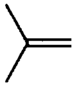
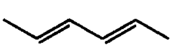
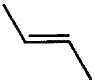
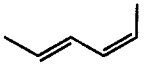
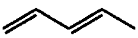
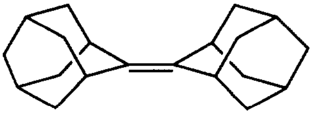
A variety of chemical methods can also be used to either generate activated 1,3-dienes or to produce singlet oxygen. As a result, in addition to the Type I and II oxidations, their dark analogues, Type ID and IID, also exist. The Type I and ID reactions occasionally allow formation of oxidized dienes which are inaccessible using Type II or IID methods. All four of these oxidation types will be discussed and illustrated with literature examples.

2. MECHANISTIC ASPECTS

2.1 Type II Photooxidations.

Alkyl substituted 1,3-dienes are the simplest organic substrates that can undergo all three of the well documented Type II photooxidation reactions.[14] The importance of each of these reaction modes for a particular diene is critically dependent on its substitution pattern.[15] Cyclic dienes are more reactive than acyclic dienes (Table 1) and in most cases their 4 + 2 reactions can effectively compete with ene or 2 + 2 cycloaddition reactions. Acyclic dienes, on the other hand, are a several of orders of magnitude less reactive

Table 1. Rate Constants for Reactions of Singlet Oxygen ($M^{-1}s^{-1}$)

	1.5×10^{8}[a]		2.7×10^{7}[b] 2.2×10^{7}[c]
			2.3×10^{6}[d] 1.3×10^{6}[c] 7.2×10^{5}[c]
	1×10^{8}[a]		6.25×10^{4}[e] 4.0×10^{3}[c]
			4.8×10^{4}[c]
	2.6×10^{5}[a]		7.2×10^{3}[c]
	1.0×10^{5}[a]	$CH_3(CH_2)_6CH{=}CH_2$	4.6×10^{2}[f]
	2.4×10^{4}[a]		1.02×10^{6}[g]

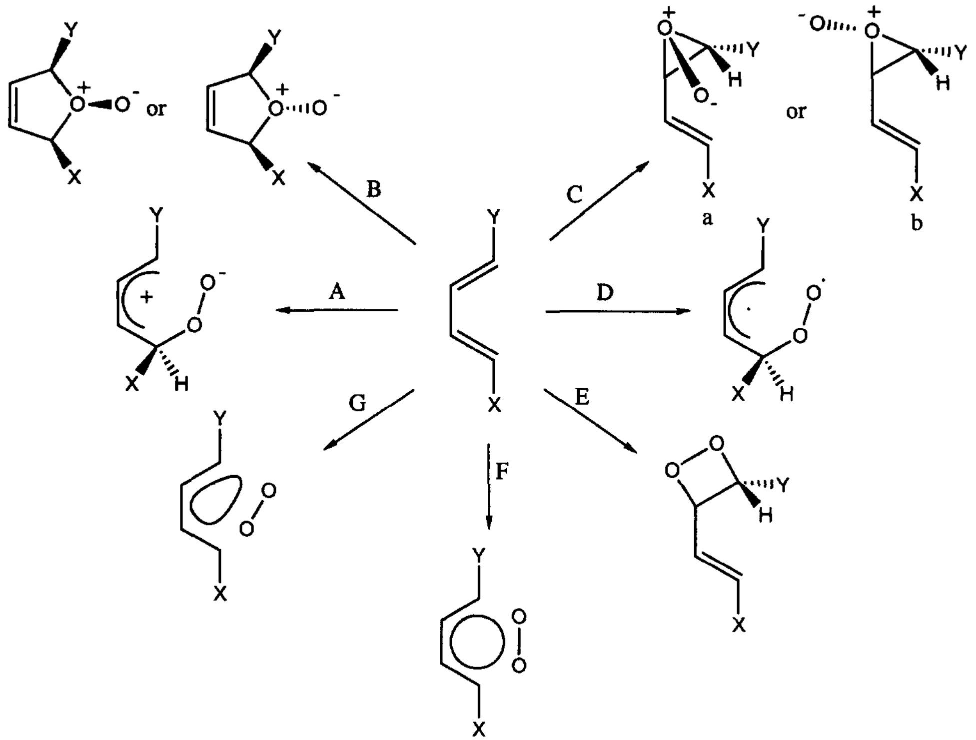
a. Reference 16. b. Reference 17. c. Reference 18. d. Reference 19. e. Reference 8a. f. Reference 20 g. Reference 21.

than their cyclic counterparts and their photooxidations can often lead to a mixture of peroxidic products.[15]

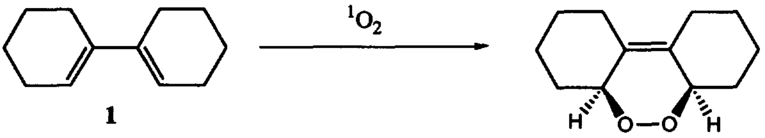
In the following discussion we will first consider the mechanisms of the three Type II processes and then examine the factors that influence competition between them.

2.1.1 The 4 + 2 Cycloaddition. The 4 + 2 cycloaddition of singlet oxygen is a versatile reaction, which occurs readily with acyclic, cyclic, and aromatic 1,3-dienes. The diene can contain a variety of different functional groups, latent functional groups,[22] and heteroatoms. Several of the intermediates and/or transition states which have been considered for the 4 + 2 cycloaddition are depicted in Figure 3

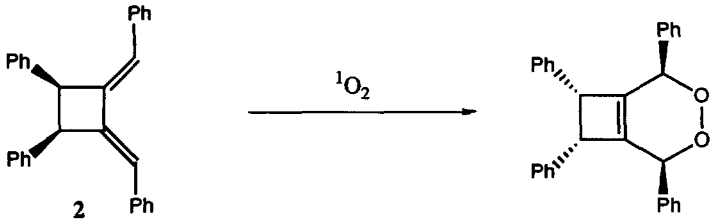
Figure 3.



Mechanisms A and D are stepwise reactions proceeding through open zwitterionic and biradical intermediates, respectively. These mechanisms have often been rejected in favor of the concerted pathway F as a result of the topographical similarity of the singlet oxygen reaction to the Diels Alder reaction and because of the observed stereospecificity of the addition of singlet oxygen to 1,1'-dicyclohexenyl,[23] **1**, and the s-cis fixed diene **2**.[24] The reactions of **1** and **2** could never-the-less be stepwise in the unlikely event that rotation in the appropriate zwitterion or biradical were slow in comparison to endoperoxide formation. The stereochemical integrity of trans-trans-2,4-hexadiene during the Diels Alder additions of difluorodichloroethylenes was maintained despite the excellent evidence for a stepwise process.[25]

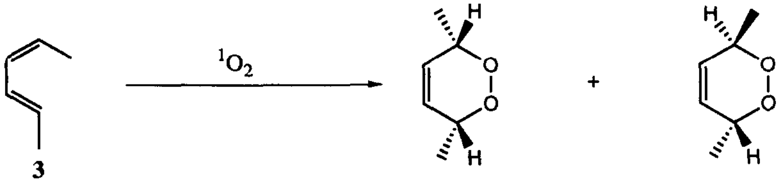


1



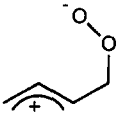
2

In 1983 Gollnick and Griesbeck[26] reported that in contrast to the reactions of singlet oxygen with **1** and **2**, *E,Z*-2,4-hexadiene **3** reacted nonstereospecifically to give a mixture of endoperoxides. O'Shea and Foote[27] followed the reactions of the *EE*, *EZ*, and *ZZ* 2,4-hexadiene isomers by low temperature NMR and directly observed their rapid singlet oxygen induced interconversion. Careful analysis of the reaction mixtures demonstrated that 4 + 2 cycloaddition was accompanied by formation of 2 + 2 and ene products. In addition isomeric methoxy hydroperoxides were detected when the photooxidations were run in methanol.



3

In order to rationalize these results zwitterions were invoked[27] as the reaction intermediates responsible for the isomerizations of the dienes. These zwitterions act as agents to generate an isomerized diene pool. They are unlikely to be intermediates on the 4 + 2 cycloaddition reaction surface since they undoubtedly form by addition of singlet oxygen to the predominant s-trans conformation of the diene, and have the open structure **4** rather than the closed structure **5**. The open structure cannot collapse directly to the endoperoxide without undergoing a prohibitively difficult isomerization about the allylic moiety.[28] Hoffmann[29] and Salem[30] have suggested that 1,4-zwitterions and biradicals are extremes on a tetramethylene continuum. Mixing biradical character into **4** would allow facile intersystem crossing and energetically favorable decomposition into isomerized diene and triplet oxygen.



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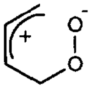


5

Mechanism C invokes the intermediacy of perepoxides **a** and **b**. The syn perepoxide **a** has the pendant oxygen and the vinyl group on the same side of the epoxide ring and can collapse directly to the endoperoxide. The anti perepoxide **b** has the pendant oxygen and vinyl group on opposite faces of the epoxide ring and must either form reversibly or isomerize to **a** before endoperoxide formation. Dewar and Thiel[31] on the basis of a MINDO/3 study reported that a mechanism invoking a perepoxide-like transition state is energetically more acceptable than the concerted mechanism F. On the other hand, Monroe[16] argues against the perepoxide mechanism based on the insensitivity of the reaction rates to diene ionization potentials.

A vinyl substituted dioxetane (Mechanism E) has also been discussed as a potential reaction intermediate. Rearrangement of vinylcyclobutanes to cyclohexenes have been reported[32] but the vinyl dioxetanes isolated by Kearns[5] and Clennan[33] decomposed without rearrangement rendering this mechanism unlikely.

Mechanism B is a cheletropic addition that has been observed in the additions of phosphenium ion,[34] germylenes (R_2Ge),[35] and silylenes (R_2 Si)[36] to 1,3-dienes. No experimental evidence exists, however, that supports this pathway for endoperoxide formation

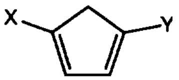
Mechanisms F and G are both concerted reactions that only differ in the timing of bond formation. Mechanism F is a synchronous reaction characterized by equivalent C-O bond orders in the transition state. Mechanism G is a nonsynchronous reaction characterized by nonequivalent C-O bond orders in the transition state.

Similar mechanistic alternatives have been debated in the Diels Alder literature[37] and have led to the development of the cooperativity test.[38] This mechanistic probe involves the placement of two substituents in identical environments in a diene or dienophile and comparison of its rate (k_3) of reaction to its unsubstituted (k_1) and monosubstituted (k_2) analogues. If all three substrates react synchronously (Mechanism F) then (k_1/k_2) = (k_2/k_3) and the rate of the monosubstituted substrate will be equal to the geometric mean of the other two rate constants. (ie. $k_2 = (k_1k_3)^{1/2}$) If one or more of the substrates react by formation of one bond at a time (Mechanisms A and D) then k_2 will be equal to the arithmetic mean ($k_1 + k_3$) of the other two rate constants. If the unsymmetrically substituted substrate reacts concertedly but asynchronously (Mechanism G) k_2 will fall between the values for these two mechanistic extremes.

The cooperativity test is plagued by the fact that by changing the substituent pattern one also changes the synchronicity of the reaction. Three approaches which have been taken to circumvent this problem include: (1) the use of substituents that provide minimal electronic and steric perturbation,[39] (2) the use of chiral substituents to induce diastereoselectivity cooperatively,[40] and (3) the comparison of a series of mono- and di-substituted substrates to the unsubstituted analogue.

Clennan and Mehrsheikh-Mohammadi[41] have taken the last approach in order to determine the mechanism of singlet oxygen addition to furans **6** and cyclopentadienes **7**. The use of the cooperativity test demonstrates that the rates of reaction of many of the monosubstituted furans fall outside the range defined by the two mechanistic extremes. (Table 2) This unusual characteristic is not shared by the Diels Alder reaction[42] and is diagnostic of a complex reaction surface and is inconsistent with the simple concerted mechanism F or G.

6



7

a. X = Y = H	e. X = H; Y= tBu
b. X = Y = tBu	f. X = H; Y = Br
c. X = Y = C_6H_5	g. X = H; Y = C_6H_5
d. X = Y = Br	

A mechanism that satisfactorily explains all the experimental data is depicted in Figure 4. The first step of the reaction involves reversible formation of an exciplex. An exciplex intermediate is supported by the observation that in contrast to Diels Alder reactions,[43] singlet oxygen 4 + 2 cycloadditions are characterized by near zero activation barriers.[8] Gorman[44,45] has suggested that these low activation barriers are indicative of a reversibly formed exciplex. The second step of the mechanism is a symmetrical or unsymmetrical concerted collapse of the exciplex to the 4 + 2 cycloadduct.

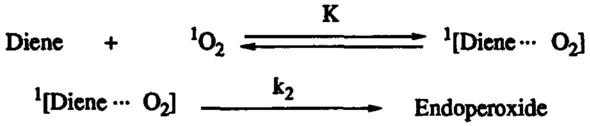
Examination of the data for **6** within the Hammett formalism (Figure 5) reveals that singlet oxygen exhibits an enhanced selectivity for unsymmetrically substituted (ρ = -4.5, r = -0.996) in comparison to symmetrically substituted furans (ρ^+ = -2.2, r =-0.996). If endoperoxide formation is preceded by a reversibly formed exciplex the rate of singlet oxygen disappearance is give by Eqn. 1 and the Hammett linear free energy

Table 2. Comparison of the Experimental to the Calculated Mechanistic Extreme Values for Endoperoxide Formation.

Compound or Compound Series	**k x 10^{-8} $M^{-1}s^{-1}$**	**$(k_1k_3)^{1/2}$ x 10^5**	**$(k_1 + k_3)/2$ x 10^5**	**$k_2{}^a$ x 10^5**
6a	0.12			
6b	0.94			
6c	0.52			
6d	0.020			
6e	0.61			
6f	0.0067			
6g	0.18			
6a,6e,6b		340	530	610
6a,6g,6c		250	320	180
6a,6f,6d		49	70	6.7

a. Experimental value for unsymmetrical furans, $M^{-1}s^{-1}$.

Figure 4.



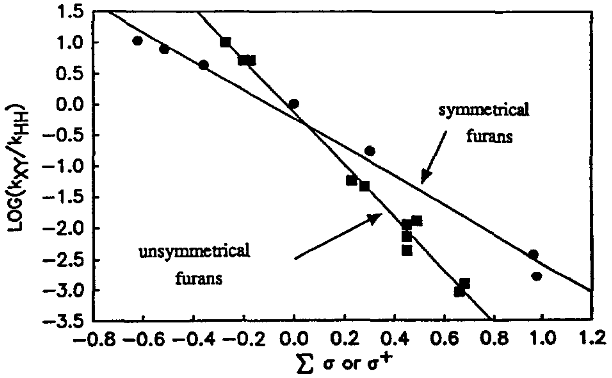
relationship (LFER) by Eqn. 2. These equations demonstrate that the slopes of the Hammett LFER's are a function of the sensitivity of the exciplex equilibrium constant, K, and the rate of 1,4-cycloaddition, k, to the substituent effects. The dual correlation in Figure 5 is consistent with synchronous reactions for the symmetrically substituted and with a continuum of structurally unsymmetrical transition states and/or exciplexes for the unsymmetrically substituted furans. The different sensitivities to substituents is a result of different electronic demands and/or solvation requirements of geometrically different species on the reaction coordinates. Ineffective solvent stabilization of the unsymmetrical transition states requires additional stabilization from the substituents. This provides an explanation for the enhanced substituent sensitivity in the reactions of the unsymmetrically in comparison to symmetrically substituted compounds.

$$-d[^1O_2]/dt = k_2K[^1O_2][\text{furan}] \qquad 1$$

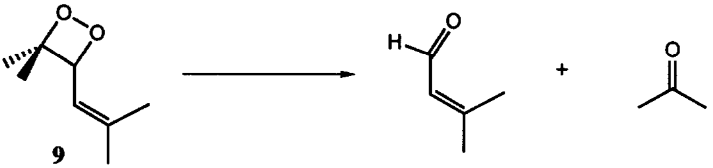
$$\log \frac{k_{obsd}(X)}{k_{obsd}(H)} = \log \frac{k_{2X}}{k_{2H}} + \log \frac{K_X}{K_H} = \sigma_X(\rho_k + \rho_K) \qquad 2$$

2.1.2 The 2 + 2 Cycloaddition. The isolation of the first 2 + 2 cycloadducts of singlet oxygen[46,47] were reported within a year of Kopecky and Mumford's[48] successful synthesis of the first dioxetane. It soon became apparent that electron rich olefins,[46,47] and olefins with inaccessible allylic hydrogens,[49] had a propensity to give the 2 + 2 adducts. The direct observation of vinyl dioxetanes formed by additions of singlet oxygen to 1,3-dienes, however, are rare. Hasty and Kearns[5] in 1973 reported the first example of a vinyl dioxetane which formed during the photooxidation of the predominantly s-trans 2,5-dimethyl-2,4-hexadiene

Figure 5. Hammett Plot for Furan Photooxidation



8. The vinyl dioxetane product, 9, decomposed in CCl_4 with a half-life of 37 min at 44° C to two carbonyl fragments. Clennan and coworkers[33,50,51] reported that electron rich dienes, **10** and **11**, which are not sterically precluded from existing in s-cis conformations, also react to form dioxetanes.



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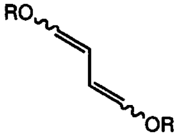
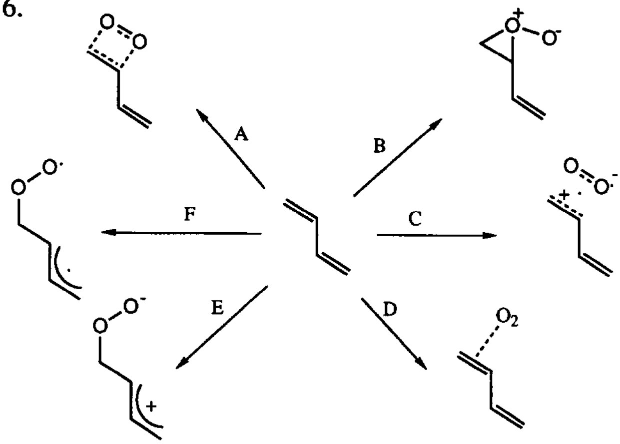
Possible transitions states and/or intermediates on the 1,3-diene singlet oxygen 2 + 2 cycloaddition surface are depicted in Figure 6. Mechanism A is a concerted 2s + 2a cycloaddition. Analysis of this reaction in terms of frontier molecular orbital HOMO-LUMO interactions[52] leads to the prediction that the 1,3-diene should be the antarafacial component[53] contrary to the results observed with simple olefins. Frontier molecular orbital stabilization of the transition state with the 1,3-diene participating as the suprafacial rather than antarafacial component is not as effective. (Figure 7)



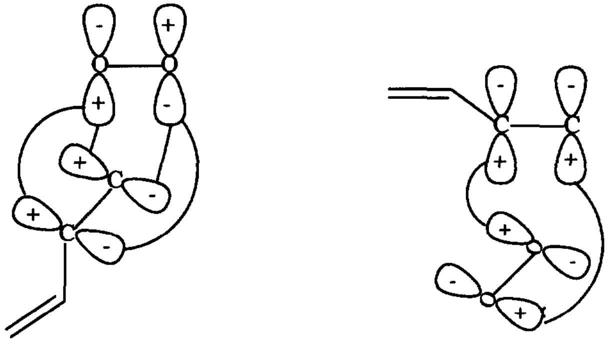
10 R = CH_3
11 R = tBu

Figure 6.



Mechanism B invokes the formation of a perepoxide intermediate. Perepoxides have received a considerable amount of experimental support as intermediates in singlet oxygen ene reactions[54] but very little support as intermediates in 2 + 2 cycloadditions. The ability of phenyl methyl sulfoxide to suppress 2 + 2 cycloaddition of singlet oxygen to adamantane adamantylidene, **12**, in favor of epoxide formation led Schaap and coworkers[55] to propose a perepoxide intermediate. A perepoxide intermediate was also used to rationalize the regiochemistry of singlet oxygen additions to E, **13**, and Z, **14**, 1-tert-butoxy-1,3-butadienes.[56]

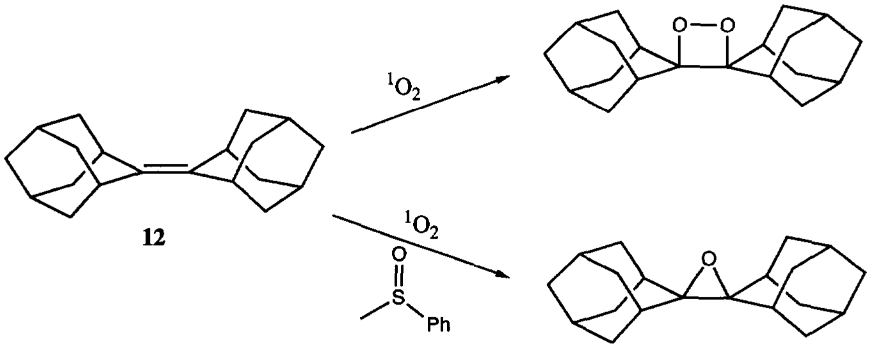
Figure 7.



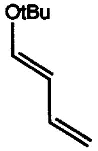
2s(LUMO) + 2a(HOMO
antarafacial 1,3-diene

2s(HOMO) + 2a(LUMO)
suprafacial 1,3-diene

Singlet oxygen reacted with these dienes predominantly at the most substituted double bond in contrast with the reactions of diphenylketene (DPK) and tetracyanoethylene (TCNE), which preferred reaction at the least substituted double bond. A frontier molecular orbital analysis[57] demonstrated that the largest P_z coefficients are at the terminal carbons of **13** and **14** and predicts reaction at the least substituted double bond as observed for DPK and TCNE. Analysis of the electrostatic potentials[58] at the four carbon atoms of 1-methoxy-1,3-butadiene also predicts that reaction at the least substituted double bond is preferred by 4.9 kcal/mol. A perepoxide, however, would be stabilized by interaction of the pendant oxygen with the oxygen lone pair



orbital in a pentadienyl anion-like HOMO of the diene and provides an attractive explanation for the observed regiochemistry. (Figure 8)



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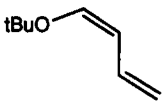

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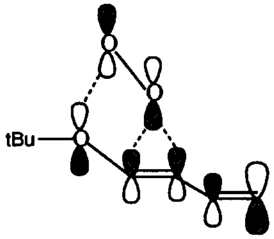
Mechanism C involves electron transfer and formation of ion pairs on the reaction surface. Schaap[59] measured the rates of 2 + 2 cycloadditions of singlet oxygen to 2,3-diaryl-1,4-dioxenes as a function of free energy of electron transfer. The slope of the resulting Rehm Weller plot[60] was only 14% of the limiting slope anticipated for complete electron transfer. Similar analyses for phenols[61] and enamines[62] also led to the same conclusion that charge transfer, but not complete electron transfer, are important in these reactions.

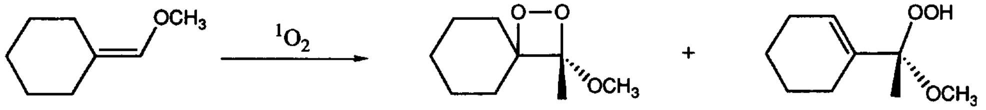
Figure 8.



Mechanism D invokes an exciplex (oxciplex)[63] as an intermediate. No activation barriers for 2 + 2 cycloadditions of singlet oxygen to 1,3-dienes have been reported. We anticipate, however, by analogy to all other barriers measured for singlet oxygen reactions, that it will be small or even negative indicative of exciplex formation.

Mechanisms E and F proceed via open zwitterionic or biradical intermediates, respectively. A strong case for zwitterion involvement in 2 + 2 cycloadditions to some very electron rich olefins and 1,3-dienes is based upon several experimental observations including; (1) unusual solvent effects,[64] (2) nucleophilic trapping experiments,[65] (3) skeletal rearrangements,[66,67,68] and (4) loss of stereochemistry in the product dioxetanes.[51]

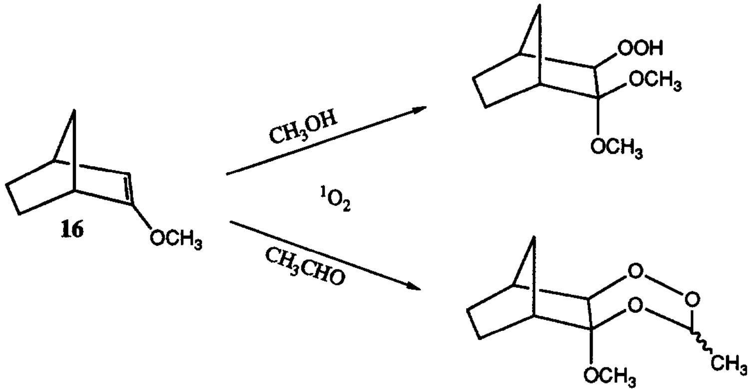
Asveld and Kellogg[64] reported that the yield of the dioxetane from addition of singlet oxygen to enol ether **15** increased from 3 to over 50% as the solvent polarity was increased. Gollnick,[69] Foote,[70] and Kearns,[5] have also attributed the solvent sensitive formation of **9** to a zwitterionic intermediate.



15

Trapping of an intermediate by the nucleophilic solvent methanol has been reported for several 1,3-dienes which give 2 + 2 adducts including 2,5-dimethyl-2,4-hexadiene, and isomeric 1,4-di-tert-butoxy-1,3-

butadienes.[33] Jefford and coworkers reported that both methanol[65] and acetaldehyde[71] trapped an open intermediate during the photooxidation of norbornyl enol ether **16**.



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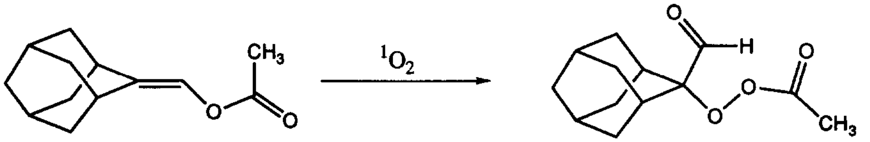
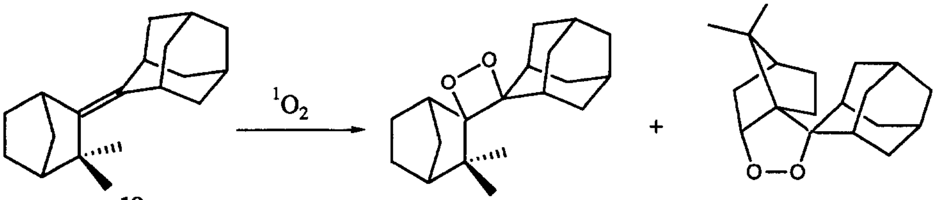
The formation of an acyl-shifted product in the photooxidation of enol ester **17**,[66] and rearranged



17

products from adamantyl olefins **18** (Wagner-Meerwein shift) and **19** also provide compelling evidence for dipolar intermediates.



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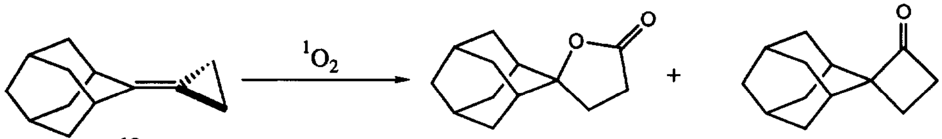
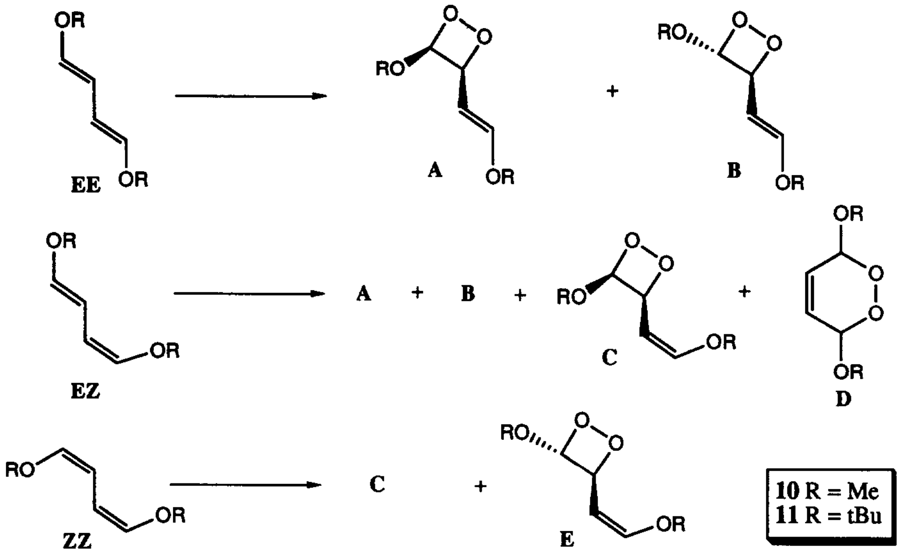


19

The first well established nonstereospecific 2 + 2 cycloadditions were observed during studies of the photooxidations of isomeric 1,4-dimethoxy, **10**,[51] and 1,4-di-tert-butoxy-1,3-butadienes, **11**.[33] (Figure 9)

Figure 9.



The product distributions in these reactions provide compelling evidence for open intermediates on the 2 + 2 cycloaddition reaction surface. (Table 3)

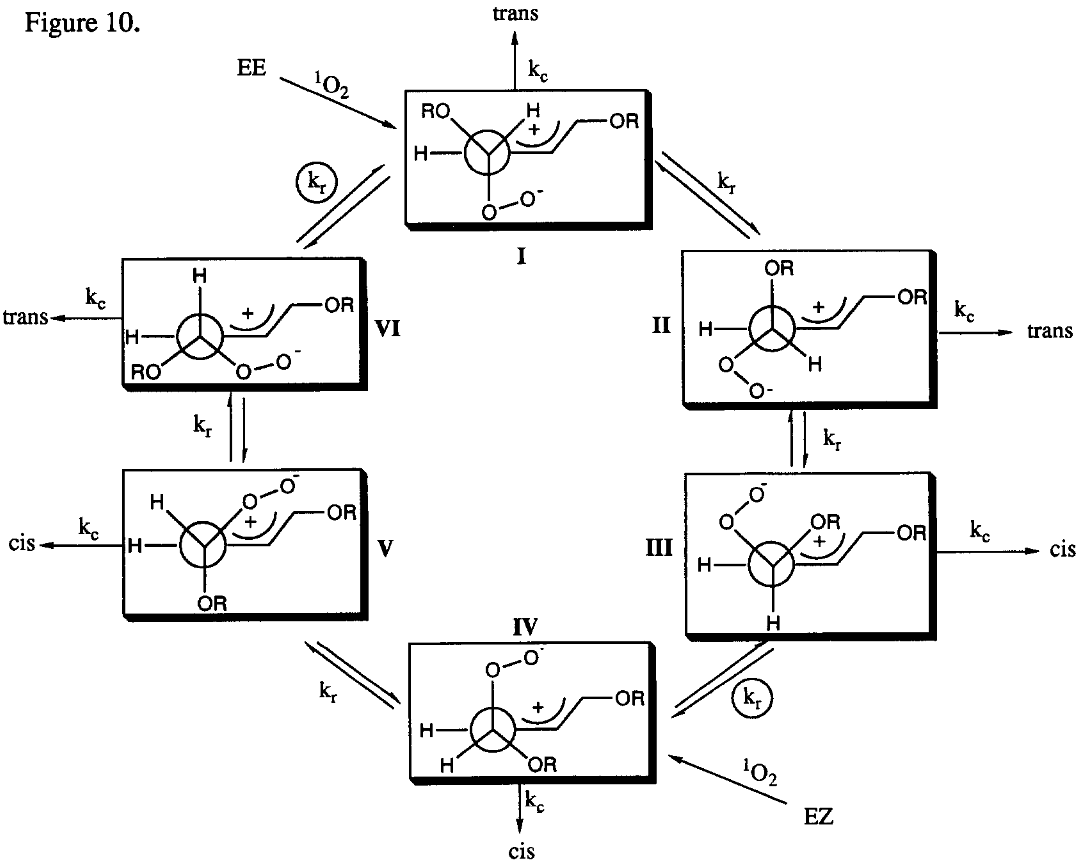
Table 3. Product Distribution in the Photooxidations of EE, EZ, and ZZ **11** as a function of Solvent Composition.

Diene	**Mole Fraction of[a]**			**%**		
	acetone-d_6	**A**	**B**	**C**	**D**	**E**
EE	1	84	16			
	0.778	88	12			
	0	91	9			
EZ	1	8	33	40	18	
	0.778	6	30	39	25	
	0.466	2	31	42	20	4
	0.178	5	22	39	27	6
ZZ	1			73		27
	0.778			71		29
	0.466			39.1		60.9
	0.178			12.4		87.6
	0			10.9		90.1

a. in acetone-d_6 CD_2Cl_2 mixtures.

Several surprising aspects of these extremely interesting reactions are readily apparent and include: (1) Diene **10EE** and **11EE** give the cis substituted dioxetanes, **A**, as the major products in every solvent mixture examined. The cis dioxetane, however, is formed in 8 to 13% lower yield in the reaction of **10EE** with the small methoxy groups than in the reaction of **11EE** with the larger tert-butoxy groups. Cis-1,2 disubstituted enol ethers[72] are thermodynamically more stable than their trans isomers and the energy difference also increases with increasing size of the alkyl group on the enol oxygen. This unusual phenomena has been attributed to an attractive interaction between the enol oxygen and cis alkyl group.[72] (2) The ratio **11A/11B** (Figure 9) is 5.25 in the reaction of the **11EE** isomer but only 0.24 in the photooxidation of **11EZ** under identical conditions. This result is incompatible with any common intermediate or set of intermediates in the two reactions. The results in Table 3, however, are consistent with partial zwitterion interconversion and approximately equal rates of collapse and rotation. The surprising near equivalence of the rates of four membered ring formation and rotation about single bonds reflects the attractive interaction between the peroxy anion and allylic cation which enhances the rate of dioxetane formation.

Figure 10.



A six-fold rotation interconversion diagram for the zwitterions formed in the reactions of the EE and EZ dienes is depicted in Figure 10. The stereochemistry of the dioxetanes formed by least motion collapse of each zwitterion rotamer are listed on the outer edge of the diagram. Rotamer I is formed by addition of singlet oxygen to the EE diene and IV by addition to the EZ diene. The fate of these initially formed zwitterions is dictated by the relative rates of collapse, k_c, and rotation, k_r. If $k_c >> k_r$ then stereospecific dioxetane formation would be observed. If $k_c << k_r$ then complete equilibration would occur and identical dioxetane mixtures would be obtained in the two reactions.

Rotamers III and VI are more stable than the other zwitterion rotamers that are hyperconjugatively destabilized by the electron withdrawing oxygens perpendicular to the allylic cation plane. It is well established that allylic oxygens prefer to be eclipsed to electron deficient and perpendicular to electron rich double bonds.[73,74] The six zwitterions in Figure 10 would form two sets of three, slowly equilibrating ions if the alkoxy crossing barriers, represented in Figure 10 by the circled rate constants, were energetically inaccessible. Such a situation would make III accessible in the reaction of the EE isomer and VI in the photooxidation of the EZ isomer and would explain the predominant stereochemistry of the dioxetanes formed in each reaction.

Compelling evidence for the mechanism in Figure 10 is derived from a kinetic analysis of the simplified kinetic scheme depicted in Figure 11, which makes the reasonable assumptions that the cis dioxetanes are derived predominantly from III and the trans dioxetanes from zwitterion VI. The phenomenological rate constants k_r and k_{-r} represent for the most part the high barriers separating III and VI. Analysis[51] of this scheme allowed the extraction of the relative rates of ring closure to rotation (k_c/k_r) for **11ZZ**. These data depicted in Table 4 demonstrate that rotation competes more effectively with closure in the

Figure 11.

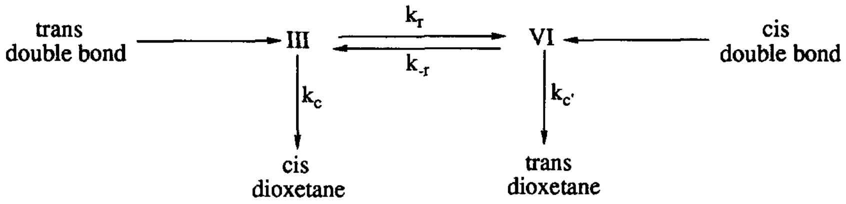


Table 4. Relative Rates of Rotation to Closure for the Zwitterions formed in the Reaction of **11ZZ**.	
Solvent[a]	k_c/k_r
acetone-d_6	1.10
4/1 acetone-d_6/CD_2Cl_2	2.01
1/1 acetone-d_6/CD_2Cl_2	4.21
1/4 acetone-d_6/CD_2Cl_2	6.09
CD_2Cl_2	6.23

a. volume ratio.

more polar, acetone rich solvents. This result is very satisfying since it is reasonable that the more highly solvated zwitterion has a longer lifetime and has additional time to rotate before closing to form the dioxetane.

2.1.3 The ene reaction. Ene reactions at 1,3-diene double bonds have not been extensively investigated from a mechanistic point of view. The most exhaustive study was that of Foote and Manring,[70b] who compared the photooxidations of 2,5-dimethyl-2,4-hexadiene, **8**, and 2-methyl-2-pentene. They observed that the solvent effect on the rates of disappearance of the two substrates were nearly identical. This is shown graphically in Figure 12 where log($k_r + k_q$), the total rate of disappearance of singlet oxygen, for the two substrates are plotted versus each other. The activation entropies for the two substrates in methanol and acetone are also the same within experimental error. As a result of this study, the authors concluded that the initial interactions between singlet oxygen and **8** and between singlet oxygen and 2-methyl-2-pentene are identical This suggests that the "perepoxide-like" initial interaction established for singlet oxygen and 2-methyl-2-pentene[54] is also a valid description for the initial interaction at diene double bonds.

Figure 12.

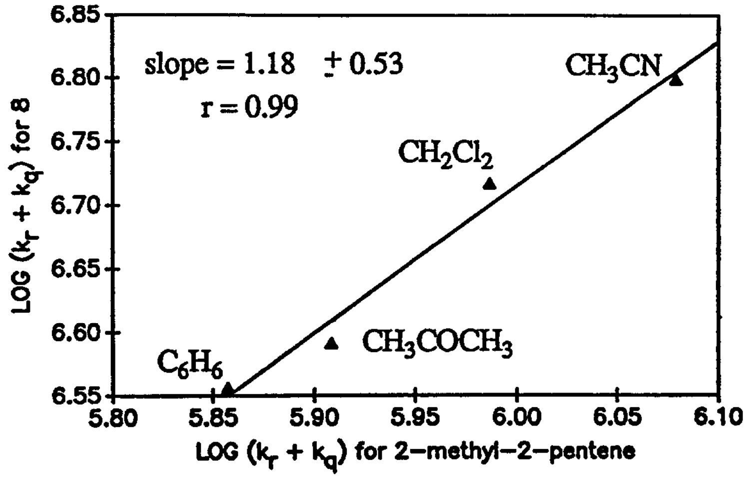
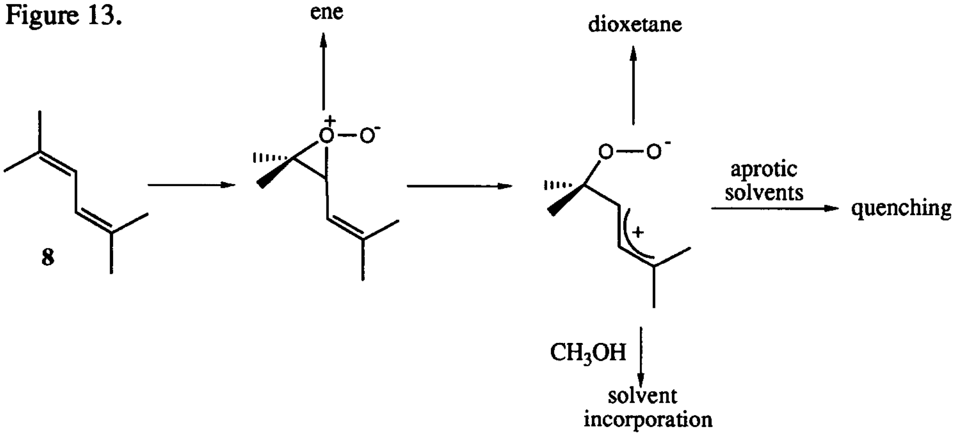


Table 5. Solvent Effects on the Rates of Disappearance of **8** and $^1O_2$ and of Appearance of the Ene Product.

Solvent	$k_r \times 10^{-6}$ $M^{-1}s^{-1}$	$k_{ene} \times 10^{-6}$ $M^{-1}s^{-1}$	$(k_r + k_q) \times 10^{-6}$ $M^{-1}s^{-1}$
CH_3OH	2.5 ± 0.6	0.29 ± 0.02	2.6 ± 0.2
C_6H_6	<0.25	0.14 ± 0.03	3.6 ± 0.2
$(CH_3)_2CO$	0.74 ± 0.08	0.34 ± 0.01	3.9 ± 0.6
CH_2Cl_2	1.4 ± 0.3	1.3 ± 0.1	5.2 ± 1.1
CH_3CN	1.6 ± 0.2	1.7 ± 0.1	6.3 ± 1.1

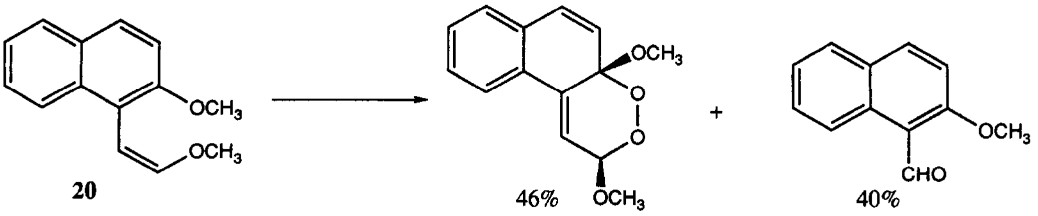
In aprotic solvents, such as CH_3CN where the ene reaction of **8** predominates, the rates of diene (k_r in Table 5), and singlet oxygen ($k_r + k_q$ in Table 5) disappearance are not equal, diagnostic of physical quenching. In methanol, where solvent incorporation and dioxetane formation occurs, the two values are equivalent. It is apparent from Table 5 that solvent incorporation and dioxetane formation occur at the expense of physical quenching. The rate of the ene reaction (k_{ene}), however, is always less than 30% of ($k_r + k_q$) suggesting the mechanism depicted in Figure 13.

Figure 13.

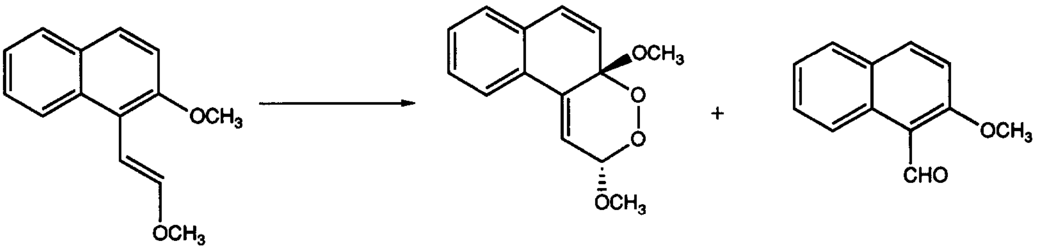


2.1.4 Factors influencing the competition between the 4 + 2, 2 + 2, and ene reactions. The factors influenced by the substitution pattern of the diene and ultimately responsible for the competition between the 2 + 2, 4 +2, and ene reaction pathways include: (1) The 1,3-diene s-cis/s-trans ratio,[4,5,75-79] (2) The distance between the C_1 and C_4 terminus of the diene,[17,50] (3) The ionization potential of the 1,3-diene,[80-84] (4) Steric factors,[81,85] and (5) Alignment of allylic hydrogens.[86-88]

2.1.4.1 The s-cis/s-trans ratio. Endoperoxide formation requires population of the s-cis conformation of the 1,3-diene prior to the addition of singlet oxygen. As a result the overall rate of product formation is given by $k_{obs} = K_{eq}k$, where K_{eq} is the equilibrium constant for the s-cis/s-trans conformational interconversion and k is the rate of addition of singlet oxygen. Any steric or electronic factor that decreases K_{eq} slows down the rate of endoperoxide formation and allows other reactions to compete. A destabilizing methoxy-methoxy interaction in vinyl naphthalene **20**, which is absent in **21**,[75] lowers K_{eq} and allows a 2 + 2 addition of singlet oxygen to occur. In contrast, it is a destabilizing peri interaction in naphthalene **22**, which is absent in **23**,[76] that lowers K_{eq} and allows a competing ene reaction to occur.

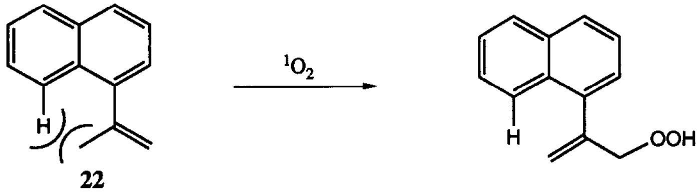


Foote,[89] Mousseron-Canet,[90] Isoe,[91] and coworkers have examined the photooxidations of 1,3-dienes that have one double bond in a cyclocitriylidene moiety. These carotenoids have very high energy s-cis conformations, which allow competitive ene reactions[92] to occur that lead to the formation of unusual allenes.



21 98% trace

The s-cis population in the carotenoid trans-β–ionol **24** is large enough to allow formation of endoperoxide **24d** (and its decomposition products **24e** and **f**) to compete with formation of the allene **24c** and the other ene products **24a** and **b**.[93] In contrast, the greatly diminished s-cis population in cis-β-ionol **25** completely suppresses endoperoxide formation and only allene **25a** and exocyclic ene product **25b** are observed.[94]



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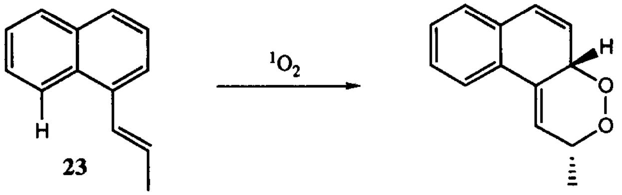
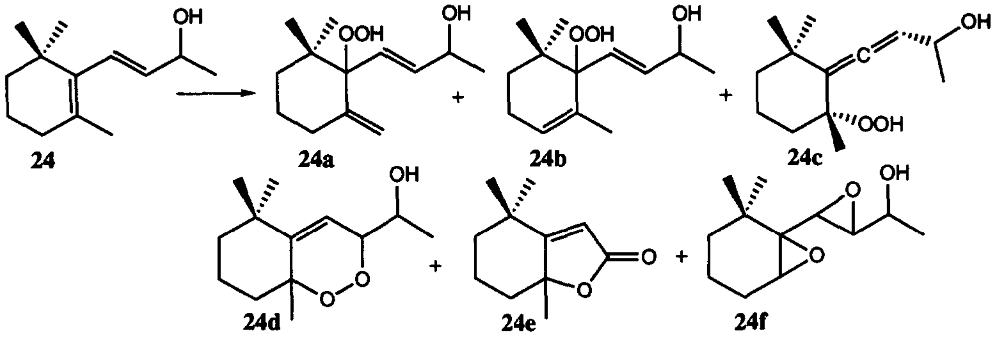


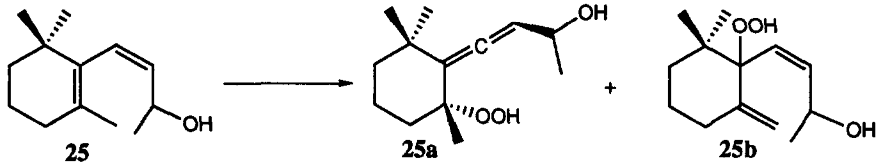
23

Photooxidation of the predominantly s-trans 2,5-dimethyl-2,4-hexadiene **8** produces only a small amount of endoperoxide **8c**. Hydroperoxide **8b** is the major product in aprotic solvents and dioxetane **8a** and methanol incorporation product **8d** are the major products in methanol.[69,70]

A detailed kinetic study of this fascinating diene has led to the conclusion that an open intermediate is formed which can either collapse to the dioxetane, react with the solvent, or decompose to the diene and triplet oxygen. This intermediate is best described as zwitterionic in the polar and nucleophilic solvent, methanol, and as a diradical which can undergo intersystem crossing, and spin allowed decomposition to triplet oxygen, in non polar solvents.

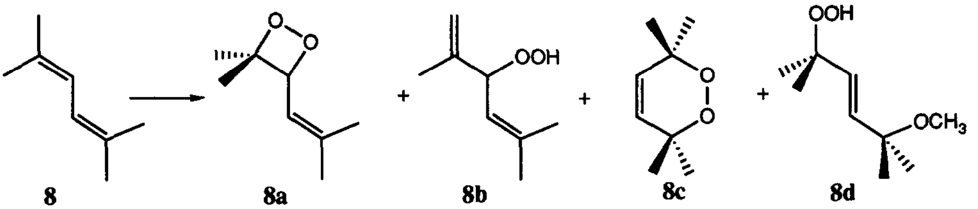


24 **24a** **24b** **24c** **24d** **24e** **24f**



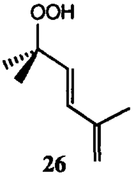
25 **25a** **25b**

Hydroperoxide **26** has also occasionally been observed during photooxidations of **8**. Adam and



8 **8a** **8b** **8c** **8d**

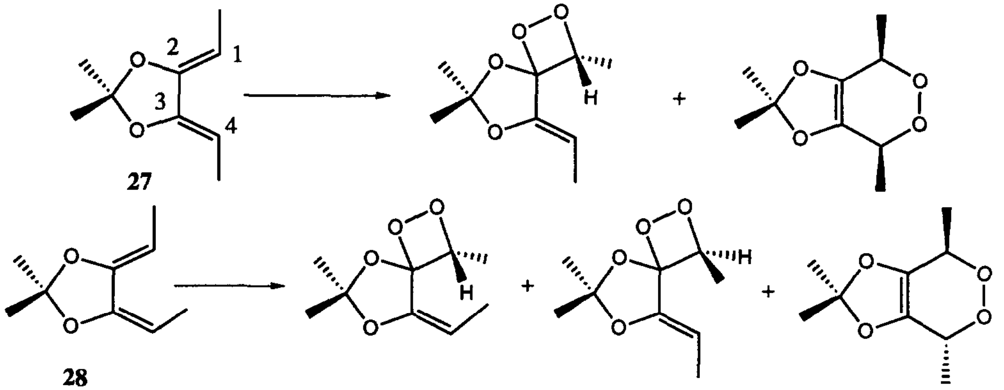
Staab[95] demonstrated that the ratio **8b**/**26** was 9/1 when **8** was photooxidized in the presence of 2,6-di-tert-butyl-4-methylphenol and 1/9 in the presence of CuCl. The enhanced yield of **26** in the presence of the radical initiator CuCl suggests that it is a secondary product formed by rearrangement of **8b**.



26

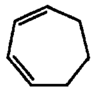
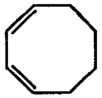
2.1.4.2 C_1- C_4 distance. The C_1-C_4 distance, ($r_{1\text{-}4}$) in a 1,3-diene, and not the dihedral angle between the olefinic units, plays an important role in determining the rate of Diels Alder reactions,[96] and a linear relationship between the log of the cycloaddition rate and $r_{1\text{-}4}$ has been observed.[97]

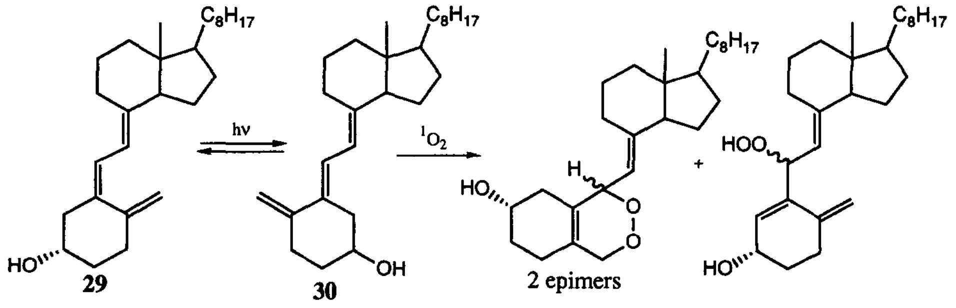
The surprising formations of dioxetanes during photooxidation of *ZZ*, **27**, and *EZ*-4,5-diethylidene-2,2-dimethyl-1,3-dioxolane **28**[50] have been attributed to a large separation between the terminal carbons in the 1,3-diene moiety. The endoperoxides were stable under the reaction conditions and could be ruled out as precursors to the dioxetanes.[98] An ideal C_1-C_4 distance is also responsible for the impressive reactivity of cyclopentadiene in comparison to larger cyclic homologues.[24] (Table 6)



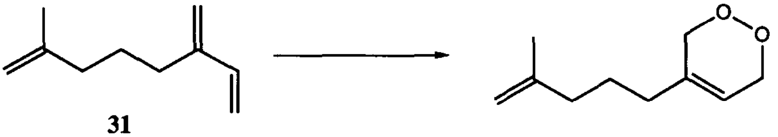
The s-cis tied 1,3-diene Vitamin D_3, **29**, undergoes cis-trans isomerization concomitant with photooxidation to give a mixture of endoperoxides and hydroperoxides.[99] A careful study of the triplet sensitized isomerization of **29** and its photooxidation with polymer bound Rose Bengal has led to the suggestion that only trans Vitamin D_3, **30**, serves as the precursor to the epimeric endoperoxides.[100] Diene **29** undoubtedly twists to avoid a severe steric interaction thereby increasing the C_1-C_4 distance and precluding endoperoxide formation. Consistent with this suggestion is the report that maleic anhydride is also 25 times more reactive with **30** than with **29**.

Table 6. Photooxidation Rate Constants[21] of Cyclic 1,3-Dienes. ($M^{-1}s^{-1}$)

				
$k_{^1O_2}$	1 x 10^8	7.1 x 10^6	1.1 x 10^6	6.5 x 10^4



2.1.4.3 Ionization Potentials. As a result of singlet oxygen's electrophilic character[101] it prefers to react with electron rich double bonds. Paquette and coworkers[102] have pointed out that this preference is a common phenomenon and that PES derived ionization potentials can be used to predict the site of reactivity. Singlet oxidation of α-myrcene, **31**, occurs at the diene (IP = 8.63eV) rather than at the more difficult to ionize double bond (IP = 9.13eV). In contrast, β-myrcene, **32**, reacts at the double bond (IP = 8.48V) rather than at the diene (IP = 8.68eV).[103]



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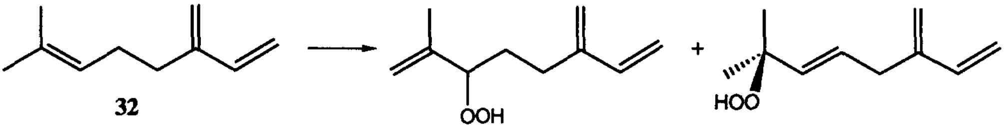
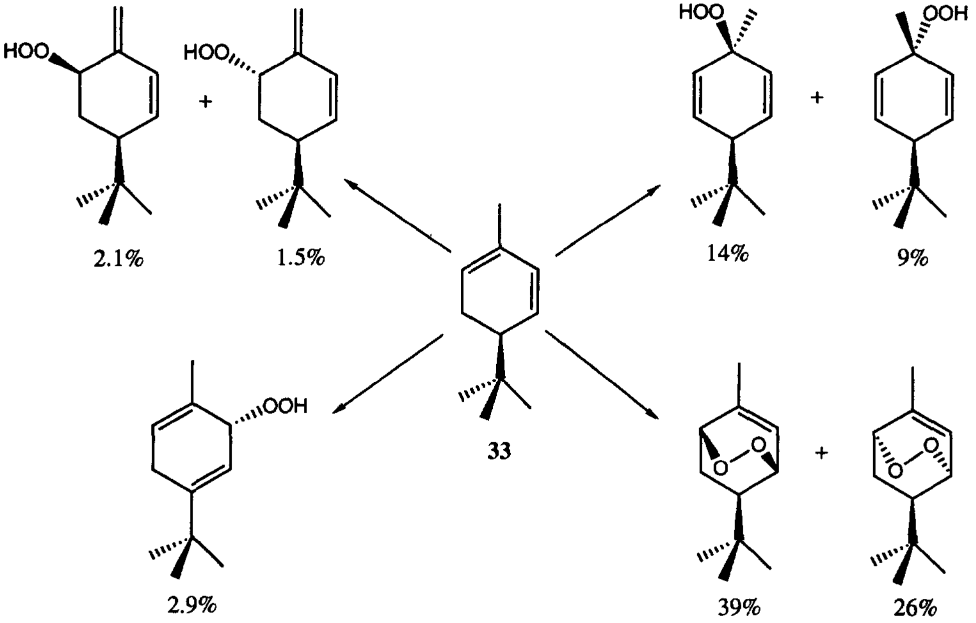


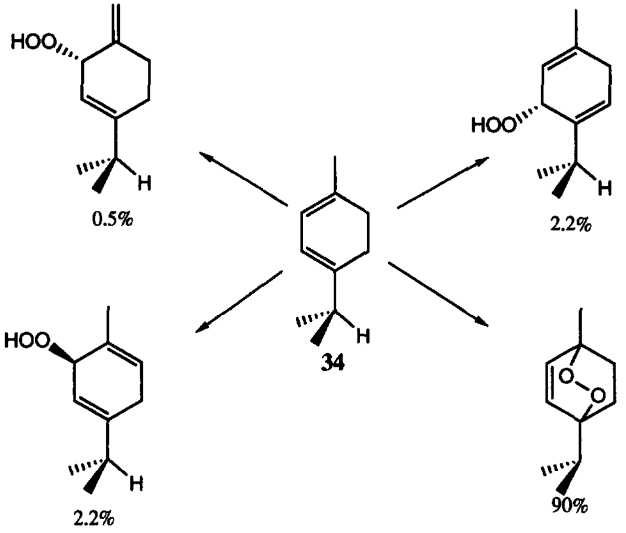
32

Matusch and Schmidt[80] in a very careful analysis of the photooxidation of the 1,3-diene R-(-)-α-phellandrene, **33**,[104] reported that singlet oxygen exhibits a 9:1 preference for the more electron rich double bond. They also argued that since the endoperoxide and hydroperoxide pairs formed in the same 3/2 ratio, that a common intermediate was involved in the ene and 4 + 2 reactions. A 3/2 thermodynamically



33

determined ratio of the two exciplexes, formed on the diastereotopic faces of **33**, are the likely intermediates in this fascinating reaction. Gorman and coworker[44,45] have argued effectively that zero or small negative



activation barriers, rates that are an order of magnitude smaller than diffusion control, and the observation of both diffusion and preequilibrium-limited behavior is strong evidence for reversibly formed exciplex intermediates. These workers also demonstrated that the exciplex is a ubiquitous intermediate and provided evidence that it is involved in both the ene and 4 + 2 reactions. In contrast to **33**, α-terpinene, **34**,[104] has an electron donating alkyl group on each double bond and as a result the amount of ene reaction at each site is comparable.

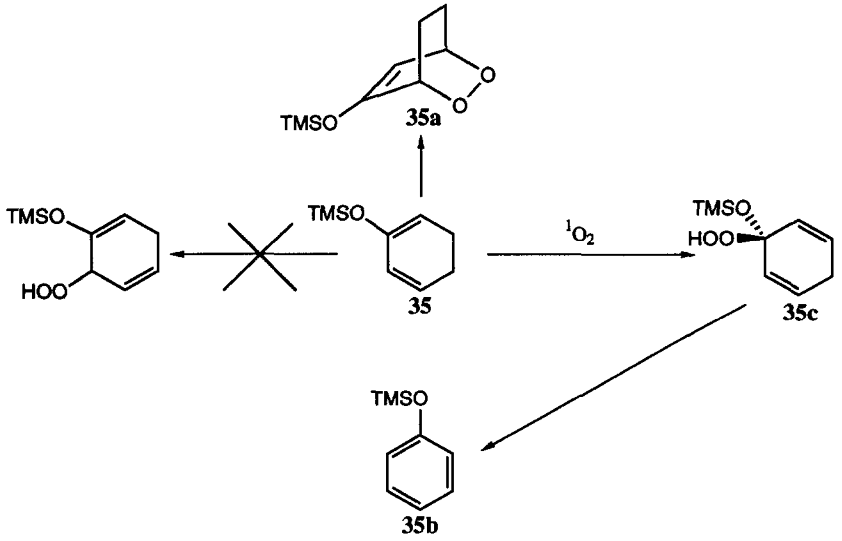
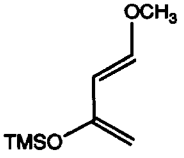
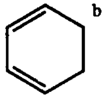
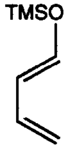
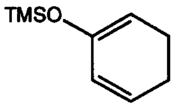
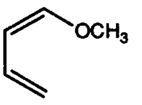


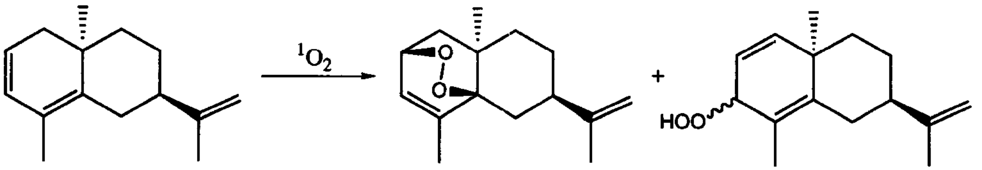
Table 7. Rate Constants of Singlet Oxygen Additions to Electron Rich 1,3-Dienes.[a]

	$k(M^{-1}s^{-1})$			$k(M^{-1}s^{-1})$
	3.8×10^5	 [b]	k_{4+2} k_{ene}	2.2×10^6 $< 5 \times 10^5$
	4.2×10^5	 35	k_{4+2} k_{ene}	2.0×10^6 6.5×10^6
	3.8×10^5			

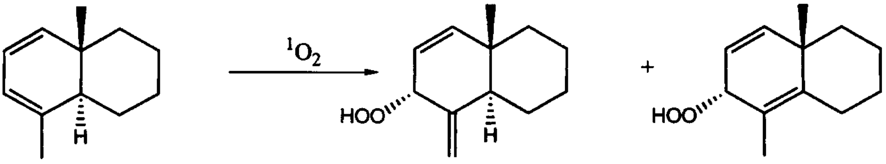
a. reference 105 b. reference 21.

Photooxidation of 2-trimethylsiloxy-1,3-cyclohexadiene **35** produces a 75% yield of the endoperoxide **35a** and a 25% yield of trimethylsiloxybenzene **35b**. Careful examination of the reaction mixture at low temperature by ^{13}C NMR demonstrated that the ene reaction occurred exclusively at the more electron rich double bond to give the symmetrical intermediate, **35c**, which decomposes at room temperature by loss of hydrogen peroxide to form **35b**.[22] Placement of the trimethylsiloxy group at the 2-position of cyclohexadiene to give **35** increases the rate of the ene reaction by more than an order of magnitude but has no effect on the rate of the 4 + 2 cycloaddition. (Table 7)

2.1.4.4 Steric Effects. A critical step in the synthesis of α-agarofuran, a furan sesquiterpene isolated from fungus infected agarwood, involved the addition of singlet oxygen to diene **36**.[81] The reaction



36



37

10-15%

85-90%

proceeded to give only one of the two possible endoperoxides by exclusive addition of singlet oxygen to the less hindered face of the diene. Steric interactions also precluded addition of singlet oxygen to the β-face of 1, 4a-dimethyl-4a, 5, 6, 7, 8, 8a-trans-hexahydronaphthalene **37** and only ene products from α-face addition were observed.[85]

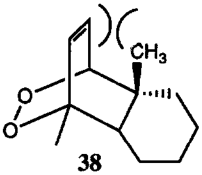
Singlet oxygen reactions are very exothermic and it is unlikely that steric effects in the products manifest themselves in the transition states for product formation. Steric effects, on the other hand, are known to be very important in determining exciplex stability,[106] and the face selectivity in the reactions of **36** and **37** can be most easily rationalized with the Curtin-Hammett[107] analysis depicted in Figure 14. E_α and E_β represent the concentrations of the exciplexes formed by complexation to, and P_α and P_β the populations of the products derived from reactions on, the diastereotopic α and β-faces. If the rates of collapse of the exciplexes to the products are approximately equal ($k_\beta/k_\alpha \approx 1$), then the face selectivity, (P_β/P_α), reflects the equilibrium constant, (K), for exciplex interconversion (eg. K < 0.02 for the reaction of **37**).

Figure 14.

$$P_\alpha \xleftarrow{k_\alpha} E_\alpha \xrightleftharpoons{K} E_\beta \xrightarrow{k_\beta} P_\beta$$

$$\frac{[P_\beta]}{[P_\alpha]} = K\frac{k_\beta}{k_\alpha}$$

The absence of endoperoxide **38** was attributed to a severe 1,3-interaction involving the 4a methyl group, however, as previously pointed out, the transition state for endoperoxide formation is too early for this interaction to be important. It is more likely that 4 + 2 cycloaddition cannot compete with abstraction of the nearly perfectly aligned bridgehead hydrogen. Endoperoxide formation, however, does occur in the photooxidation of 1,3-diene **39**. This seems to be inconsistent with the observation that both faces of **39** have nearly perfectly aligned bridgehead hydrogens. However, unlike **37**, diene **39** has two equivalent faces and he ene reaction on the face occupied by H_b must occur at the disubstituted double bond and cannot compete with endoperoxide formation.



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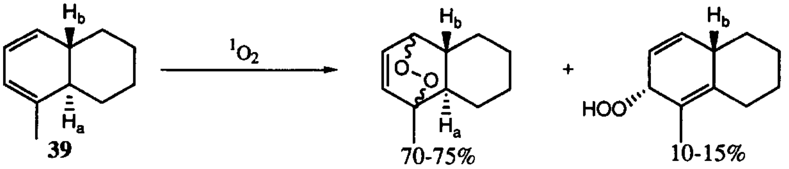
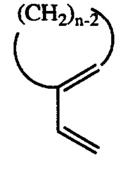


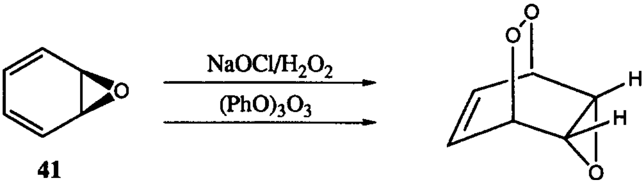
2.1.4.5 Allylic hydrogen alignment. Herz and Juo[87] observed a dramatic change in the ene/4 + 2 product ratio during photooxidation of 1-vinylcyclohexenes **40** as a function of ring size. They suggested that the s-cis/s-trans ratio and the rate of 4 + 2 cycloaddition are independent of ring size and that the product ratios reflect the changing rates of the ene reactions. The ene reaction is known to be very sensitive to the availability of hydrogens which can align approximately orthogonally to the olefinic plane.[108]



n = 5-10, 12

40

2.2 Type IID Oxidations. Type IID reactions, using chemical methods to produce singlet oxygen,[109] have been run for a variety of reasons including: (1) In order to obtain evidence for the Type II origin of photooxidation products the photosensitized reaction is compared to the same reaction run under Type IID conditions.[89] (2) To produce a known quantity of singlet oxygen for mechanistic purposes. (3) To assess the importance of Type II reactions in biological tissue, and (4) To circumvent perceived disadvantages in the photooxidation method.



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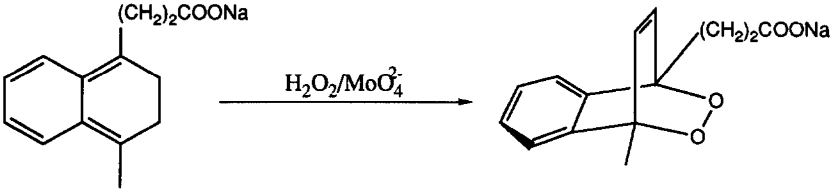
Examples of Type IID oxidations of simple and aromatic dienes include: (1) The hydrogen peroxide sodium hypochlorite and the triphenylphosphite ozonide oxidation of oxepin **41**;[110] (2) The hydrogen peroxide molybdate ion oxidation of water soluble naphthalenes, **42**,[111] and rubrene.[112]



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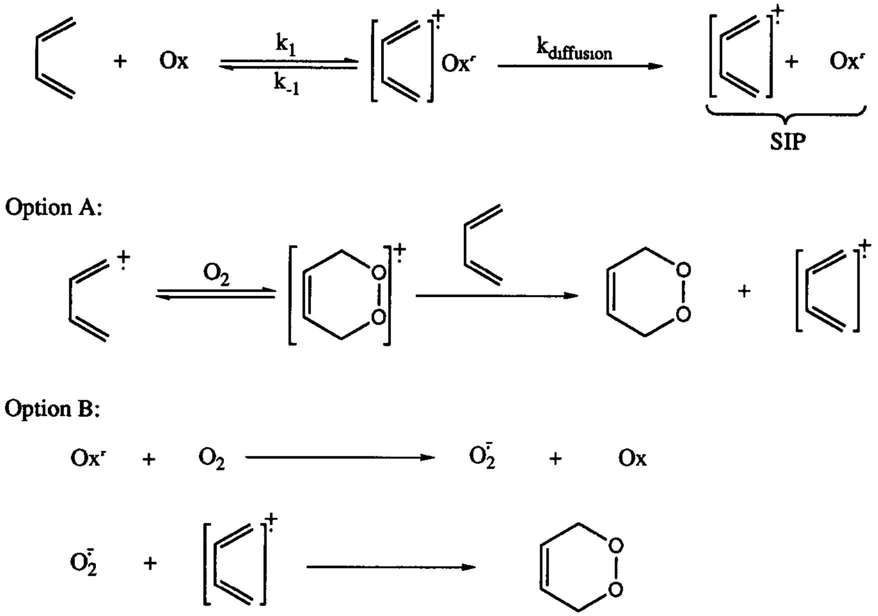
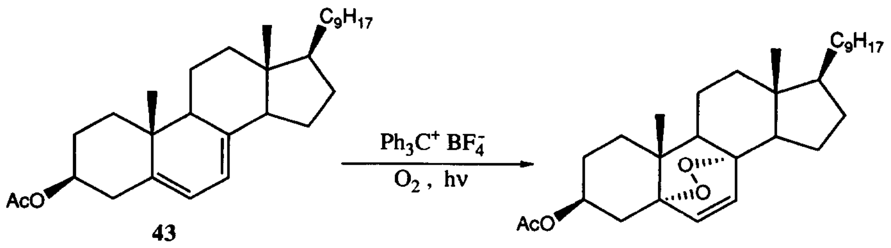
2.3 Type I and ID oxidations. In recent years the Type I and ID oxidations initiated by electron transfer have been extensively investigated. The success of these oxidations is related to the efficiency of solvent separated ion pair (SIP) and/or free ion formation. In nonpolar solvents reaction with oxygen does not compete with back electron transfer (k_{-1} in Figure 15) and no oxidation occurs. In polar solvents oxygen can react with the solvent separated diene radical cation (Option A) via a chain reaction or with the reduced oxidant to give superoxide. (Option B)

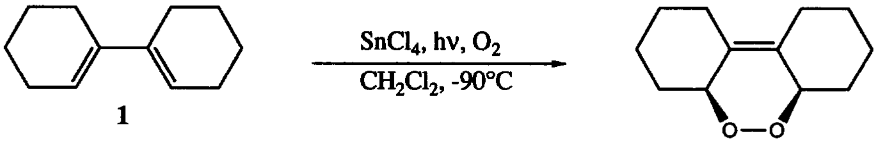
Figure 15.



In 1972 Barton and coworkers[113] reported that ergosteryl acetate, **43**, could be converted thermally, or more efficiently photochemically, in the presence of trityl fluoroborate to the5α, 8α endoperoxide. Subsequently it was shown[114] that Lewis acids were also successful catalysts for this interconversion. Non transition metal catalysts such as SnI_4, BCl_3, BBr_3, BF_3, $AlCl_3$, $SnCl_4$, SbF_5, $SbCl_5$, and I_2 required



irradiation for the best results. Transition metal catalysts such as $FeBr_3$, $FeCl_3$, $VOCl_3$, WCl_6, and $MoCl_5$, on the other hand, were effective thermal catalysts. Other dienes such as 1,1'-bicyclohexenyl, **1**,[115]



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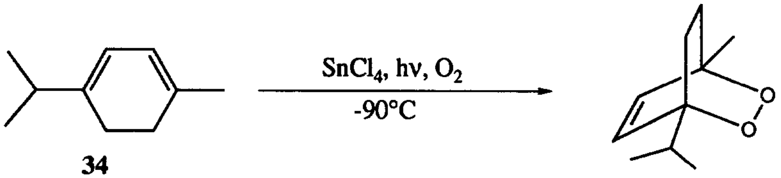

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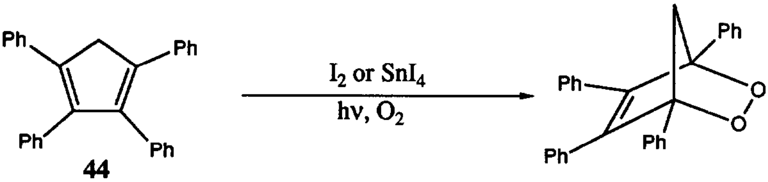
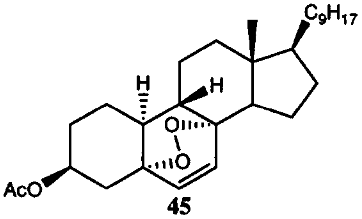


44

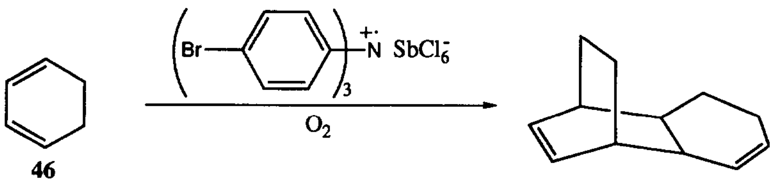
α-terpinene, **34**,[116] and 1,2,3,4-tetraphenylcyclopentadiene, **44**,[117] could also be converted to their endoperoxides under Lewis acid catalyzed conditions. Singlet oxygen could be ruled out as an intermediate in these reactions since lumisteryl acetate was unreactive under a variety of Lewis acid catalyzed conditions but could be readily converted to its endoperoxide, **45**, with singlet oxygen.[118]

Tang,[119] Haynes,[118] and Bartlett,[120] recognized that radical cations were involved in these reactions



45

and suggested a chain reaction mechanism (Option A Figure 15). Nelsen and coworkers[121] reported that steric inhibition of the rapid cation radical Diels Alder reaction[122] is necessary in order to see these Type I oxidation reactions. The reaction of an oxygen saturated solution of 1,3-cyclohexadiene, **46**, with tris(4-



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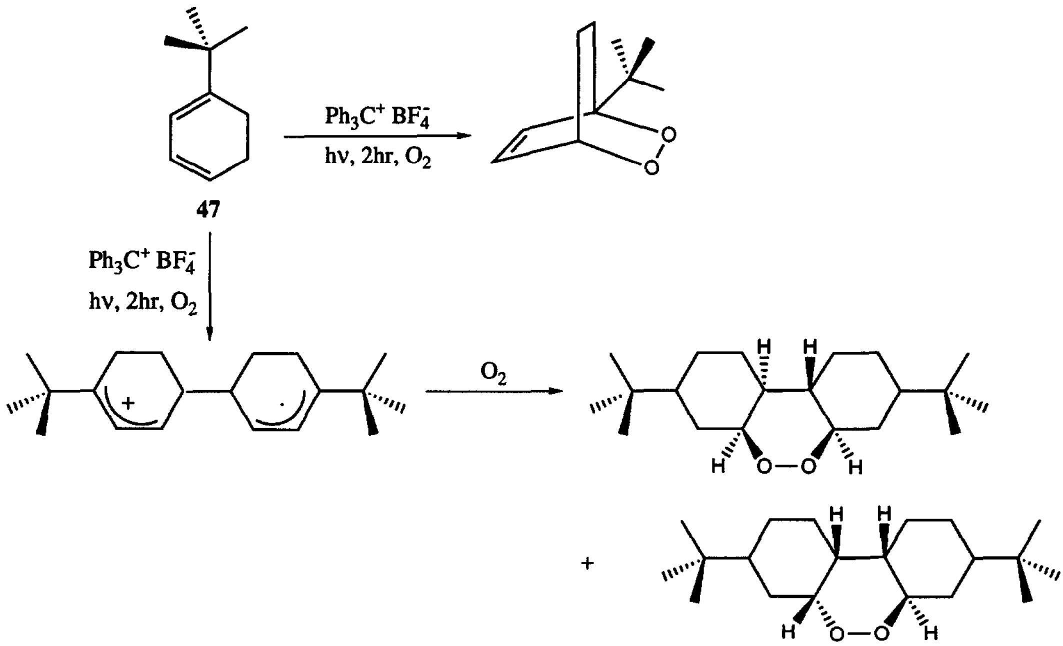
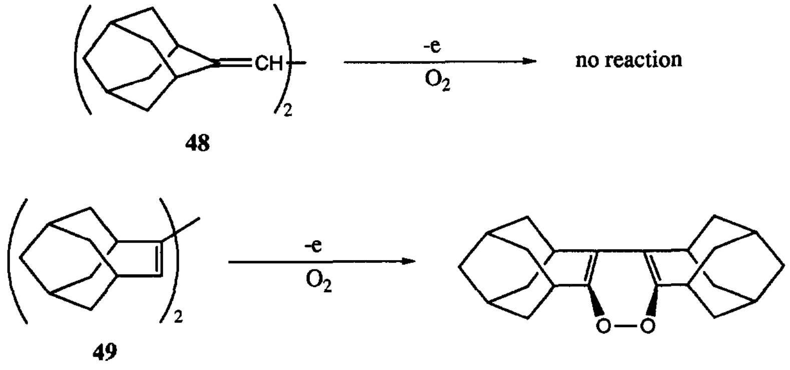
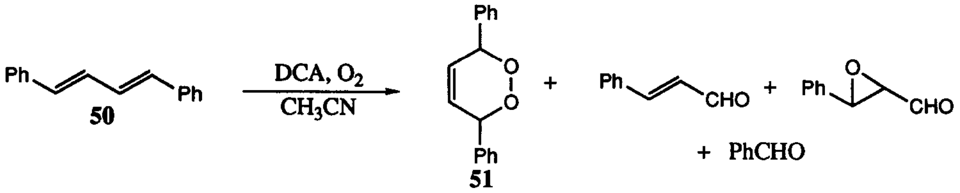
bromophenyl)ammoniumyl hexachloroantimonate resulted in Diels Alder dimerization but no oxidation. The reaction of α-terpinene, **34**, under identical conditions, however, led to efficient endoperoxide formation with chain lengths as long as 260. When only one end of the diene is sterically encumbered,[123] **47**, the expected endoperoxide is formed in only 5-10% yield. The major products are formed via a dimer radical cation, which forms by coupling at the sterically accessible end of the diene moiety.



A reasonable s-cis population of the diene is also required to observe Type I reactivity. Biadamantylideneethane, **48**, which is sterically prohibited from acquiring an s-cis conformation, does not react under these Type I conditions to give an endoperoxide. In contrast, 4,4'-bihomoadamantenyl, **49**, which can adopt the s-cis conformation, does react to give the endoperoxide.[121]



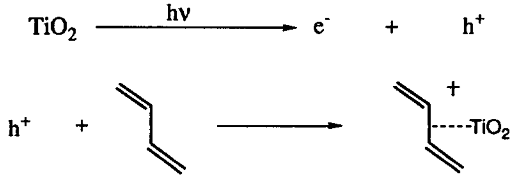
In 1977 Foote and coworkers[124] reported that 9, 10-dicyanoanthracene (DCA) photooxidations of alkenes and sulfides can occur via the Option B (Figure 15) electron transfer route. Singlet oxygen reactions also occur in competition with these Type I photooxidations as a result of enhanced formation of ^{3}DCA which acts as a Type II sensitizer.[125] DCA photosensitized oxidations of 1,4-diphenyl-1,3-butadiene, **50**, in CCl_4 and benzene gave endoperoxide **51**, exclusively. In contrast, photooxidations in the more polar solvents, CH_3CN and CH_2Cl_2, resulted in competitive formation of **51** and electron transfer products.[126] Miyashi and coworkers[127] demonstrated that in these more polar solvents approximately 4% of the free ions were produced.

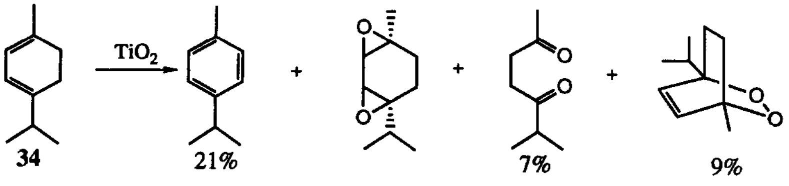


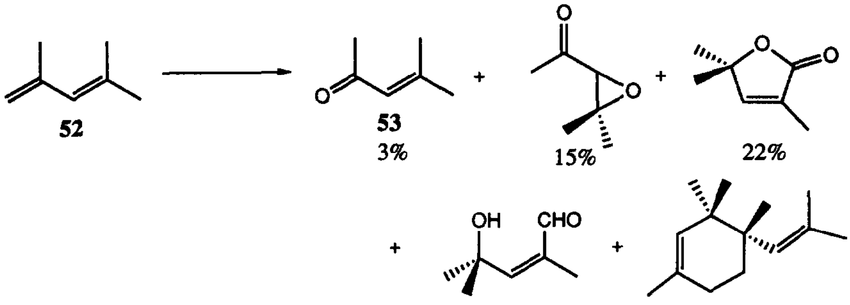
Fox and coworkers[128] reported a different kind of Type I photooxidation which is initiated by the interaction of the diene with a hole in a valence band created by irradiation of the semiconductor powder TiO_2.(Figure 16) The diene radical cation in these reactions is adsorbed on the surface of the semiconductor and as a consequence a radical cation free in solution is not formed. Oxygen is necessary in these reactions both as a reactant and as an electron acceptor for the conduction band electron of photoexcited TiO_2. Formation of superoxide prevents unproductive back electron transfer to the absorbed substrate.

The endoperoxide from **34** is formed in only 9% yield in the semiconductor catalyzed reaction in comparison to a quantitative yield in the Lewis acid catalyzed reaction. A 2 + 2 cycloaddition to the adsorbed radical cation of 2,4-dimethyl-1,3-pentadiene, **52** to form the dioxetane radical cation and its subsequent reduction was postulated in order to explain the formation of 4-methyl-3-penten-2-one **53**.[128] The formation of the dioxetane radical cation is reminiscent of the reaction of adamantylidene adamantane which produces a stable dioxetane.[129,130]

Figure 16.



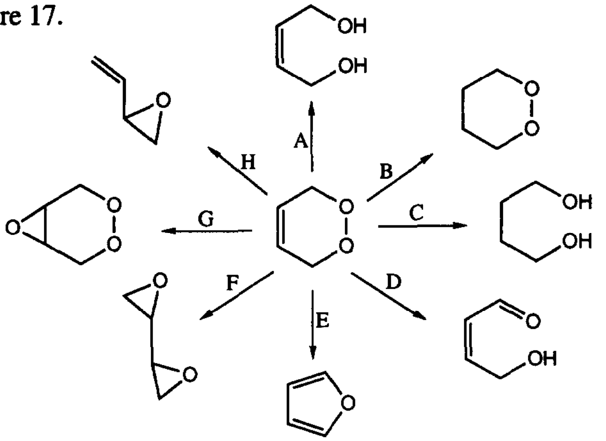




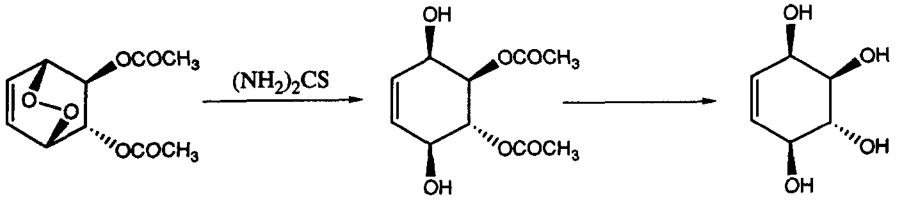
3. SYNTHETIC ASPECTS

The synthetic utility of the singlet oxygen diene reaction is a direct result of the myriad of transformations available to the endoperoxide products. Some of the most commonly utilized transformations are depicted in Figure 17. We will discuss these transformations only briefly since two excellent reviews have recently examined endoperoxide reactions in detail.[2,132]

Figure 17.



The reduction of the O-O bond, process A, can be conveniently accomplished with thiourea. Balci[28] used a thiourea reduction during the synthesis of conduritol F, **54**, a potential inhibitor of glycosidases. The



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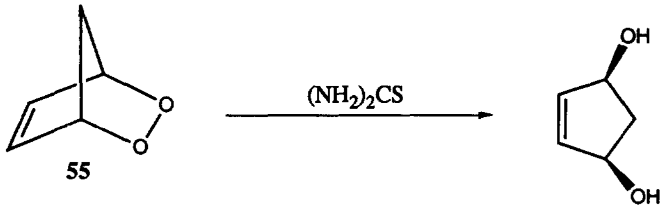
reduction left the ester carbonyls intact and required their removal in the last step of the reaction. The exceptionally mild character of the reaction also allowed its use at and below room temperature to reduce the very sensitive 5,6-dioxabicyclo[2.2.1]hept-2-enes, **55**,[133] and **56**[134] prior to their decomposition.



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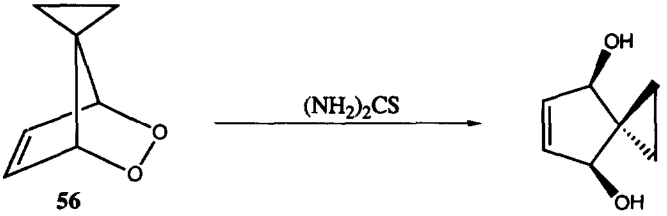

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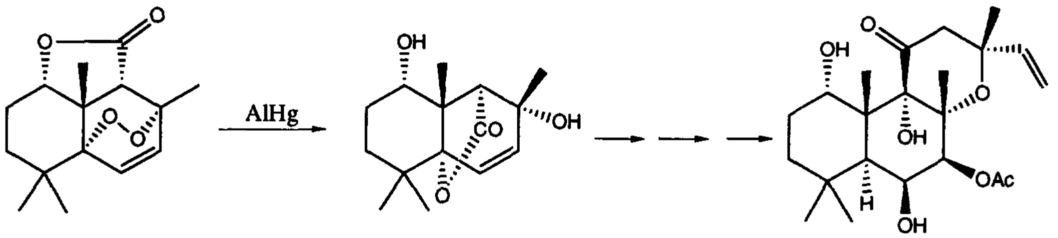
In 1988 Corey and coworkers[135] reported that AlHg successfully reduced the peroxide linkage in a key intermediate in the synthesis of (±)-forskolin, **57**, also without concomitant double bond or ester (lactone) reduction.



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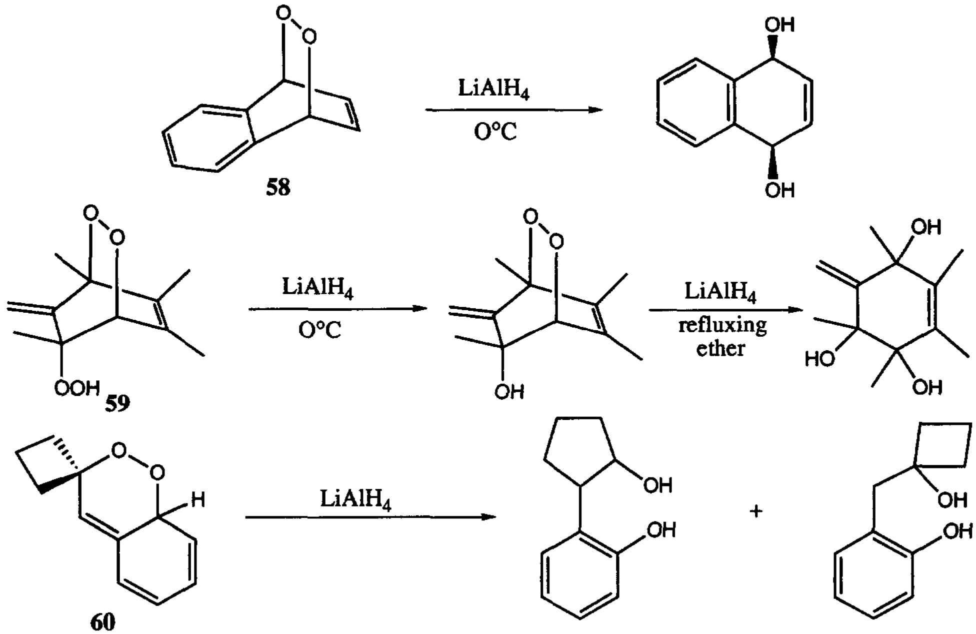
The Process A reduction of the O-O bond in **58** was accomplished with lithium aluminum hydride at 0° C.[136] Utilization of these mild conditions to reduce **59**, however, resulted in reaction specifically at the hydroperoxy group,[137] and refluxing ether was necessary to affect cleavage of the endoperoxide linkage. Hart and Oku[138] reported that the endoperoxide derived from octamethylnaphthalene was completely inert to $LiAlH_4$ at room temperature, and attempts to run the reaction at higher temperatures resulted in retrocycloaddition and loss of oxygen rather than reduction. Reductions with $LiAlH_4$ can also be accompanied by reactions initiated by its basic character. For example, reaction of the spirocyclic endoperoxide **60**[139] resulted in the formation of a rearrangement product as well as the anticipated product formed by reduction and subsequent aromatization.



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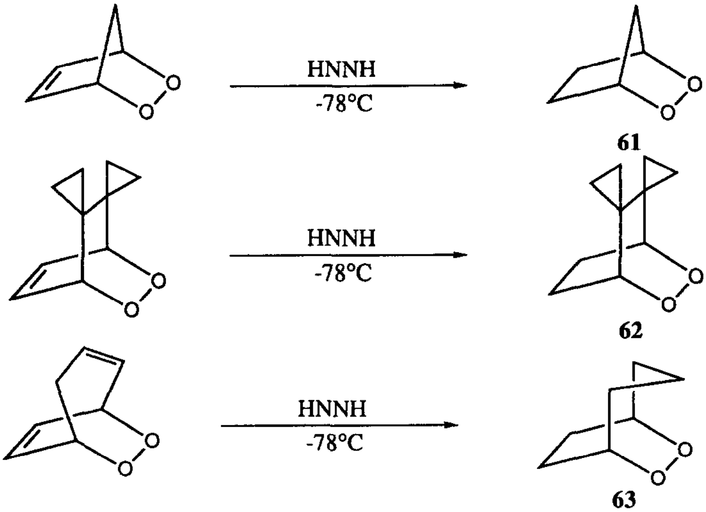
59

60

Diimide, which was introduced by Salomon and Coughlin[140] in 1977, is the most commonly used reagent in bicyclic systems for double bond reduction with retention of the peroxide linkage. (Process B Figure 17) This reaction can be used to produce [2.2.1], **61**,[141] [2.2.2], **62**,[142] [3.2.2], **63**,[143] and [4.2.2], **64**,[144] saturated bicyclic endoperoxides.



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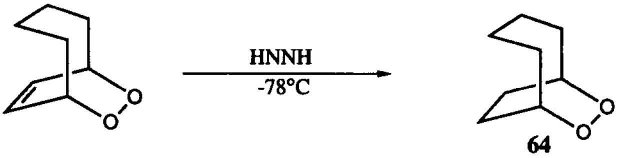
62

63

Salomon and Coughlin[145] used deuterium labeling to demonstrate that diimide addition to form **61** was cis and anti to the peroxide bridge. Bloodworth and Eggelte[146] examined the face selectivity of diimide addition as a function of bridge size (Figure 18) and argued that both steric and electronic effects play roles in dictating the stereochemistry of addition.



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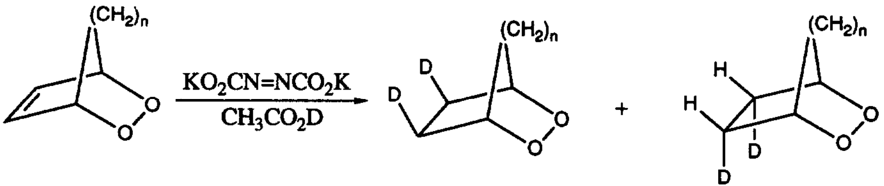
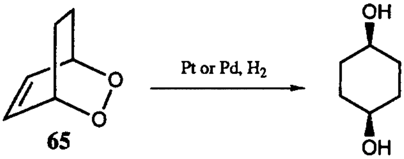
The double bonds in endoperoxides derived from ascaridole **34**,[147] and dehydroergosterol epidioxide[148] can be reduced with PtO_2 and hydrogen without O-O cleavage but do not represent general procedures. The more typical outcome of reductions with platinum, palladium, and nickel catalysts, as exemplified by the reaction of endoperoxide **65**,[149] is the loss of the peroxide linkage and the double bond.(Process C, Figure 17)

Figure 18.



	anti	syn
n = 1	100%	0%
n = 2	34%	66%
n = 3	0%	100%
n = 4	0%	100%



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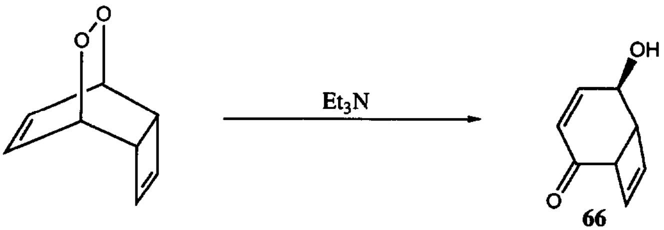
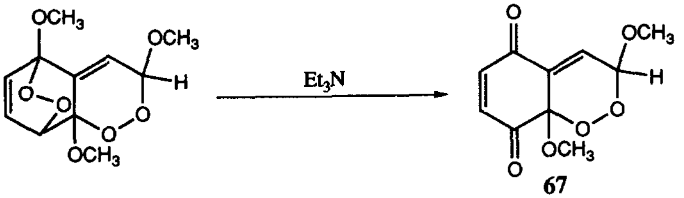
Process D is formally a 1,3 hydrogen shift often referred to as the Kornblum-DeLaMare reaction.[150] This reaction occurs in the presence of bases and produces γ-hydroxy ketones, **66**[151] or γ-diketones, **67**.[152]



66

The hydroxy ketones derived from monocyclic, **68**[153] and **69**, and some bicyclic endoperoxides, under acidic conditions often react further to form furans. (Process E) The synthetic utility of this reaction has resulted in the development of a large number of reaction conditions which promote furan formation including the recently reported CoTPP catalyzed process[154] (eg. **69**). When bicyclic or polycyclic endoperoxides, **70**, are treated with CoTPP, bisepoxides (Process F) rather than furans, are formed.[155] This CoTPP catalyzed process is the preferred method for synthesis of bisepoxides and gives much better yields than pyrolysis, which is plagued by side reactions. CoTPP catalyzed decomposition of endoperoxide **71** is one of the rare cases that produce byproducts, but even in this case the bisepoxide is the major product.[156]



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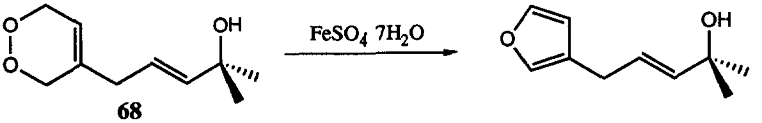

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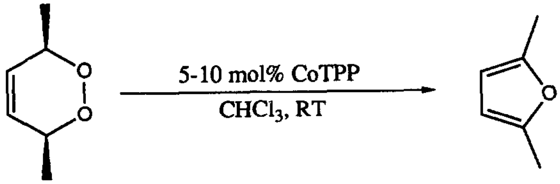

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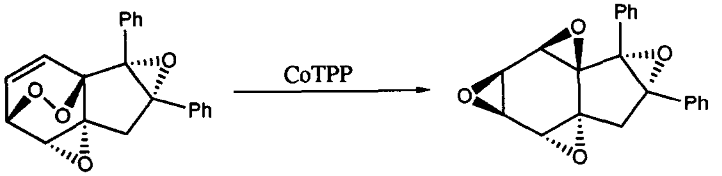

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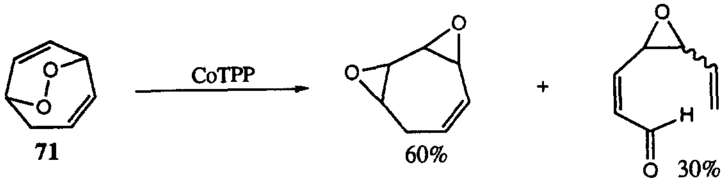
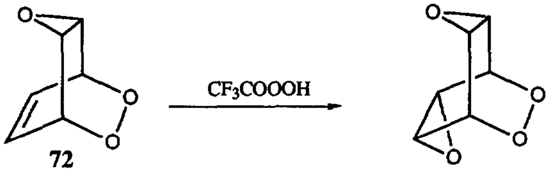


71

The double bond in an endoperoxide is a functional group which can be manipulated, in many cases, without cleavage of the peroxide linkage. Process G in Figure 17 is an example of such a reaction where the double bond is converted to an epoxide. Foster and Berchtold[157] accomplished this transformation on endoperoxide **72** using trifluoroperacetic acid. Other examples of double bond manipulations include, bromination,[157] chlorination,[144] and hydrogenation.

The reactions of triaryl or trialkyl phosphines or phosphites with endoperoxides result in the formation of epoxy olefins. (Process H in Figure 17) Bloodworth[2] has suggested that the reaction occurs by nucleophilic attack at the peroxide linkage to give zwitterion **73** followed by Sn2' displacement of phosphine oxide or phosphate. In some situations the reaction can be stereospecific; for example, the unsymmetrical endoperoxide **74** gave only one of the two possible epoxy olefins.[158]



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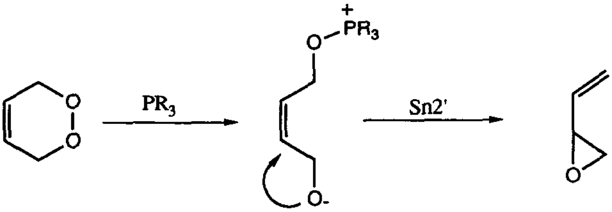

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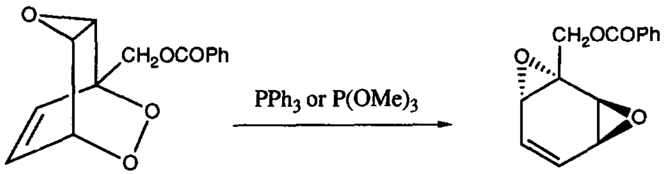

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