The Photo-oxygenation of Olefins and the Role of Zwitterionic Peroxides

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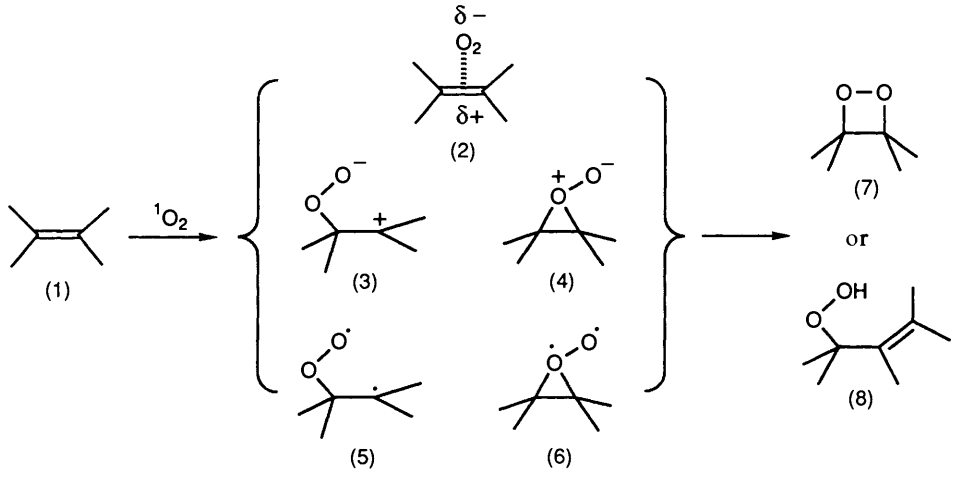
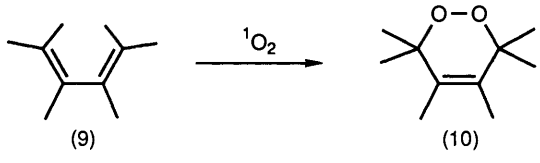
1 Introduction

Oxygen, in its singlet state, is a versatile reagent.[1] Depending on the availability of an allylic hydrogen substituent, mono-olefins (1) react with it to give either dioxetanes (7) or hydroperoxides (8) (Scheme 1), whereas *cis*-dienes (9) yield *endo*-peroxides (10) (Scheme 2). The mechanisms of these reactions have excited considerable interest in recent years. Although it is generally conceded that the last reaction proceeds through a concerted [4 + 2] cycloaddition, the mechanism of the first and second reactions remains controversial. Concerted [2 + 2] additions and ene-type reactions are attractive for their mechanistic economy,[2] but two-step processes are more likely. As a first event, oxygen may interact with olefins (1) to give exciplexes (2),[3] zwitterionic peroxides (3) or perepoxides (4),[4] or their biradical analogues (5) and (6).[5,6] Subsequent skeletal or electronic reorganization of these different intermediates generates the appropriate hydroperoxide or dioxetane (Scheme 1). As none of these intermediates have been isolated, they were deemed to be unstable. Consequently, evidence for their existence has been difficult to obtain and necessarily has been of the indirect kind. We now present an account of experiments, in which zwitterionic peroxides or perepoxides have been characterized by trapping experiments. Apart from obtaining mechanistic insights, new reactions for preparing members of a hitherto relatively unknown class of oxygen heterocycles, the 1,2,4-trioxanes, have been uncovered.



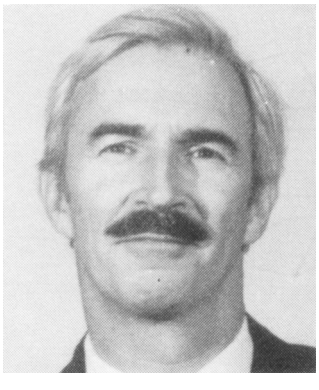
Scheme 1



Scheme 2

Charles William Jefford was born in Farnborough, Hampshire, England, in 1929. He attended Oxford University (1949–1954) where he obtained the M.A., B.Sc., and D.Sc. degrees in chemistry. After a brief spell in industry, he pursued graduate studies at Princeton University, earning a Ph.D. degree with E. C. Taylor (1962). Thereafter he was a postdoctoral fellow with N. L. Allinger at Wayne State University, Detroit, which was followed by a seven year interlude as a professor at Temple University, Philadelphia. In 1969 he returned to Europe as a full professor in organic chemistry at the University of Geneva, Switzerland, where he has stayed ever since.

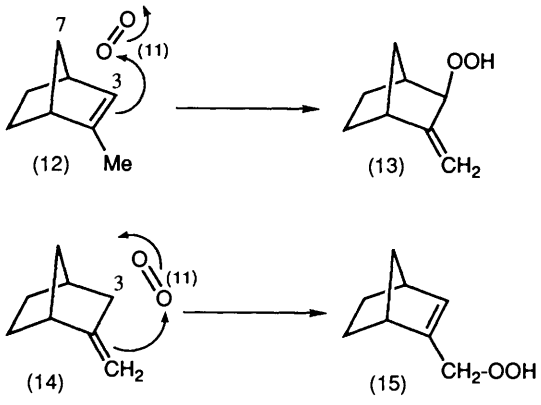
Dr. Jefford's research activities concern the reactions of oxygen with organic substrates. The chemistry of saturated oxygen heterocycles such as lactones, furans, peroxides, 1,2-dioxetanes, and 1,2,4-trioxanes are of particular interest, especially the last of these as a potential anti-malarial remedy. Two other areas of current activity are the synthesis of indolizidine alkaloids and the directed rearrangement of cyclobutene derivatives. Dr Jefford has published more than 250 research articles.



2 Formation of Hydroperoxides

Originally, the ene-type reaction of singlet oxygen (11) to produce hydroperoxides was regarded as being a concerted process. Evidence now exists to show that an ionic intermediate is involved.[7] The photo-oxygenation of 2-methylnorbornene (12) and 2-methylidenenorbornane (14) is pertinent.[8] The sole products are the allylic hydroperoxides (13) and (15) (Scheme 3). From rate studies, it was established that the ionization potential of the olefin is a guide to reactivity provided steric factors are absent.[9,10] In other words, hydroperoxidation is an electrophilic reaction, the rate of which is governed by the energy of the highest occupied molecular orbital (HOMO) of the double bond.

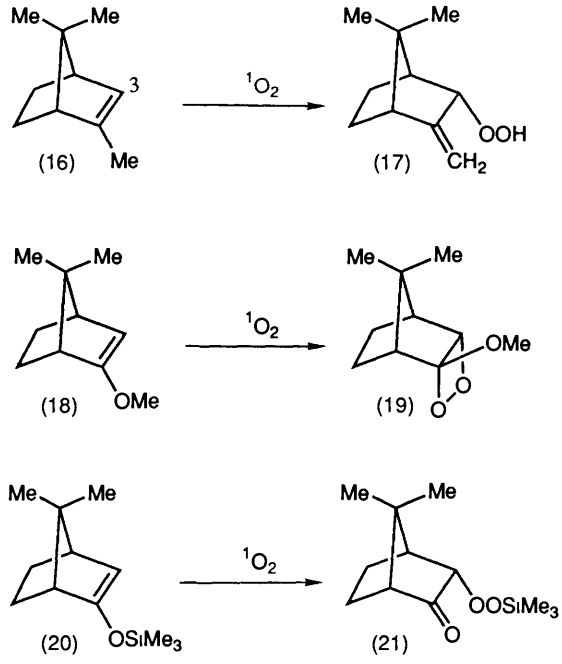
The act of abstraction of the *exo* allylic hydrogen atom from



Scheme 3

C-3 in the reaction of (14) is sterically insensitive, since the intermolecular kinetic isotope effect for the C-3 deuterated derivative was found to be 1 14 ± 0 01 On the other hand, the creation of the carbon–oxygen bond on the *exo* side of the vinyl carbon atom at C-3 in (12) for example is subject to steric hindrance by bulky substituents at C-7

The introduction of methyl groups at C-7 in (12) suppresses attack on the *exo* side to favour *endo* products The *exo*/*endo* product ratios for 2,7,7-trimethylnorbornene (16) and the methyl and silyl ethers [(18) and (20)] were 0 19, 0 25, and 0 064 respectively (Scheme 4) The smallness and similarity of these ratios means that the transition states are sensitive to steric effects and that the same mechanism is operating, although in all three cases the final major products were different, namely hydroperoxide (17), dioxetane (19), and silaperoxy ketone (21) (Scheme 4) It can be concluded that some zwitterionic character develops in the transition state as bonding by the oxygen molecule to the C-3 atom is advanced The resulting positive charge is stabilized by the substituents on the double bond, presumably to a greater degree for (18) and (20) Charge is annihilated by abstraction of a proton or the silyl substituent from (16) and (20) to give (17) and (21) respectively Possibly (18) yields an ionic intermediate before closure to the dioxetane (19) occurs (see later)



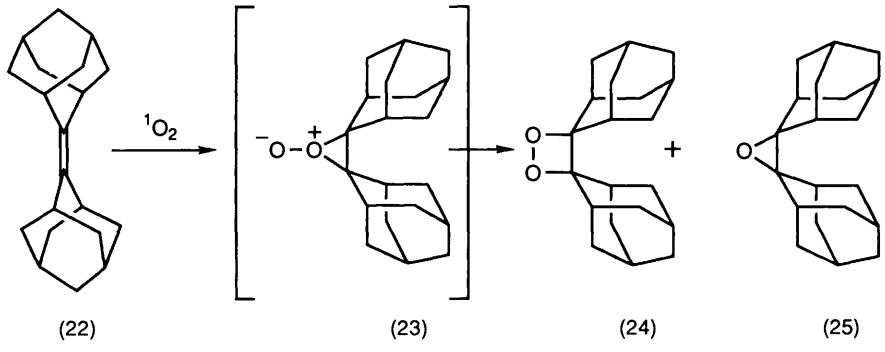
Scheme 4

3 Formation of Dioxetanes and Epoxides

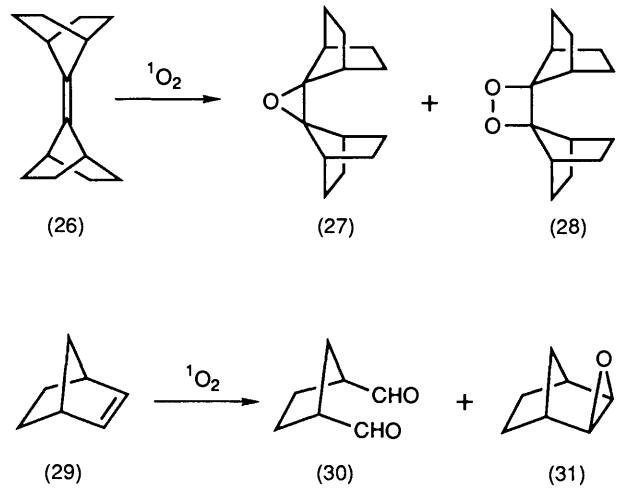
The first intimation that a peroxide or rather a perepoxide might be a primary intermediate was provided by the photo-sensitized oxygenation of adamantylideneadamantane (22) using *meso*-tetraphenylporphin as sensitizer in pinacolone as solvent [11] Two products were reported, the expected dioxetane (24) and the epoxide (25) (Scheme 5) These products were thought to stem from a common precursor, namely the perepoxide (23) which, because of crowding by the two bulky adamantane groups, would have time to be chemically intercepted Solvent or some other reagent could remove the distal oxygen atom from (23) to give the epoxide (25) Normally, (23) would undergo ring expansion to dioxetane (24)

Other olefins, equally devoid of reactive allylic carbon–hydrogen bonds, behaved similarly 7,7′-Bis-norbornylidene (26) and 2-norbornene (29) gave, in addition to the expected products (28) and (30), sizeable amounts of the corresponding epoxides (27) and (31) even in inert solvents such as benzene and acetonitrile (Scheme 6) Significantly, there was no indication of any appreciable oxidation of the solvent,[12 13] which means that the epoxide cannot be taken as proof for the initial formation of perepoxide

These findings prompted a reinvestigation of the photo-oxygenation of adamantylideneadamantane (22) It was found that dioxetane (24) and epoxide (25) were indeed the only products, but their proportion depended crucially on the nature and amount of the sensitizer [14] With *meso*-tetraphenylporphin or methylene blue (MB) dioxetane was essentially the only product formed, but nonetheless traces of epoxide were still produced Sensitizers of the fluoresceine type, in particular rose bengal (RB), brought about a dramatic change by making epoxide the main product Nevertheless, the solvent affected the product ratio slightly Even with *meso*-tetraphenylporphin, the replacement of ethanol by carbon tetrachloride led to more epoxide When (22) was immobilized on florisil which was mixed with sensitizer (RB or MB) absorbed on resin and tumbled together in an oxygen stream under irradiation, dioxetane (14) was consistently produced in 97% yield, but always accompa-



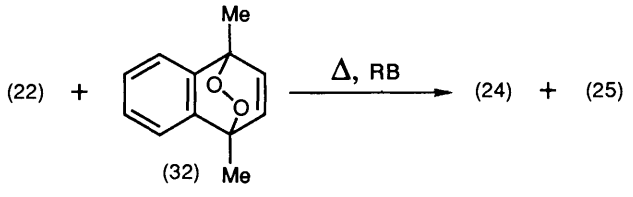
Scheme 5



Scheme 6

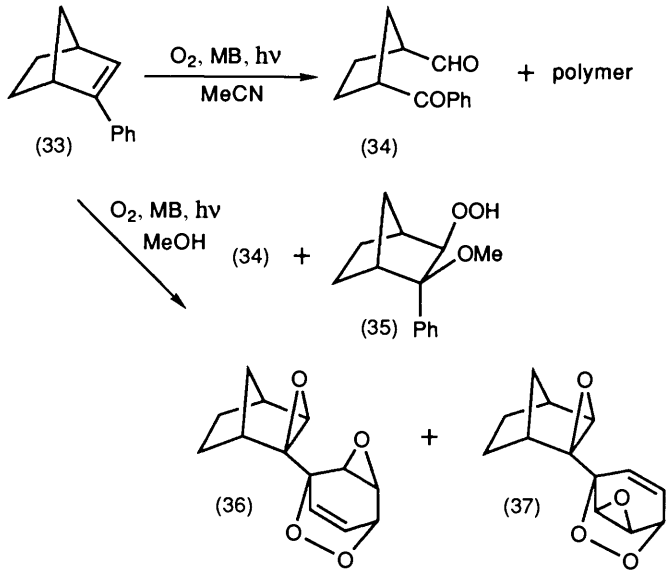
nied by 3—4% of epoxide (25) regardless of the sensitizer used [15] Therefore, traces of (25) probably arise by aerial oxidation of (22)

Subjection of (22) to singlet oxygen generated chemically by thermal decomposition of 1,4-dimethylnaphthalene-*endo*-peroxide (32) in acetone also gave dioxetane (24) and epoxide (25) in 11 1 ratio in a yield of 85% (Scheme 7) [16] When di-t-butyl-*p*-cresol (DTBPC), a radical inhibitor, was added (25) was suppressed completely Repetition of the experiment with (22) and (32) in the presence of RB resulted in substantial amounts of epoxide Moreover, greater amounts of added RB progressively increased the proportion of epoxide to the detriment of dioxetane, making it finally the main product Once again, further addition of DTBPC to the aforementioned mixture reversed the trend and suppressed epoxide formation (Scheme 7)



Scheme 7

These experiments show that RB in solution renders singlet oxygen, whatever its origin, epoxidizing and that a radical is implicated It was further deduced[16] that in solution RB is in equilibrium with its dimer and that the latter donates an electron to a molecule of singlet oxygen to produce superoxide radical anion Evidence for superoxide was obtained by trapping it with 5,5-dimethyl-1-pyrroline 1-oxide which gave a characteristic ESR spectrum [16] Conversion of superoxide into hydrogen peroxide accounts for the epoxidation of (22)

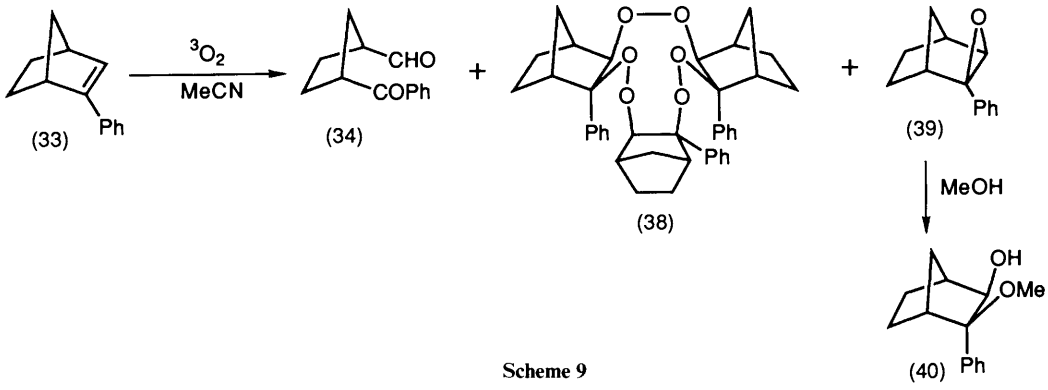


Scheme 8

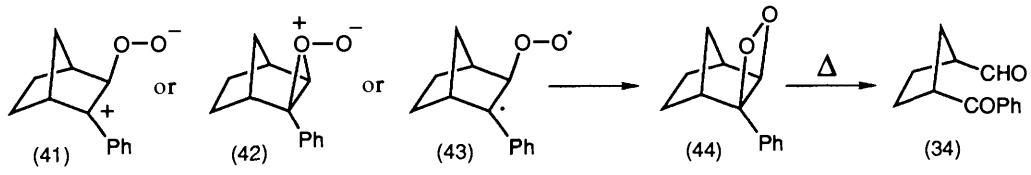
The conclusion is that singlet oxygen reacts with adamantylideneadamantane to give dioxetane in a non-radical process by concerted addition or in two steps through (23) or its operational equivalent [17] However, a second, concurrent oxidation occurs giving the epoxide in the presence of RB and singlet oxygen, but which involves superoxide radical anion The common intermediacy of perepoxide for both pathways is therefore ruled out

Another indication of a peroxy species was provided by the oxygenation of 2-phenylnorbornene (33) [18] Photo-oxygenation of (33) in aprotic solvents (carbon tetrachloride, acetonitrile) using MB as sensitizer gave only 3-formylcyclopentylphenyl ketone (34) accompanied by much polymer (Scheme 8) When the experiment was carried out in methanol (34) was obtained but accompanied by the hydroperoxy ketal (35) and the products of double addition of oxygen (36) and (37) This result was in contrast to that obtained from the reaction of (33) with triplet oxygen (Scheme 9) Auto-oxidation was some 50 times less rapid than photo-oxygenation Only three products were obtained, the *cis*-ketoaldehyde (34), the dioxetane trimer (38), and a small amount of the *exo* epoxide (39) The ratio of epoxide/trimer varied with the nature of the solvent The amount of ketoaldehyde (34) remained more or less constant, but in methanol the epoxide (39) reacted spontaneously to give the *exo*-hydroxy ketal (40) [19] Hydroperoxy ketal (35) was not detected

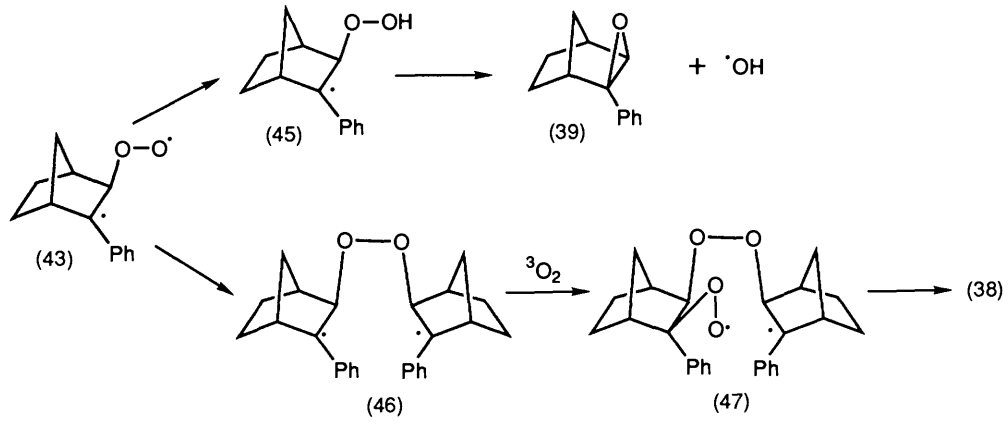
The remarkable difference in product composition and solvent sensitivity for these oxygenations can be attributed to the initial formation of two structurally similar, but chemically different peroxy intermediates Singlet oxygen forms the zwitterionic peroxide (41) or its perepoxide tautomer (42) In contrast, triplet oxygen generates the triplet peroxy species (43) In inert solvents, both the ionic and radical species will close to the same



Scheme 9



Scheme 10



Scheme 11

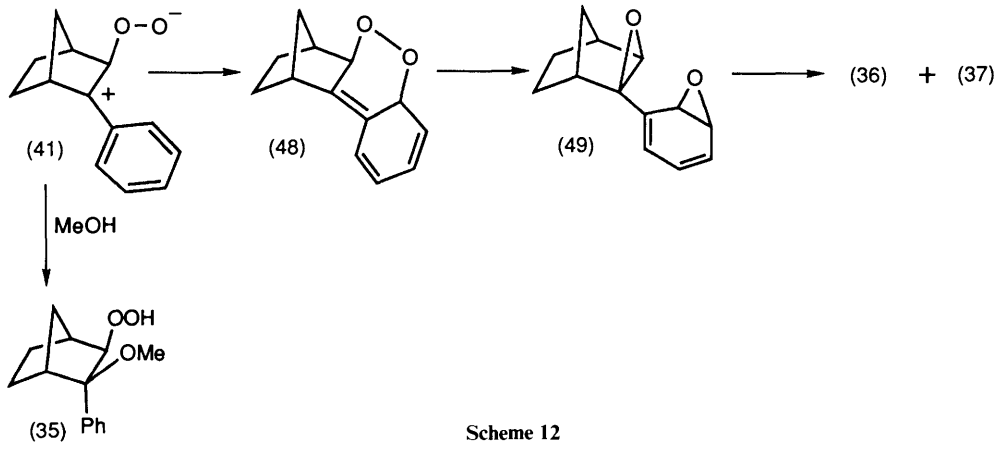
dioxetane (44) and by cleavage to (34) (Scheme 10) However, immediate closure of (43) is forbidden by the spin barrier Consequently, it will endure for quite a while before inversion occurs by encounter with traces of transition metal ions [20] Therefore, (43) has the chance of abstracting a hydrogen atom from the medium to form the hydroperoxy radical (45) which by scission of the oxygen–oxygen bond gives epoxide (39)[21] (Scheme 11) Like other oxygen radicals, (43) has a propensity to add to double bonds [22] The addition of (43) to (33) creates the radical (46) which then captures another molecule of triplet oxygen to form (47) and finally the trimer (38)

In contrast to the radical, the ionic peroxide (41) is much shorter lived It collapses immediately either to the dioxetane (44) and thence to the scission product (34) (Scheme 10) or vinylogously to the *endo*-peroxide (48) (Scheme 12) The latter, by rearrangement to the di-epoxide (49), sets the scene for the Diels–Alder addition of a second molecule of singlet oxygen to give the the two adducts (36) and (37) [23] What is chemically revealing is the hydroperoxy ketal (35), it undoubtedly arises from the zwitterionic peroxide (41) which has captured a molecule of methanol

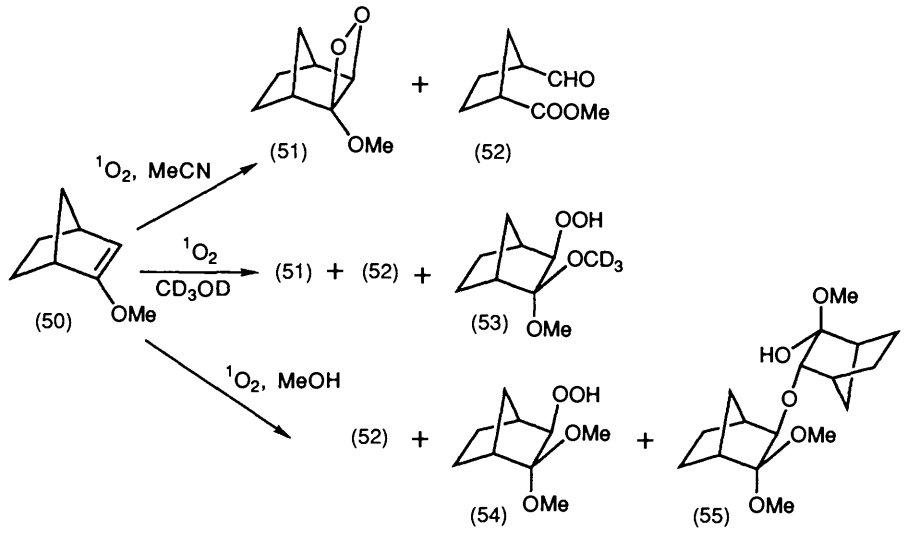
In summary, 2-phenylnorbornene acts as a mechanistic index by permitting a clean chemical distinction between radical and zwitterionic peroxides [24]

Further evidence for the intermediacy of zwitterionic peroxides was secured from the photo-oxygenation of 2-trimethylsiloxy and 2-methoxy derivatives of norbornene Placing an oxygen substituent on the double bond of the norbornene entity raises the energy of its HOMO and therefore accelerates immensely the rate of reaction with singlet oxygen The photo-oxygenation of norbornene[25] was typically slow, requiring several hours for incomplete reaction, while 2-methoxynorbornene (50) was completely oxygenated in under 30 minutes [26] In aprotic solvents, just the *exo* dioxetane (51) (63% yield) and its cleavage product the aldehydic ester (52) (37%) were obtained (Scheme 13) However, in protic solvents (CD_3OD, CH_3OH) the product composition changed drastically In CD_3OD (51) (58%) and (52) (4%) were obtained as before, together with the hydroperoxy ketal (53) (38%) In plain methanol, oxygenation was some five times slower, giving (52) (12%) and the corresponding ketal (54) (39%), but yielded an entirely new condensation product (55) in substantial amounts (49%) In fact, (55) was obtained instantaneously when dioxetane (51) and norbornene (50) were mixed in equimolar amounts in methanol

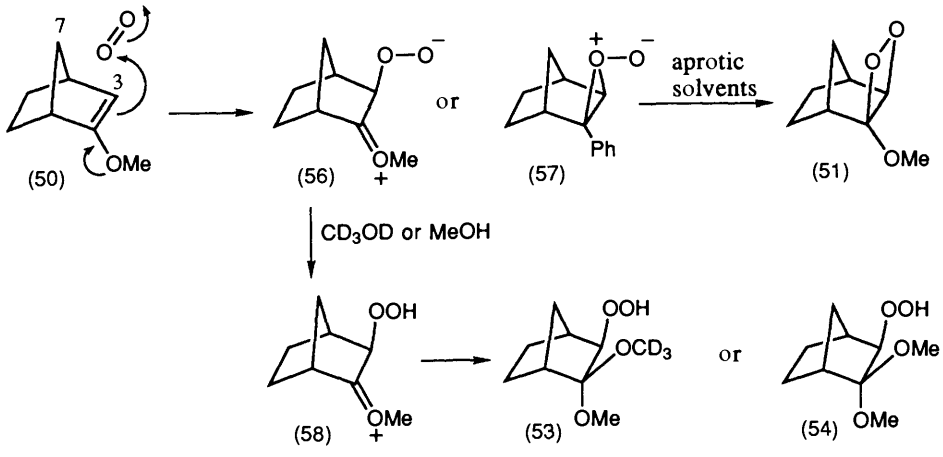
Apart from the novelty of the condensation reaction of dioxetane, the telling result is the formation of the hydroperoxy ketals (53) and (54), especially as dioxetane (51) itself is inert to methanol They constitute evidence for the intermediacy of a zwitterionic peroxide which can be depicted as the peroxide (56) or possibly as the perepoxide (57) (Scheme 14) Just like their phenyl analogue (41), they quickly close to the dioxetane (51) Methanol, when present, protonates them The resulting meth-



Scheme 12



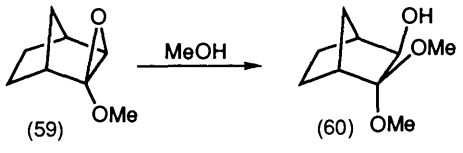
Scheme 13



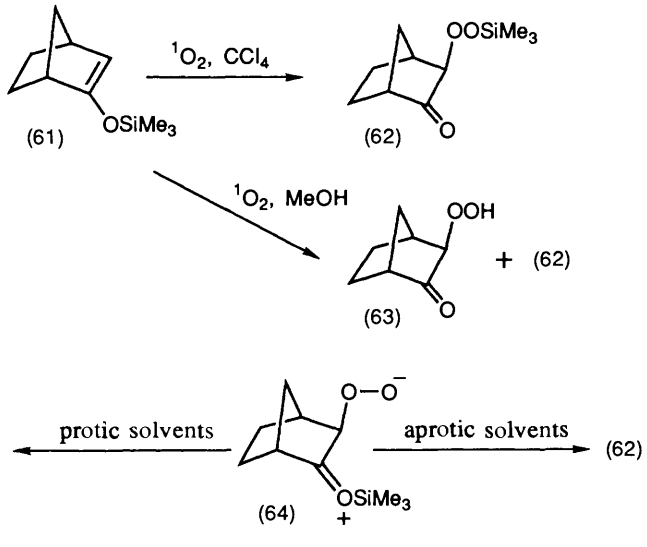
Scheme 14

oxonium cation (58) is subsequently attacked by CD_3OD or methanol giving ketals (53) and (54). Clearly, these side-products are not characteristic of radical reactions, which would be expected to generate molecules like the trimer, *cf.* (38), and the hydroxy ketal (60) arising from 2-methoxynorbornene epoxide (59) (Scheme 15). Significantly, none of these were detected. Moreover, no reaction of (50) occurred with triplet oxygen either in the dark or on irradiation.

A similar result was found for 2-trimethylsiloxynorbornene (61), except that the susceptibility of the silicon substituent to nucleophilic attack provided a mechanistically revealing diversion. Photo-oxygenation in aprotic solvents gave exclusively *exo*-3-trimethylsilaperoxy-2-norbonanone (62) (Scheme 16). In methanol, 3-hydroperoxy-2-norbornanone (63) was obtained as well. This latter product was not an artifact, as (62) was inert to methanol under the conditions of photo-oxygenation. Once again, these products are entirely characteristic of an ionic peroxide, namely (64). In aprotic solvents, silatropic shift occurs by the peroxide function abstracting the trimethylsiloxy group, (64) → (62). In methanol, the chances of this happening are smaller, since protonation neutralizes the peroxide ion, while a molecule of methanol detaches the silicon substituent, (64) → (63).



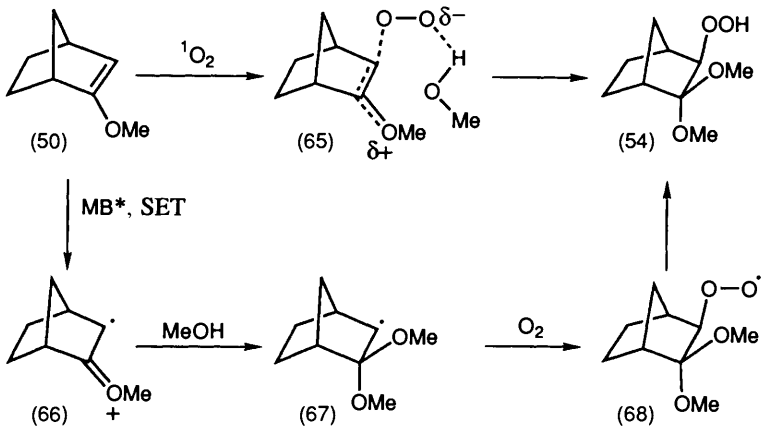
Scheme 15



Scheme 16

4 Formation of 1,2,4-Trioxanes

Despite the plausibility of the aforementioned arguments, alternative mechanisms have been proposed to account for the products incorporating solvent. It has been suggested,[3] on the



Scheme 17

basis of rate and activation parameters determined for 2-methoxynorbornene (50) in different solvents, that singlet oxygen reacts rapidly and reversibly to give an exciplex (65) which benefits from H-bonding when methanol is used as solvent Collapse of (65) then affords the ketal (54) (Scheme 17) Another suggestion[27] is that (50) transfers a single electron (SET) to an excited molecule of sensitizer, such as MB, to give the radical cation (66), which then undergoes successive addition of methanol and triplet oxygen to form (67) and (68) and finally product (54) by acquisition of a hydrogen atom Structurally, (65) resembles the partially formed peroxide (56), so a clear distinction between them is not possible However, the radical species (66) and (67) are chemically different from the zwitterionic peroxide (56) and could be differentiated by the correct choice of reagent Aldehydes are ideal for this purpose as they should bring out nucleophilic or radical character Accordingly, the RB-sensitized photo-oxygenation of (50) was conducted in acetaldehyde as solvent[28] (Scheme 18) Besides the oxidative cleavage product (52) (31% yield), a pair of epimeric *cis*-fused *exo*-1,2,4-trioxanes (69) was isolated in a ratio of 2 3 in 13% yield This result provides proof for a non-radical intermediate By choosing an anionic dye, RB instead of MB, electron-donation by (50) to the dye to give (66) is unlikely In any event, radicals were not involved in the photo-oxygenation Radicals such as (66), (67), and (68) would have produced the stable acetyl radical by hydrogen atom abstraction from acetaldehyde rather than add to the carbonyl function [29] Consequently, the best candidate as intermediate is the peroxide (56) which annihilates its charges by combining with acetaldehyde in the *syn* or *anti* orientation with respect to the methoxy substituent (Scheme 18) The new oxygenated ring in (69) is created with *cis*-fusion to the pre-existing ring and with *exo* configuration since singlet oxygen had added *exo* to the double bond of (50) in the first place

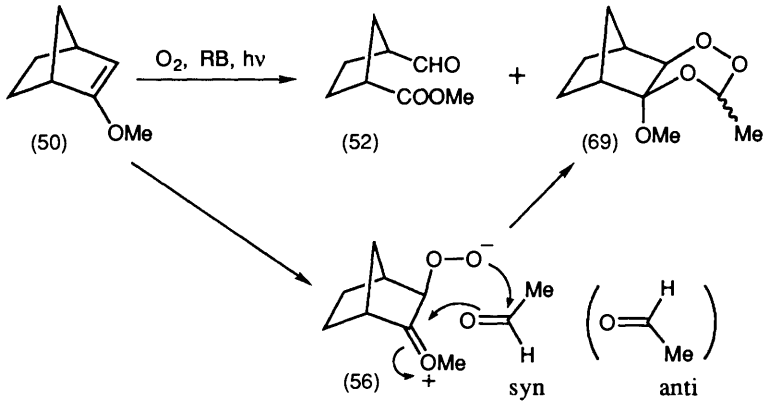
The condensation of an aldehyde, singlet oxygen and an electron-rich olefin, proved to be general Aldehydes of all types were captured, but ketones were unreactive Enol ethers such as 2-(methoxymethylidene)adamantane (70) and the dihydropyran (73)[30] gave the corresponding 1,2,4-trioxanes (71) and (74) (Scheme 19) 1,3-Dimethylindole (75) behaved similarly[31] and produced the *cis*-fused trioxanes (76) (Scheme 19)

Further proof for a zwitterionic peroxide was obtained by studying the effect of solvent and temperature on the production of (71) from (70) [32] Low solvent polarity (*e g* toluene) and temperatures (−78 °C) favoured the formation of (71) (~80%) Conversely, highly polar solvents (*e g* MeOH) and warm conditions (~10 °C) benefited the production of 1,2-dioxetane (72) at the expense of (71) (Scheme 19)

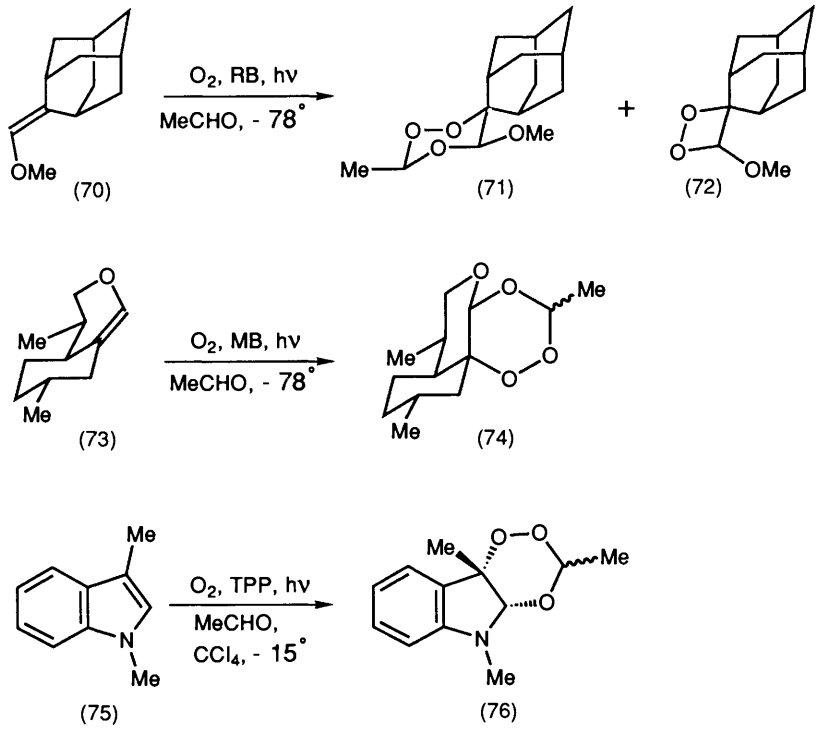
An intriguing aspect of the condensation reaction is its mechanistic resemblance to the recombination step of the ozonolysis of olefins The primary ozonide (77) invariably undergoes cleavage to carbonyl oxide and carbonyl fragments (78) (Scheme 20) However, closure to the secondary ozonide (80), after appropriate reorientation (78) → (79), only occurs with facility if the carbonyl fragment is an aldehyde [33] Thus, zwitterionic peroxides, just like their lower homologues, carbonyl oxides, are inert towards ketones but add readily to the more electrophilic aldehydes

5 Conclusion

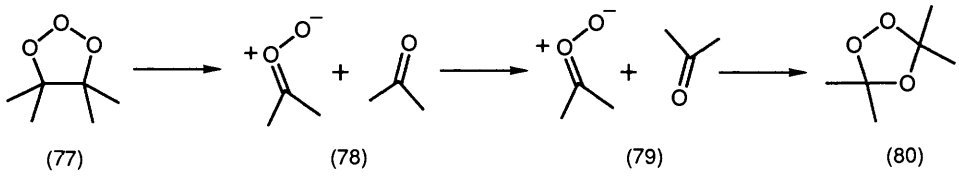
The results presented in this account demonstrate that the dye-sensitized photo-oxygenation of trisubstituted olefins of the norbornene type passes through a zwitterionic peroxide, which is sufficiently long-lived to be trapped by alcohols and aldehydes Furthermore, it has been shown that peroxy diradicals behave as discrete species,[24] at least in the compounds studied, and display a markedly different chemistry to that of the ionic peroxides



Scheme 18



Scheme 19



Scheme 20

The 1,2,4-trioxanes which revealed the mechanisms of photo-oxygenation are important entities in their own right. Unlike their lower homologues, the 1,2,4-trioxolanes or secondary ozonides which constitute an important chapter in organic chemistry, they are relatively unknown. However, the discovery in 1979 that artemisinin (81), a naturally occurring trioxane, is a potent anti-malarial remedy[34] has awoken interest in this class of oxygen heterocycles (Scheme 21). Consequently, the mechanism of the trapping experiment has served as the basis for the development of new methods for preparing a wide variety of 1,2,4-trioxanes.[35] Recent studies show that they can be used as protecting groups[36] and as intermediates in synthesis.[37]

It is not surprising that trioxanes arising from (73) such as (82), which embody part of the structure of (81), like (81) and its derivatives, also retain commensurate anti-malarial activity.[38] More importantly, several easily accessible *cis*-fused bicyclic trioxanes, exemplified by (83), which do *not* resemble the architecture of (81), display high anti-malarial activity just like that of (81) and its derivatives.[39] Additionally, *Toxoplasma gondii*, a parasite related to the *Plasmodium* species, is also susceptible to trioxanes of the same type.[40]

In conclusion, what started out as an exercise in mechanistic chemistry has led to the development of a new class of oxygen heterocycles displaying much potential as chemical intermediates and anti-parasitic drugs.

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6 References

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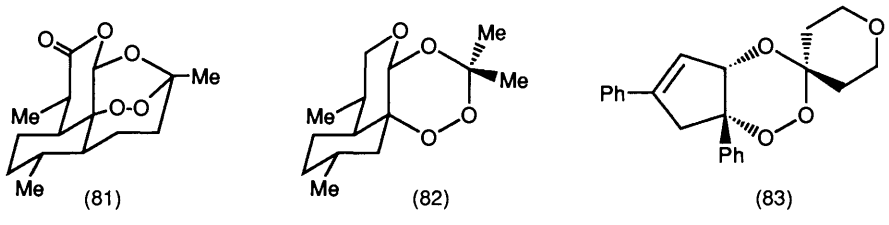

Scheme 21

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