MECHANISM OF ADDITION OF SINGLET OXYGEN TO OLEFINS AND OTHER SUBSTRATES*

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ABSTRACT

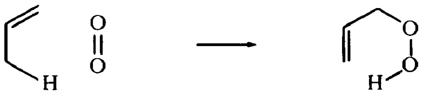
Mechanisms of addition of singlet oxygen to various classes of substrates are surveyed. The experimental data for the allylic hydroperoxidation are best fit by a concerted, 'ene-type' mechanism; the addition to dienes is probably a Diels–Alder reaction. 1,2-Cycloadditions to electron-rich olefins may proceed by a 1,4-dipolar mechanism, although there is as yet little evidence, while the addition to sulphides may go by a very similar nucleophilic addition to oxygen.

INTRODUCTION

Singlet molecular oxygen (almost certainly in the $^1\Delta_g$ state) is produced by energy transfer from triplet sensitizers (Sens) to oxygen; the species thus produced is chemically and kinetically indistinguishable from singlet oxygen generated by the reaction of sodium hypochlorite and hydrogen peroxide, or by a variety of other oxygen-producing reactions[1]. Oxygen in the $^1\Delta_g$ state has been detected by its luminescence[2] and paramagnetic resonance spectra[3] as a product of photosensitization in the gas phase, and its intermediacy in solution is now generally accepted[1,4].

$$\text{Sens} \xrightarrow[h\nu]{} {}^1\text{Sens} \rightarrow {}^3\text{Sens} \xrightarrow[{}^3O_2]{} {}^1O_2({}^1\Delta_g) \leftarrow \text{NaOCl} + H_2O_2$$

Two classes of reaction of singlet oxygen are particularly important, (1) additions to olefins, giving allylic hydroperoxides, analogous to the Alder 'Ene' reaction, and (2) additions to diene systems to produce endoperoxides, analogous to the Diels–Alder reaction[4].



(1)

(2)

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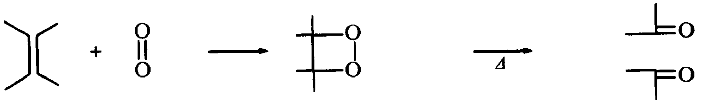
* Contribution No. 2689.

To these should be added two other classes, of somewhat less generality, (3) a 2 + 2 cycloaddition to electron-rich olefins, to produce dioxetanes, which are sometimes of moderate stability but readily cleave into two carbonyl-containing fragments[5], and (4) oxidation of certain heteroatoms, notably sulphur and phosphorus, a reaction exemplified by the oxidation of diethyl sulphide to diethyl sulphoxide, in which two moles of sulphoxide are formed for each mole of oxygen consumed[4].



(3)

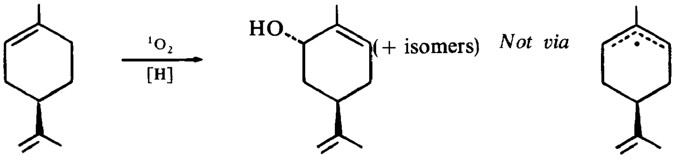
$$2(C_2H_5)_2S + O{=}O \rightarrow 2(C_2H_5)_2\overset{+}{S}{-}O^- \qquad (4)$$

Although not all of these reactions are cycloadditions, and thus may not fall within the scope of this symposium, they have certain features in common which makes it profitable to discuss all of them together. In this paper, I concentrate on the oxygenation step of the reaction; other aspects of the reaction have been reviewed[4]. Several of the following reactions have been studied with both photochemically and non-photochemically[1] generated singlet oxygen; the results are in every case the same, and no distinction will be made here between different modes of generation.

THE ENE REACTION

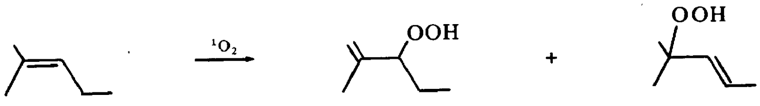
The addition of singlet oxygen to olefins to give allylic hydroperoxides has been the most extensively studied of these reactions. The characteristic features of this reaction are the following.

(1) The double bond shifts cleanly to the allylic position; no allylic free radical is involved. This feature is perhaps best exemplified by the singlet oxygen oxidation of limonene (**1**) which gives, among other products, alcohol **2** which is optically pure, ruling out the intermediacy of radical **3** which is optically inactive[6].



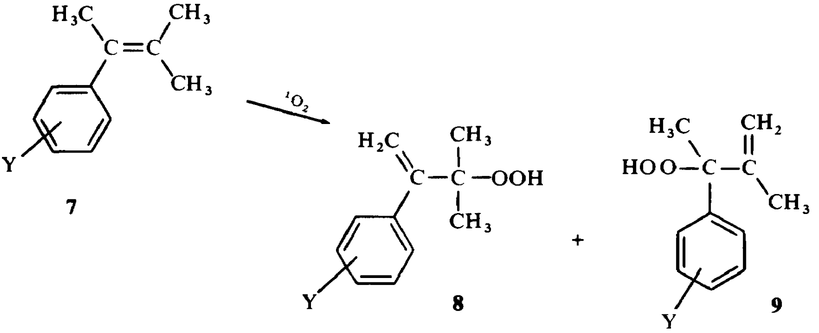
1 **2** (optically pure) **3**

(2) The products from unsymmetrical olefins are formed with essentially no Markovnikov-type directing effect; thus, for example, 2-methyl-2-pentene (**4**) gives hydroperoxides **5** and **6** in 49 and 51 per cent yield, respectively[1,4].



4 **5** **6**

This behaviour is further illustrated by the substituted trimethylstyrenes **7**, which give products **8** and **9** in a ratio of 2.7:1; this ratio is independent of substituent Y, over the range *p*-methoxy to *p*-cyano[1,7]. These effects argue against a transition state with either localized charge or radical character.



(3) The reaction is modestly electrophilic, 2,3-dimethyl-2-butene being about 40 times as reactive as 2-methyl-2-butene[1,4,8]. The Hammett ρ for the photooxygenation of the trimethylstyrenes (**7**) is about -0.9; the reaction correlates well with σ and poorly with σ^+ [1,7].

(4) The preferred conformation for the reaction is the one in which the C—H bond being broken is aligned parallel to the *p*-lobes in the double bond; the oxygen enters *cis* to the hydrogen being transferred[1,4,9].

(5) Methylcyclohexene derivatives are anomalously unreactive, and the formation of products with endocyclic double bonds is unfavourable relative to exocyclic double bonds[1,4]. For example, 1,2-dimethylcyclohexene (**10**) gives mainly **11** and little **12**[1].

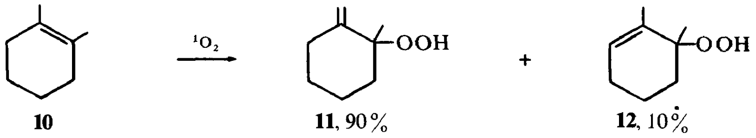
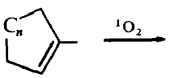
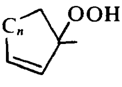
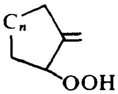
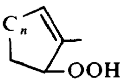


Table 1. Photooxygenation of 1-methylcycloalkenes

					Partial rate factor, exocyclic olefin product
Olefin Ring Size ($n + 4$)	k_{rel}	Percentage of product			
5	6.2[b]	53	4	43	0.25
6[a]	1.0	36	44	20	0.44
7	9.4	48	4	48	0.38
8	1.5	31	27	42	0.41

[a] Refs. 1 and 4.

[b] In good agreement with the reactivity reported in ref. 8.

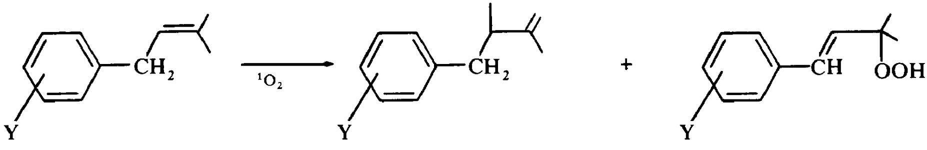
These characteristics are general for cyclohexenes, but do not apply to other ring sizes. The photooxygenation of the 1-methylcycloalkenes has been studied[10], and the results are shown in *Table 1.*

1-Methylcyclohexene is about six times less reactive than typical trisubstituted acyclic olefins, and the products involve largely methyl attack, since the product with exocyclic double bond predominates[1,4]. The results show that 5- and 7-ring olefins are about as reactive as normal acyclic olefins, and endocyclic products predominate; the cyclooctene is intermediate in both reactivity and product distribution. The 'partial rate factor' for formation of exocyclic product (methyl attack) is essentially constant, over the series, so that most of the rate difference is due to relative ease or difficulty of formation of endocyclic product.

The results suggest that the same factor (presumably conformational) which makes the formation of products with endocyclic double bonds unfavourable in the cyclohexene case also makes the overall reaction slow, and that rates and products behave in a parallel fashion. This observation suggests that the C—H bond is involved in the rate-determining step of the ene reaction.

(6) The reaction has very little solvent effect. Rates vary by a maximum of four for solvents as diverse as benzene and dimethylsulphoxide, and there is no correlation with polarity of the solvent[1,7], so that the transition state does not appear to have much charge separation.

(7) In an attempt to establish the degree of C—H bond breaking at the transition state, a series of olefins (**13**) is being studied[11]. The preliminary results with a limited number of substituents are that the product distribution is not far from 1:1 secondary unconjugated (**14**) to conjugated (**15**) hydroperoxide, and that this ratio is *invariant* with substituent. The rates vary only slightly, and are roughly in the inductive order, with *p*-methoxy being slightly *slower* than *p*-methyl. These results suggest that the electron density *in the double bond* controls the rate, and that the amount of C—H bond breaking at the transition state is probably small. These results are difficult to interpret unambiguously, and it is emphasized that they are preliminary. Kinetic isotope effect studies are also highly desirable, but have not yet been reported†.



13 **14**, 47% **15**, 53%

The mechanism which has been suggested[1,4,9], and which is consistent with the reaction characteristics described above has a more or less concerted reaction with a cyclic transition state like that suggested[12] for the ene reaction.

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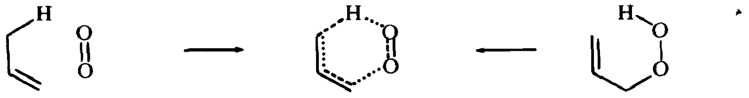
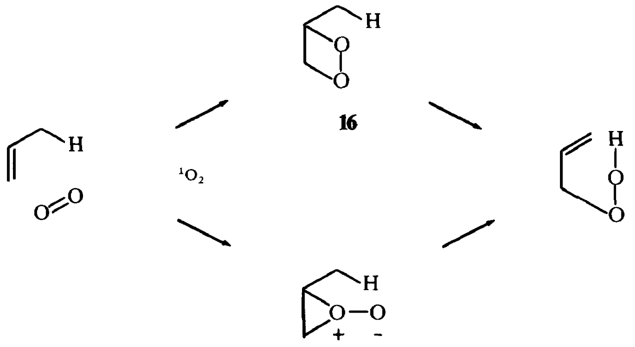
† Prof. K. Kopecky and Prof. A. Nickon have such studies in progress (private communication); the deuterium isotope effect is non-zero but small (<2).



In this mechanism, the transition state would not be far advanced; the electron density in the double bond and the conformational availability of the hydrogen atom would be rate determining, but no appreciable charge or radical character is localized on any of the three carbon atoms, nor has much C—H bond breaking occurred.

It has recently been suggested that these additions involve an intermediate cycloadduct, either a dioxetane[13] (**16**) or a perepoxide[14] (**17**), as suggested earlier by Sharp[15] and by Kopecky[8].



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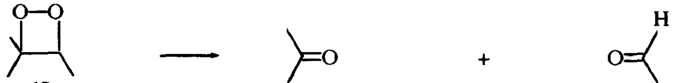
(**17**)

The dioxetane mechanism is not consistent with the behaviour of the known 3,3,4-trimethyl-1,2-dioxetane (**18**) which cleaves to acetaldehyde and acetone[16], instead of giving allylic hydroperoxide. This mechanism must therefore be ruled out. The perepoxide mechanism might have been expected to be affected by solvent polarity, at least to some degree, since some charge separation would be involved; furthermore, the direction of opening of a perepoxide would be expected to be affected by substituents, since the C—O bond would be weakened by electron donation. Furthermore, the parallel between product and rate observed in the 1-methylcycloalkenes cannot be explained by this mechanism. In support of the perepoxide mechanism is the observation that addition of sodium azide leads to formation of azidohydroperoxides (**19**) at the expense of the normal product[14]. This finding was rationalized by the suggestion that the perepoxide reacts with azide, giving **19**.



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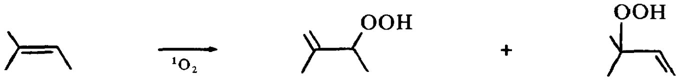
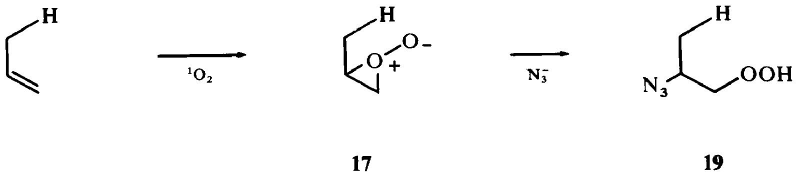


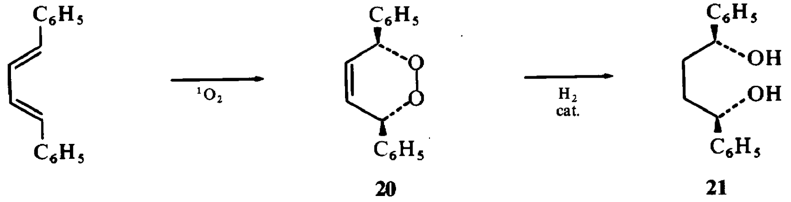
(after Fenical, Kearns and Radlick)



However, preliminary studies show that this reaction is complex[17]. Azide causes a very large decrease in overall reaction rate, apparently by quenching of $^1O_2$, and the relative reactivities of tetramethylethylene and 2-methyl-2-pentene are different in the presence and in the absence of azide ion, so that the effect of azide is not simply to divert an intermediate which would otherwise give ene products. While the perepoxide mechanism cannot be ruled out, the cycloaddition mechanism seems more satisfactory.

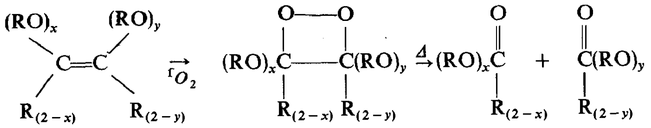
DIELS–ALDER REACTION

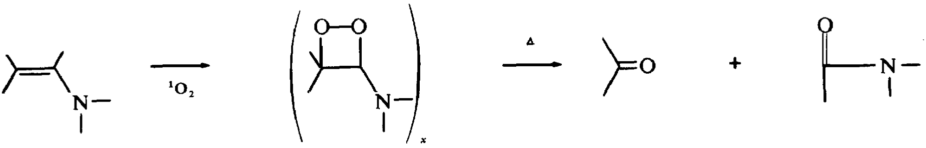
The oxygenation of dienes, aromatics and heterocycles by 1,4-addition of singlet oxygen has not had as complete a mechanistic characterization of the product-forming step as has the reaction with olefins. The following characteristics are known. Like the ene reaction, the reactions with dienes and furans are electrophilic[18], as is the reaction with anthracenes[4]; electron donors increase the reaction rate, and electron withdrawing groups decrease it. The only solvent effects reported are puzzling, and cannot be explained by any known effect; however, in particular, there is no correlation with polarity[19]. The stereochemistry of the addition is pure *cis*. Perhaps the clearest example (of the very few in which stereochemistry is not constrained by a ring to be *cis*) is the photooxygenation of 1,4-diphenylbutadiene, which gives the *cis*-peroxide (**20**); on reduction, *meso*-diol (**21**) was obtained[20]. It seems likely that the addition of $^1O_2$ to dienoid compounds is mechanistically equivalent to a Diels–Alder reaction.



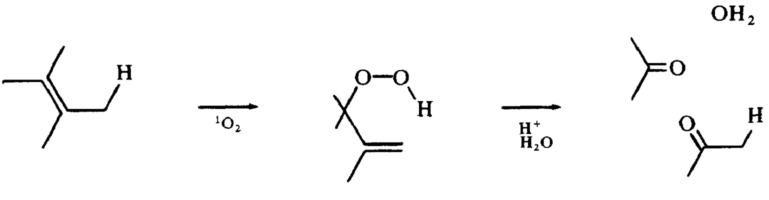
1,2-CYCLOADDITION

Several examples of 1,2 cycloaddition of singlet oxygen to electron-rich olefins have been reported[5]. The products from several polyalkoxyethylenes are 1,2-dioxetanes, which are stable enough to isolate. In the case of enamines, intermediates of similar structure are formed, but these intermediates may not be solely monomeric; however, they cleave to carbonyl compounds and amides smoothly below 0°[21].

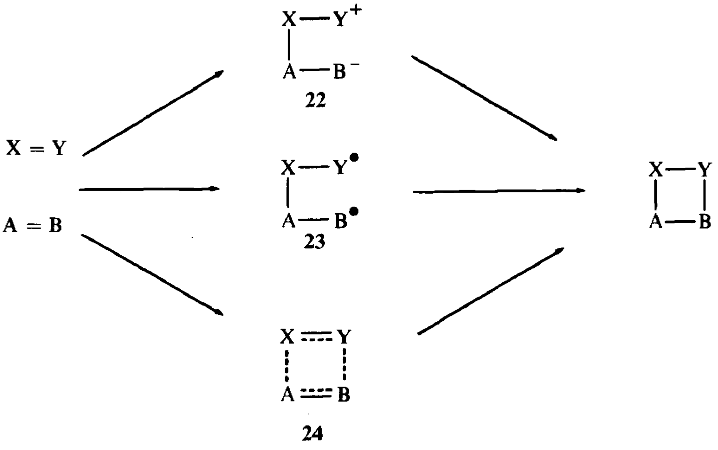




Other reports of similar olefin cleavages have appeared, although intermediates have not been detected[3, 22]; not all of the olefins are particularly electron-rich (for example, indene[13]); it is probable, but not certain, that these cleavages also proceed by way of dioxetanes[13]. It should be noted that allylic hydroperoxides can undergo a similar cleavage (normally acid-catalysed), with the same overall result[4]. The mechanism of both the addition of singlet oxygen to electron-rich olefins, and of the cleavage reaction are of considerable interest.

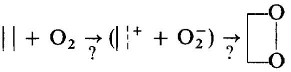


1,2-Cycloaddition reactions can proceed depending on the system by way of an intermediate 1,4-dipolar species (zwitterion **22**), a 1,4-diradical (**23**), or by an apparently concerted four-centre addition **24**[23].



Compounds which can act as dienophiles in the Diels–Alder reaction appear to react commonly with electron-rich olefins by the dipolar mechanism[23]; one might expect this to be the case with singlet oxygen as well.

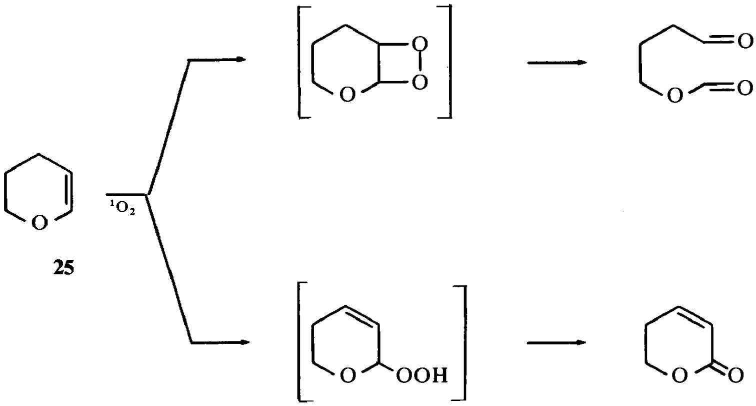
However, Kearns has recently suggested, on the basis of rather complex orbital-symmetry considerations, that the $2s + 2s$ 1,2-addition of singlet oxygen, leading to dioxetanes, may be an allowed process[24]. A careful analysis of Kearns's scheme[25], however, shows that the reaction is only allowed (for the $2s + 2s$ process) when charge-transfer from the olefin π orbital to the oxygen π^* orbitals can occur, which is certainly a reasonable possibility with the vinyl ethers and enamines under discussion. Thus, the addition might be occurring by way of the electron-transfer reaction 5. For reasons discussed above, 1,2-addition probably does *not* occur in the less electron-rich olefins, and is not intermediate in the ene reaction. In all probability, singlet oxygen will have the same orbital symmetry behaviour as ethylene, since, as mentioned above, the addition to dienes occurs with the normal *cis*-stereochemistry. However, Bartlett has suggested that $2s + 2a$ concerted addition of singlet oxygen to olefins may be possible[5b].



$$\|\ + O_2 \xrightarrow[?]{} (\|^{+} + O_2^{-}) \xrightarrow[?]{} \quad (5)$$

Experimental evidence on the mechanism of the reaction is very limited. We have established that the photosensitized oxygenation of *N*,*N*-dimethylisobutenylamine occurs by reaction of singlet oxygen with the enamine, rather than by (for example) electron transfer to excited sensitizer, or by a free-radical chain mechanism of some sort. The reaction is competitively inhibited by tetramethylethylene, a good singlet oxygen acceptor, and shows no inhibition by 2,6-di-*t*-butyl phenol, a good radical inhibitor[26]. So far, the only evidence concerning the mechanism of the addition has been presented by Bartlett and co-workers[27]. They showed that for dihydropyran (**25**), a system in which the ene-reaction and 1,2-cycloaddition appear to compete, polar solvents favour the 1,2-cycloaddition (ultimately giving **26**)

(after Bartlett, Mendenhall and Schaap)



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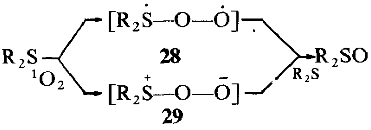
27

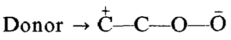
over the ene reaction (which gives **27**). This finding, if general, suggests that the transition state for the 1,2-cycloaddition is more polar than that for the ene reaction, and supports either the 1,4-dipolar or electron-transfer mechanism. Further work on these systems is in progress.

As for the mechanism of the cleavage of the dioxetanes, McCapra has pointed out that this breakdown is a reverse 2 + 2 cycloaddition, and correlation with one of the carbonyl products in an excited state would be expected if the reaction is concerted[28]. Indeed, many chemiluminescence reactions may involve dioxetanes as intermediates[28]. In fact, breakdown of the few dioxetanes which have so far been isolated is uniformly accompanied by chemiluminescence[5, 16]. However, there may be difficulties with the concerted mechanism giving excited products, in some cases at least. For example, with tetramethoxydioxetane[5a], the product is dimethyl carbonate; bond energy calculations suggest that there may not be sufficient energy released in the breakdown (even with the addition of an activation energy), to excite even the lowest triplet of dimethyl carbonate. Study of the mechanism of these reactions is hampered by the low efficiency of the chemiluminescence.

SULPHIDES

Sulphides can be photooxygenated smoothly to sulphoxides[4, 29]. This reaction presumably involves an intermediate; Gollnick has formulated this as **28**[4], but perhaps a more reasonable alternative would be **29**. The close analogy of the latter intermediate to the 1,4-dipole **30**, a possible intermediate in the enamine and vinyl ether oxidation, should be noted.

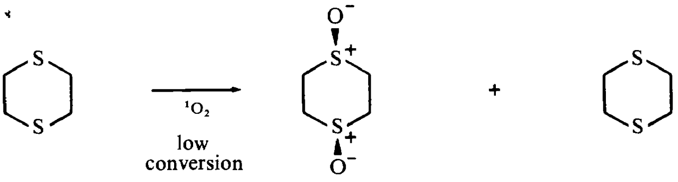




$$\text{Donor} \rightarrow \overset{+}{C}—C—O—\overset{-}{O}$$

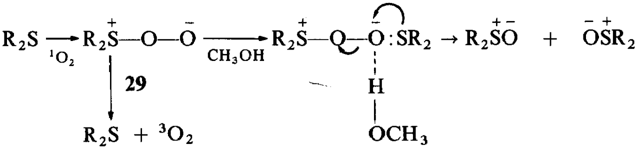
30

The following information has been obtained in preliminary experiments. The oxygenation of diethylsulphide proceeds by way of singlet oxygen, since it is competitively inhibited by diphenylanthracene and β-carotene[30]. In methanol, the reaction is efficient, but in benzene, it is far less so, and is accompanied by considerable quenching of $^1O_2$. Photooxygenation of 1,4-dithiane (**31**) under the proper conditions can be made to produce exclusively *cis*-disulphoxide (**32**) and unreacted **31** when carried out to low conversions. The fraction of intramolecular reaction (compared to intermolecular reaction, giving two moles of monosulphoxide) is very sensitive to solvent, being very large in benzene and comparatively low in methanol; in benzene, at least, the reaction is intramolecular at low concentrations, but appears intermolecular at higher concentrations. Similar effects have been observed with other bis-sulphides[31].



31 **32**

These observations confirm the presence of an intermediate, though they do not completely clarify its formulation. Perhaps the effect of methanol is to stabilize zwitterion **29**, and remove some of the negative charge by hydrogen bonding to make nucleophilic attack by a second sulphide possible. In the absence of methanol, the adduct may tend to revert to sulphide and ground-state oxygen, resulting in quenching. It seems likely that the additions to sulphides and enamines are closely related, and are perhaps best represented at present as nucleophilic additions, although the evidence is not yet convincing.



$$R_2S \xrightarrow[{}^1O_2]{} R_2\overset{+}{S}{-}O{-}\overset{-}{O} \xrightarrow[CH_3OH]{} R_2\overset{+}{S}{-}O{-}\overset{-}{O}{:}SR_2 \rightarrow R_2\overset{+}{S}\overset{-}{O} + \overset{-}{O}\overset{+}{S}R_2$$

$$\mathbf{29}: \; R_2\overset{+}{S}{-}O{-}\overset{-}{O} \rightarrow R_2S + {}^3O_2 \qquad \overset{-}{O}\cdots H{-}OCH_3$$

The purpose of this paper has been to survey the state of knowledge of the mechanisms of addition of singlet oxygen to various types of substrate; it is obvious that only a beginning has been made, and that much more work will be required before the details of these biologically significant reactions are understood.

ACKNOWLEDGEMENTS

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