The Schenck rearrangement of allylic hydroperoxides

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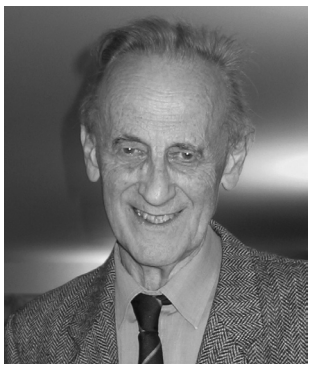


Alwyn Davies did his BSc at University College London and his PhD under the supervision of Sir Christopher Ingold. After four years at Battersea Polytechnic collaborating with Joseph Kenyon, he returned to UCL. His research has involved the interconnected fields of organic peroxides, organometallic chemistry, free radical mechanisms and ESR spectroscopy. He has published books on organic peroxides, organotin chemistry, and ESR spectra. He has been Editor-in-Chief of *Journal of Chemical Research* since it separated from the British, German and French chemical societies in 1999.

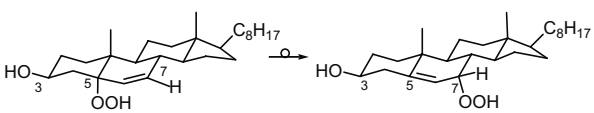
It is 50 years since Schenck's discovery of the ubiquitous rearrangement of allylic hydroperoxides, and its unique homolytic mechanism has now been clarified by a combination of experimental and computational methods. The recognised examples of the reaction are surveyed and the way in which the present mechanistic picture has emerged is reviewed. A brief account is given of the closely related Smith epimerisation of allylic hydroperoxides.

Keywords: allyl hydroperoxides, allylperoxyl radicals, autoxidation, mechanism, Schenck rearrangement, Smith rearrangement

1 Introduction

Allyl hydroperoxides are the principal products when unsaturated compounds undergo autoxidation. They are involved in processes as diverse as the drying of a paint, the development of rancidity in a fat, the disruption of a lipid membrane, or the biosynthesis of a prostaglandin, and a great deal of attention has been given to their synthesis, structure and properties.[1,2]

In 1958, Georg Schenck showed that the 5α-hydroperoxide (**1**) derived from the reaction of cholesterol with singlet dioxygen, underwent, in 3 days in chloroform solution, a shift of the OOH group to the 7α-position with allylic isomerisation [Equation (1)],[3,4] and this type of process has become known the Schenck rearrangement.



(1)

1 **2**

In 1973, Smith identified a further type of rearrangement of allyl hydroperoxides [Equation (2)].[5] In ethyl acetate at 40 °C for 48 h, the 7α–hydroperoxide (**2**) underwent 20–30% of epimerisation to the 7β–hydroperoxide [**3**; Equation (2)]. Relatively few examples of this reaction have been firmly established, but the Schenck and the Smith reactions are closely related both in their structural features and their mechanisms.

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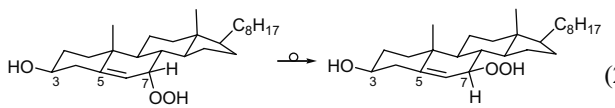


(2)

2 **3**

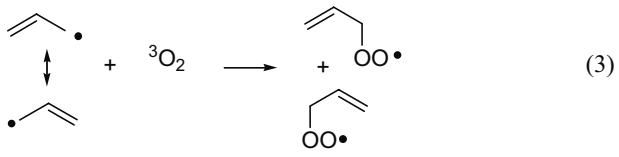
Half a century after they were discovered, the mechanisms of these deceptively simple reactions are now becoming clear as a result of a combination of experimental and computational methods, and they are apparently mechanistically unique amongst known rearrangements. This review surveys the known examples of the reactions and traces the evidence by which the mechanisms have been elucidated.

2 Preparation of allylic hydroperoxides

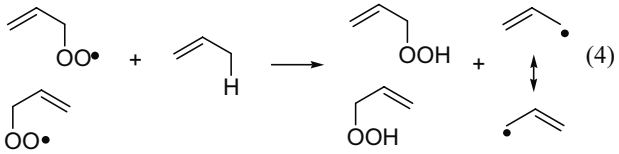
Allyl hydroperoxides can be prepared by reaction of an alkene with triplet dioxygen (autoxidation) or with singlet dioxygen (an ene reaction), or by nucleophilic substitution of an allylic derivative such as a halide, with the HOO^- anion.

The autoxidation occurs through a radical chain reaction in which the resonance-stabilised allyl radical and the allylperoxyl radical are the chain carriers as illustrated in Equations (3) and (4). If hydrogen can be abstracted from one α CH, CH_2, or CH_3 group, two hydroperoxides can be formed [Equation (4)], or, if from two α or α' groups, then four hydroperoxides (Scheme 1) can be formed. The reaction may be self-initiated, or induced with some other source of radicals.[1]

In the reaction of an alkene with singlet dioxygen [an ene reaction, Equation (5)] the $^1O_2$ is usually generated by reaction of $^3O_2$ with a photoexcited sensitiser. There is good

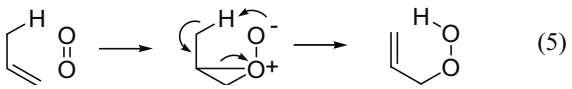


(3)



(4)

evidence, particularly from hydrogen isotope effects, that the singlet oxygen forms an initial adduct at the olefinic double bond, followed by intramolecular transfer within the complex, which in Equation (5) is represented as a perepoxide. It was by this type of reaction that Schenck prepared the 6,7-unsaturated 5-hydroperoxide (**1**) from cholesterol with a 5,6-double bond and it is, somewhat confusingly, sometimes referred to as the Schenck reaction.



(5)

In principle then, autoxidation of a medial alkene can give a maximum of four positional isomeric hydroperoxides (the positions labelled 1, 2, 3 and 4 in Scheme 1), and the ene reaction can give a maximum of two (positions labelled 2 and 3), though it is frequently regiospecific. On this basis, if the 1- or 4-hydroperoxides are formed during a singlet dioxygenation, they must result from a subsequent Schenck isomerisation. This assumption is behind some of the entries in Table 1.

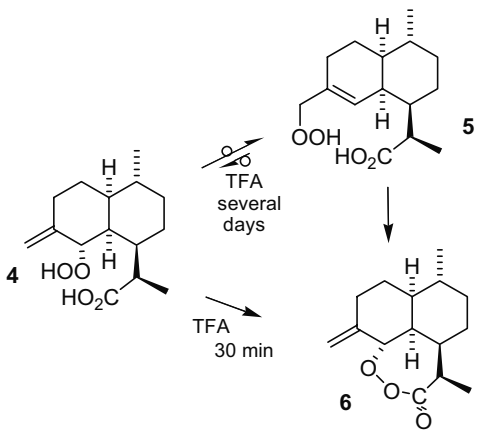
The third synthetic method, which involves nucleophilic HOO^-, is preparatively important,[1] but is not directly relevant to the Schenck rearrangement and will not concern us here.

3 Occurrence of the Schenck rearrangement

Examples of the Schenck rearrangement are shown in Table 1 which attempts, but doubtless fails, to be comprehensive. Reactions and reaction kinetics are at room temperature unless otherwise stated. The first order rate constants are for self-initiated rearrangements. Most of the starting hydroperoxides **A** in Table 1 were prepared by the singlet dioxygen ene reaction [Equation (5)].

Some of the reactions occur to completion (*e.g.* the cyclic hydroperoxides of entries 19, 23 and 32), and sometimes so rapidly that the primary product of singlet oxygenation has not been isolated, but only the product of rearrangement (*e.g.* entries 12, 13, 40, 49 and 53). When the two isomers are similar in energy, *e.g.* when derived from oleic acid (entries 28–31), an approximately equimolar mixture is formed at equilibrium. When the two isomers are identical, as they are, for example in cyclohex-2-enyl hydroperoxide, it would be possible to observe the rearrangement by use of isotopic labelling, but this has not been reported.

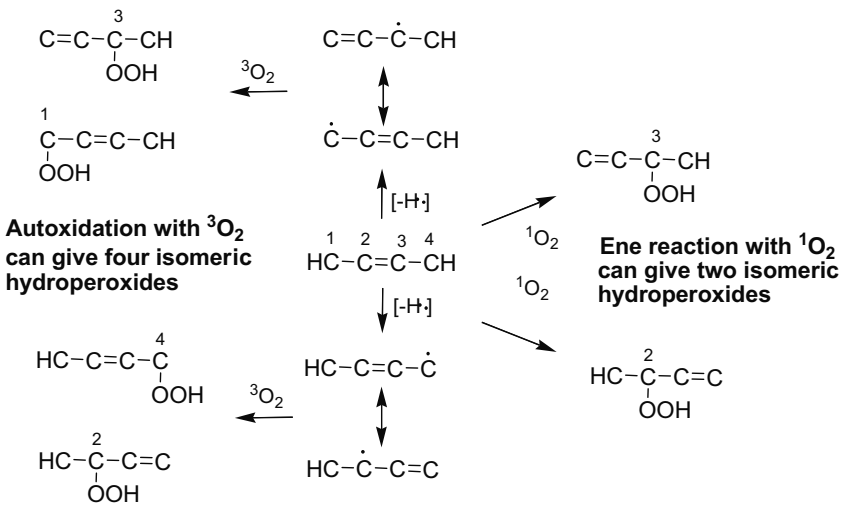
The compound **4** rearranges, apparently completely, to **5** (Table 1, entry 22). In the presence of trifluoroacetic acid, **4** is dehydrated to the *endo* acyl peroxide **6** in 30 minutes, but under the same conditions the Schenck isomer **5** gives the same product during several days, presumably through slow equilibration with a trace of **4**.[17]



(6)

The reactions are accelerated by radical initiators such as AIBN or TBHN, or by Cu^{II} in which case the hydroperoxide product may be dehydrated to a carbonyl compound. Phenols inhibit the reaction and a trace of a phenol such as BHT may be added to a sample, for example during or after photoxidation, to stabilise it against rearrangement. Yields may be increased by carrying out the reaction in the presence of a large excess of *tert*-butyl hydroperoxide.[31]

The rearrangement always occurs suprafacially [*e.g.* Equation (1)], any antarafacial product (*e.g.* entries 50–52) being assumed to arise through subsequent Smith



Scheme 1 Positionally isomeric hydroperoxides which can be formed by reaction of an alkene with singlet or triplet dioxygen.

Table 1 Examples of the Schenck rearrangement

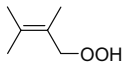
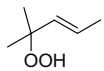
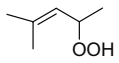
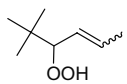
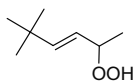
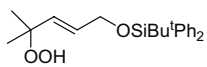
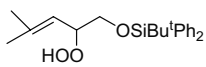
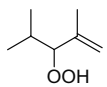
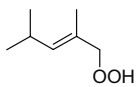
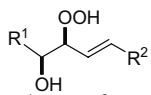
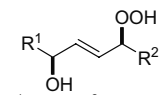
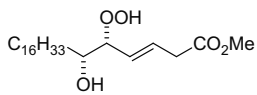
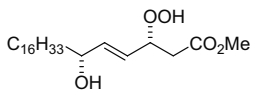
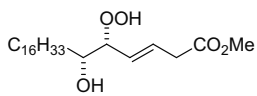
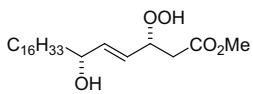
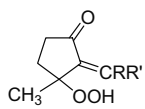
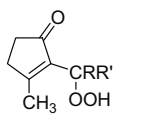
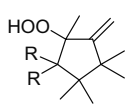
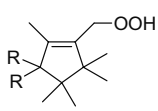
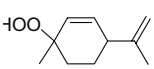
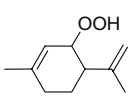
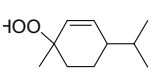
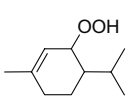
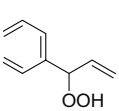
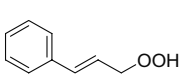
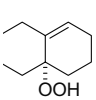
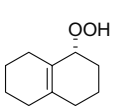
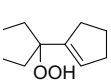
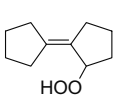
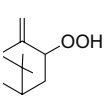
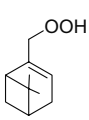
Entry	Allylic isomer **A**	Allylic isomer **B**	Comments	Ref.
1			Rearrangement (15%) in $CDCl_3$ occurs at 80 °C in 3 h in the presence of AIBN.	6
2			At 40 °C in non-polar solvents, pure **A** or **B** rearrange to give an approximately equal mixture of **A** and **B**.	7
3			During a few days a 3.3:1 mixture of *trans*-**A** and *cis*-**A** gave a 1.7:1.0:5.3 mixture of *trans*-**A**, *cis*-**A** and **B**. For *trans*-**A**, k_1 ($CHCl_3$) = *ca* 1.5×10^{-6} s^{-1}.	8
4			At equilibrium, starting from either isomer, the relative concentration of **A** and **B** is 55:45.	9
5			In hexane, pure **A** rearranges to give an equilibrium mixture of *ca* 80% **A** and 20% **B**.	10
6	 R^1 = Bu. R^2 = C_5H_{11}	 R^1 = Bu. R^2 = C_5H_{11}	Rearrangement occurs at 55–68 °C in the presence of 20 mol% TBHN as initiator, giving **A** and **B** in almost equal amounts. The yield is increased by the presence of 10 equiv. of Bu^tOOH.	11
7			Equilibration in the presence of TBHN and Bu^tOOH gave a 44:56 mixture of **A** and **B**.	11
8			Rearranges at 60–70 °C in C_6H_6 or MeCN in the presence of TBHN or AIBN in 16–22 h to give *ca* 50:50 A:B.	11
9	 CRR' = CH_2 or CD_2	 CRR' = CH_2 or CD_2	Rearrangement occurs during 5 days in solution at room temperature and is inhibited by 2,6-di-*tert*-butylphenol.	12
10	CRR' = CHMe	CRR' = CHMe	Rearrangement occurs during 5 days in solution at room temperature and is Inhibited by 2,6-di-*tert*-butylphenol.	12
11	 R = Me	 R = Me	In $CDCl_3$, rearrangement is complete in 2 days. Methylhydroquinone completely suppresses the rearrangement. When R = H, there is very little tendency to rearrange.	13
13	 From limonene		Anomalous product from the photooxidation of limonene.	3
12	 From carvomenthene		Anomalous product from the photooxidation of carvomenthene.	3
14			Rearrangement involved in the autoxidation of allylbenzene or thermal decomposition of $PhCH{=}CHCH_2CO_3Bu^t$.	14
15			In CCl_4 at 40 °C, 80% rearrangement occurs in 141 h.	6
16			In $CDCl_3$ at room temperature, rearrangement is 25% complete after 30 h and 40% complete after 192 h.	6
17	 From α-pinene	 From β-pinene	In hexane, pure **A** or **B** rearranges to give an equilibrium mixture of *ca* 26% **A** and 74% **B**.	10

Table 1 *Continued*

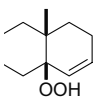
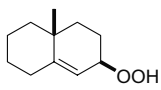
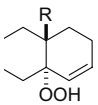
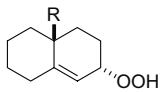
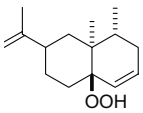
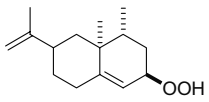
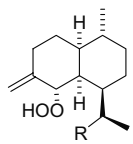
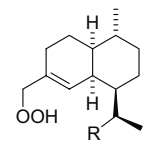
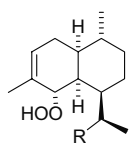
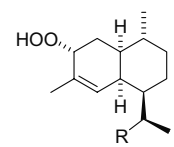
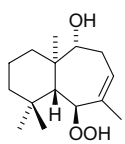
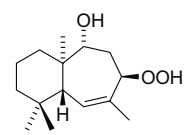
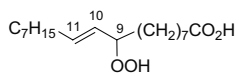
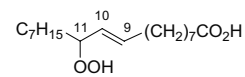
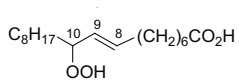
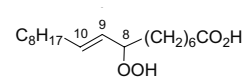
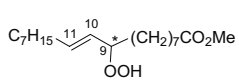
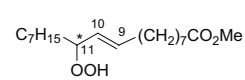
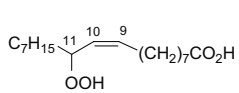
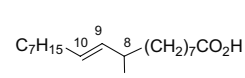
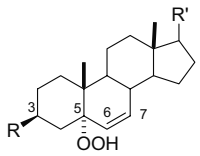
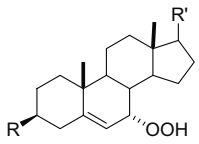
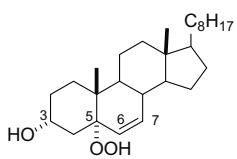
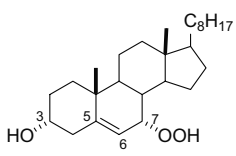
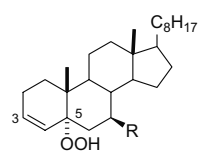
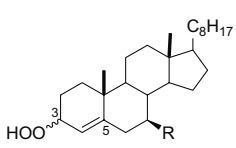
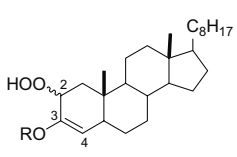
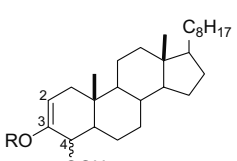
Entry	Allylic isomer **A**	Allylic isomer **B**	Comments	Ref.
18			In $CDCl_3$, the rearrangement **A** → **B** was 10% complete in 259 h.	15
19	 R = CH_3	 R = CH_3	In $CDCl_3$, the rearrangement **A** → **B** was complete within 24 h.	15
20	R = C_2H_5	R = C_2H_5	In $CDCl_3$, the rearrangement **A** → **B** was half complete in 45 h and 80% complete in 72 h.	15
21	 From valencene		After 123 h in MeOH/C_6H_6, a mixture of *ca* 68% **A** and 32% **B** isomerised to 28% **A** and 72% **B**.	16
22	 R = CO_2H From dihydroartemisinic acid	 R = CO_2H	Rearrangement is inhibited by DBHT In $CDCl_3$, the reaction is first order. In $CDCl_3$, rearrangement is complete in 4 weeks. $k_1 = 1.8 \times 10^{-6}$ s^{-1}.	17
23	R = CO_2Me	R = CO_2Me	k_1 ($CDCl_3$) = 1.3×10^{-6} s^{-1}	17
24	R = CH_2OH	R = CH_2OH	k_1 ($CDCl_3$) = 1.4×10^{-6} s^{-1}	17
25	R = CH_3	R = CH_3	k_1 ($CDCl_3$) = 1.9×10^{-6} s^{-1}; complete rearrangement in 3 weeks.	17
26			In $CDCl_3$, the reaction is first order. Rate constants are below.	17
27	R = CO_2H From dihydroartemisinic acid	R = CO_2H	k_1 ($CDCl_3$) = 2.7×10^{-6} s^{-1}	17
28	R = CO_2Me	R = CO_2Me	k_1 ($CDCl_3$) = 2.8×10^{-6} s^{-1}	17
29	R = CH_2OH	R = CH_2OH	k_1 ($CDCl_3$) = 5.0×10^{-6} s^{-1}	17
30	R = CH_3	R = CH_3	k_1 ($CDCl_3$) = 3.9×10^{-6} s^{-1}	17
31	 From allohimachalol		Rearrangement in $CDCl_3$ is complete in 2 days at room temperature. $k_1 = 1.5 \times 10^{-5}$ s^{-1}. Rearrangement is complete in 2 days.	18
32	 From oleic acid		After 5 h at 40 °C in hexane, with TBHN as initiator, the isomers **A** and **B** are present in approximately equal amounts.	19
33			After 5 h at 40 °C in hexane, with TBHN as initiator, the isomers **A** and **B** are present in approximately equal amounts.	19
34	 From methyl oleate		Rearrangement of optically pure 9(*R*)- or 9(*S*)-**A** in hexane at 40 °C with TBHN as initiator, gives essentially complete retention of configuration in **A** and the opposite configuration in **B**.	20
35			At 40 °C in hexane, with TBHN as initiator, the (*Z*)-isomer of **A** is also formed.	21

Table 1 *Continued*

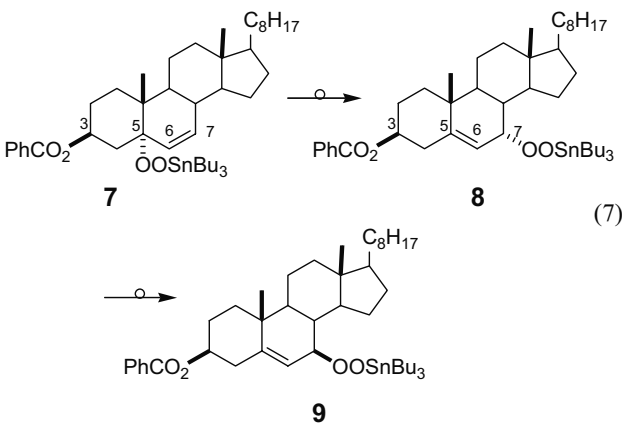
Entry	Allylic isomer **A**	Allylic isomer **B**	Comments	Ref.
36	 R = OH, R' = C_8H_{17} From cholesterol and $^1O_2$	 R = OH, R' = C_8H_{17}	In EtOAc at 40 °C, the half life **A** → **B** is 48 h; at room temperature, reaction is complete in 3 days. k_1 ($CDCl_3$) 2.8×10^{-5} s^{-1} at 293 K.	4 22 5 23 24 25
37	R = OH, R ' = COMe	R = OH, R ' = COMe	In $CHCl_3$, rearranges in 35 h in the dark.	3
38	R = OCOMe, R' = =O	R = OCOMe, R' = =O	Rearranges in $CHCl_3$.	4
39	R = H, R' = C_8H_{17}	R = H, R' = C_8H_{17}	Rearrangement occurs in 24 h in $CHCl_3$.	26
40	R = OCH_3, R' = C_8H_{17}	R = OCH_3, R' = C_8H_{17}	Reaction of the cholesterol derivative in MeCN with $^1O_2$ gives 43% **A** and 57% **B**.	24, 25
41	R = $OSiMe_3$, R' = C_8H_{17}	R = $OSiMe_3$, R' = C_8H_{17}	Reaction of the cholesterol derivative in $CHCl_3$ gives some **A** but mainly **B**.	24
42	R = OCOMe, R' = C_8H_{17}	R = OCOMe, R' = C_8H_{17}	Reaction of cholesteryl acetate in MeCN with $^1O_2$ gives 70% **A** and 30% **B**.	24, 25
43	R = OCOPh, R' = C_8H_{17}	R = OCOPh, R' = C_8H_{17}	In $CDCl_3$, rearrangement is complete in 72 h.	27
44	R = $=CH_2$, R' = C_8H_{17}	R = $=CH_2$, R' = C_8H_{17}	Rapid rearrangement in $CDCl_3$ to give 30% of the 7α hydroperoxide is accompanied by 70% addition to the methylene group to give an epidioxide.	28
45	R = OH, R ' = $C_{10}H_{19}$ From stigmasterol	R = OH, R ' = $C_{10}H_{19}$	Singlet oxygenation of the 5-ene in pyridine gave a mixture of the 5α-OOH-6-ene and the 7α-OOH-5-ene.	29
46	R = OCOMe, R ' = $C_{10}H_{19}$	R = OCOMe, R ' = $C_{10}H_{19}$	Singlet oxygenation of the 5-ene in pyridine gave a mixture of the 5α-OOH-6-ene and the 7α-OOH-5-ene.	29
47	R = Cl, R ' = $C_{10}H_{19}$	R = Cl, R ' = $C_{10}H_{19}$	Singlet oxygenation of the 5-ene gave only the 7α-OOH-5-ene.	29
48	R = F, R ' = $C_{10}H_{19}$	R = F, R ' = $C_{10}H_{19}$	Singlet oxygenation of the 5-ene gave only the 7α-OOH-5-ene.	29
49	 From epicholesterol		Singlet oxygenation of (Δ5) epicholesterol gave only the 7α-OOH and not the 5α-OOH which is the reactant illustrated.	6
50	 R = H From cholest-4-ene		Singlet oxygenation of (Δ4) cholestene, with a 4,5-double bond, gave 29% of the 5-OOH **A** and 37% of the 3α- and 7.5% of the 3β-OOH. After 48 h in $CHCl_3$, Only the 3α- and 3β-OOH were present in the ratio of 8:1.	26
51	R = OH From pseudocholesterol	R = OH	In MeCN, singlet dioxygenation of pseudocholesterol gave a mixture of the 5α, 3α and 3β hydroperoxides.	25
52	R = OMe	R = OMe	In MeCN, singlet dioxygenation of the methyl ether of pseudocholesterol gave a mixture of the 5α, 3α and 3β hydroperoxides.	25
53	 R = MeCO or PhCO		Assumed reaction to account for the products of singlet dioxygenation of 3-acetoxy- or 3-benzoyloxy-cholest-2-ene in pyridine for 40 h.	30

AIBN = azoisobutyronitrile, $(NC)Me_2CN{=}NCMe_2(CN)$. TBHN = *tert*-butyl hyponitrite, $Bu^tON{=}NOBu^t$. DBHT = 2,6-di-*tert*-butyl-4-methylphenyl (butylated hydroxytoluene).

rearrangement of the Schenck product. The rates vary widely; thus, if it is accepted that singlet oxygenation of alkenes always occurs with allylic isomerisation [Equation (5)] the 7α-5-ene products of entries 50–52 must imply a rapid Schenck rearrangement in contrast to the slower reaction of cholesterol itself. The *cis*-octahydronaphthalene isomer of entry 19 is unchanged under the conditions where the *trans* isomer undergoes 80% rearrangement. Kinetic measurements have been carried out by monitoring the ^{1}H NMR spectra or, when appropriate, the optical rotation. Under appropriate conditions (dilute solutions in apolar solvents, usually $CDCl_3$, at room temperature) the reactions are first order. Rate coefficients are given in Table 1 and cover the range 1.5×10^{-5} to 5.0×10^{-6} s^{-1}, corresponding to half-lives of 4.6×10^4 s (13 h) and 1.4×10^5 s (38 h) respectively.

Dussault has used the rearrangements in entries 6–8 as key steps in the synthesis of the alkoxy-1,2-dioxines chondrillin and plakorin which are found in some marine sponges and have potentially useful biological properties. The 2-hydroperoxy-3-alkenols were prepared by reaction of $^1O_2$ with allyl alcohols, then the Schenck rearrangement was initiated with AIBN or TBHN in the presence of *tert*-butyl hydroperoxide.[11,31]

Metals often behave as hydrogen equivalents,[32] and it might be expected that allylic stannyl peroxides would undergo Schenck- and Smith-types of rearrangements similar to those of hydroperoxides. This is indeed observed [Equation (7)[27,33]] and the 5α-stannylperoxy derivative (**7**) of entry 44, in $CDCl_3$, rearranges to the 7α-stannylperoxy isomer (**8**, 33–40%) and the 7β-stannylperoxy isomer (**9**, 10%) during a few days at room temperature. No reaction occurred in the presence of 5 mol% of 2,6-di-*tert*-butylphenol,[27] confirming the radical chain nature of the mechanism. The 5α stannylperoxide reacts with trityl chloride to give only the 7α and 7β tritylperoxides, but the homolytic nature of this rearrangement has been questioned.[33]



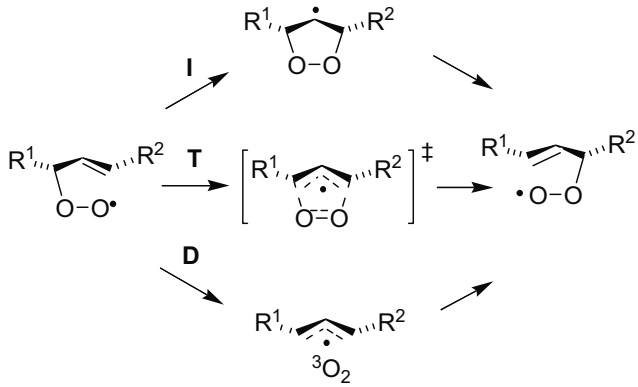
(7)

Alkylboranes readily undergo autoxidation to give alkylperoxyboranes and allylboranes would be expected to give allylperoxyboranes, which might be susceptible to the Schenck rearrangement, but this system has not been explored.

4 The mechanism of the Schenck rearrangement

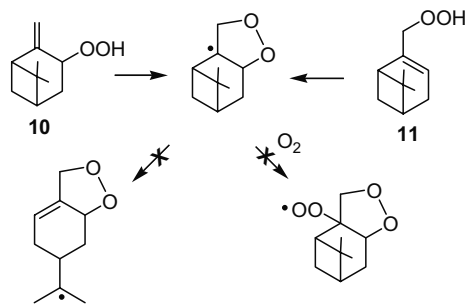
The effect of radical initiators and inhibitors clearly identifies Schenck rearrangements as radical chain reactions involving the allylperoxyl radicals. Three main mechanisms for the [3,2] shift have been considered as shown in Scheme 2.

Mechanism **I** assumes ring-closure to give a carbon-centred radical intermediate. In route **T**, the cyclised radical is a transition state, and route **D** assumes dissociation into a free allyl radical and triplet dioxygen.

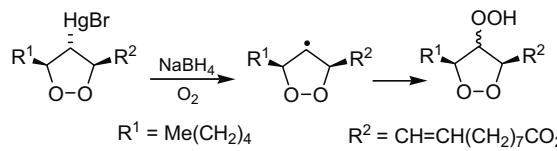


Scheme 2 Possible mechanisms for the Schenck rearrangement, involving an intermediate (**I**), transition state (**T**), or dissociated components (**D**).

Route **I**, which initially seemed to be the most likely, was readily ruled out, because, by this route, the isomerisation of pinocarveyl (**10**) or myrtanyl (**11**) hydroperoxides (Table 1, entry 18) should lead to ring opening by β-scission [Equation (8)]. This was not observed,[10] and neither could the carbon-centred radical be trapped with dioxygen,[10] whereas Porter confirmed that an authentic dioxacyclopentyl radical could be trapped [Equation (9)].[34]

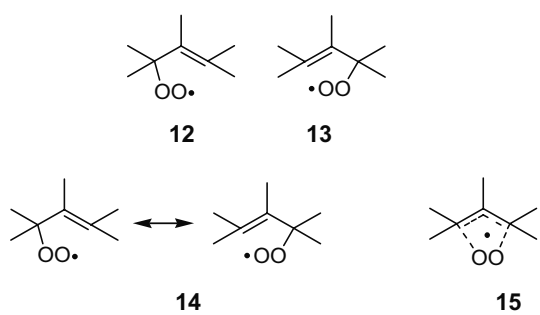


(8)



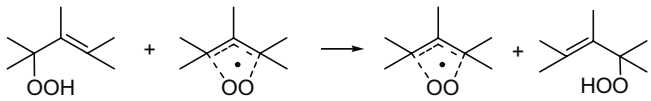
(9)

Brill[10] suggested that there were not two separate allylperoxyl radicals (**12** and **13**) corresponding to the two hydroperoxides, but only one, which could be represented as a resonance hybrid (**14**) of the two structures, or as a cyclic structure (**15**) in which 4 electrons are involved in the partial bonds shown.[10]



Isomerisation would then be brought about by the process shown in Equation (10).

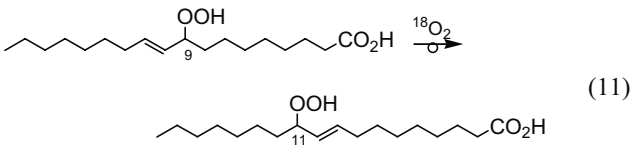
This was ruled out by the demonstration that photolysis of the 5α- and 7α-hydroperoxides **1** and **2** [Equation (1) and



(10)

Table 1, entry 36] derived from cholesterol show the ESR spectra of two different peroxyl radicals, a singlet from the former, and a doublet from the latter with *a*(H7) 2.73 G, which is typical for a secondary alkylperoxyl radical.[24]

Porter showed by ^{18}O labelling that the two hydroperoxides derived from autoxidation of oleic acid underwent the Schenck rearrangement without incorporating dioxygen from the atmosphere [*e.g.* Equation (11)],[19] and Beckwith and Davies showed the same for the cholesteryl hydroperoxide (**1** → **2**; Table 1, entry 36)[24] and for the hydroperoxide from valencene (Table 1, entry 21).[16]



(11)

It appeared then that free triplet dioxygen was not generated during the reaction; the dissociative process (route **D**) seemed to be ruled out in favour of the cyclic transition state (route **T**); this was supported by the demonstration that optically pure oleic hydroperoxides rearranged stereoselectively.[35]

However, the isomerisation of a dienyl hydroperoxide derived from methyl linoleate hydroperoxide[36,37,38] had been shown to involve exchange with atmospheric dioxygen [Equation (12)], and theoretical investigations[39] failed to find a low energy cyclic transition state, suggesting that a dissociative mechanism might yet be possible, where the key would be the reversibility of the reaction of an allyl radical with dioxygen [Equation (13)].

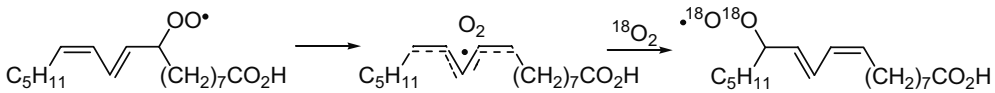
Porter therefore investigated the rearrangement of hydroperoxides derived from methyl oleate [*e.g.* Equation (11)] using the tools of stereochemistry, oxygen-isotopic labelling and solvent viscosity.[21,40] In hexane, a small amount of the oxygen atmosphere was incorporated into the product, with a small loss of enantiomeric purity and as the solvent was changed to the more viscous dodecane and then octadecane, these figures decreased. The conclusion is that the rearrangement involves a caged allyl radical – dioxygen pair (route **D**) in which a small escape from the cage can occur in the less viscous solvents. This mechanism is illustrated for an oleate hydroperoxide in Scheme 3 where the bold bar indicates caging by the solvent.. Such a mechanism had in fact been suggested by a referee of Brill's 1984 paper, [10] but considered unlikely partly because no dimerisation of the allyl radicals is observed

Porter crowned this by preparing a singly ^{18}O-labelled hydroperoxide and following its rearrangement under an atmosphere of $^{16}O_2$. Typical yields of isotopomers are shown in Equation (14).[9]

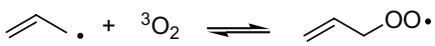
5 Kinetics

The various steps in the chain mechanism are shown in Equations (15)–(18).

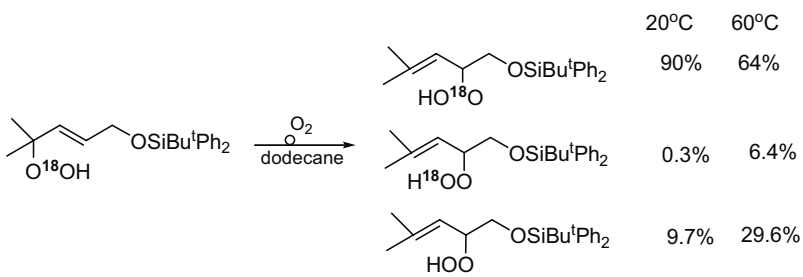
An important factor will be the rates of the termination reactions which depend strongly on the structure of the allylperoxyl radicals. Primary and secondary alkylperoxyl radicals self-react much more rapidly than tertiary alkyl peroxyl radicals, leading to short chains and termination products rather than the required hydroperoxides. This can



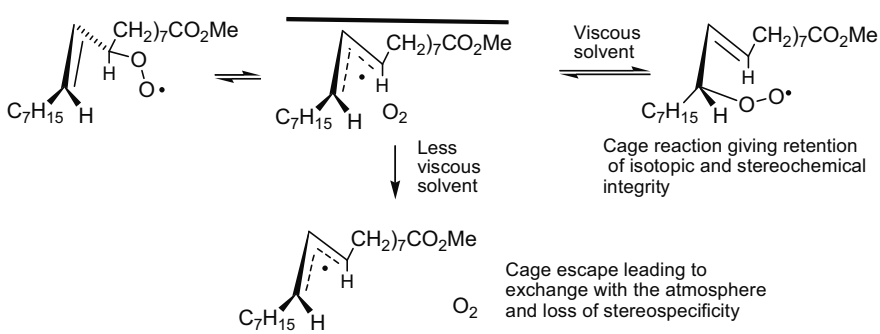
(12)



(13)



(14)



Scheme 3 Dissociative mechanism for the rearrangement of oleate hydroperoxide.

Initiation $Bu^tON{=}NOBu^t \xrightarrow{2k_i} 2Bu^tO\bullet \xrightarrow[\text{Rate } R_i]{ROOH} ROO\bullet$ (15)

Propagation
$ROO\bullet \rightleftharpoons R'OO\bullet$ (16)
$R'OO\bullet + ROOH \xrightarrow{k_p} R'OOH + ROO\bullet$ (17)

Termination $2R'OO\bullet \xrightarrow{2k_t}$ products (18)

be overcome by adding to the reaction system a large excess of *tert*-butyl hydroperoxide. Chain transfer occurs through the *tert*-butylperoxyl radical [Equations (19) and (20)] and the yield of hydroperoxide is increased (Table 1, entries 6–9).[31]

$R'OO\bullet + Me_3COOH \longrightarrow R'OOH + Me_3COO\bullet$ (19)

$Me_3COO\bullet + ROOH \longrightarrow Me_3COOH + ROO\bullet$ (20)

Brill found that the rearrangement of the hydroperoxide of entry 2 in Table 1 was slow in acetone and did not occur at all in 70% aqueous acetone, while in non-polar solvents, the rate depended inversely on the total hydroperoxide concentration.[7] This may be due in part to hydrogen bonding which inhibits the removal of hydrogen to give the allylperoxyl radical[10] but there will also be a solvent effect on the β-scission of the allylperoxyl radical as the peroxyl radical is more polar and more heavily solvated than the transition state for its dissociation. Thus, for example, the dissociation of the 3-phenylallyl-3-peroxyl radical is about 10^2 times slower in propionitrile than it is in hexane.[14]

The rate of equilibration of the isomers of entry 5 of Table 1, in dilute solution in hexane during 40 days was second order, but approached zero order above 0.1 M concentration. Again, the complication could be due to hydrogen bonding.[10]

5α-Hydroperoxy-3-β-hydroxycholest-6-ene [**1**; Equation (1)], showed simpler behaviour. IR spectroscopy indicated that there is no hydrogen bonding complication in dilute solution, and it can be assumed that termination is solely through the secondary alkylperoxyl radical R'OO•, which usually terminates 10^3 times faster than a tertiary alkylperoxyl radical. The rate of rearrangement in $CDCl_3$ at 20 or 30 °C, or in C_6D_6 at 30 °C was followed with TBHN as the initiator.[24]

By the steady state approximation the rate of termination will be equal to the rate of initiation, *i.e.*

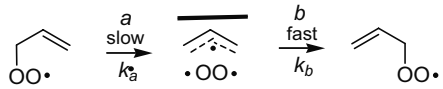
$$R_i = 2k_t[R'OO\bullet]^2 \quad \text{whence } [R'OO\bullet] = (R_i / 2k_t)^{1/2}$$

The overall rate of rearrangement of the hydroperoxide is then given by

$$\frac{-d[ROOH]}{dt} = k_p[R'OO\bullet][ROOH] = k_p[ROOH](R_i/2k_t)^{1/2} = k_{obs}[ROOH]$$

The reaction showed a good first order dependence of the rate on the concentration of the hydroperoxide in both benzene and chloroform, and half-order dependence on the concentration of hyponitrite, in accord with this kinetic analysis.

In the model of the rearrangement which involves prior dissociation then recombination of the allyl radical and dioxygen, the first, β-scission, step [Equation (21, *a*)], will be much slower than the second step [Equation (19, *b*)] and will be rate-determining and should be equal to the rate of rearrangement if an appropriate statistical factor is included to account for recombination at either end of the allylic system.



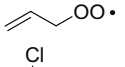
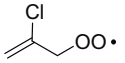
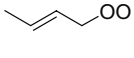
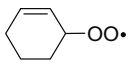
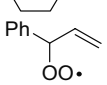
(21)

Table 2 lists rate constants from the literature for the β-scission of allylperoxyl radicals; most of these relate to measurements in the gas phase on simple structures. By the above argument, allowing for a factor of 2 as the combination can occur at either end of the allyl radical, the first order rate constant for the Schenck rearrangement of the allylperoxyl radical the gas phase would be about 4 s^{-1} at 298 K. In solution, the rate will be affected by solvation of the peroxyl radical and solvent caging of the allyl radical-$^3O_2$ intermediate, but some support comes from Courtneidge's estimation of the rate from measurements of the yields of various products from reactions in which the Schenck rearrangement was in intramolecular competition with 5-*exo* ring closure (see below). He suggested that the rearrangements had rate constants about two orders of magnitude less than the cyclisations which were estimated to have a rate constant of about 8×10^2 s^{-1} at 303 K.[31]

Jha and Pratt showed that the β-scission was slower in a polar solvent, between the extremes of hexane $1.4(1) \times 10^5$ s^{-1} and ethyl acetate $2.1(1) \times 10^4$ s^{-1}, suggesting that the transition state was less polar and less solvated than the reactant.[14]

In the 7α-hydroperoxides derived from cholesterol, or the compounds derived from stigmasterol (Table 1, entries 47 and 48), which have an electronegative group in the 5β-position, the higher reactivity is rather surprising. In the stigmastane system, AM1 calculations suggested that this is due to the stereorepulsive effect between the groups on the 5β- and 7α-positions.[29]

Table 2 Rate constants for the β-scission of allylperoxyl radicals

Peroxyl radical	Medium	*t*/K	k/s^{-1}	BDE/kJ mol^{-1}	Ref.
	Gas	298	7.7	76.2(2.1)	41
	Gas	352	29.2	77	42
	Gas	340	43.2	76.5(2.8)	43
	Gas	345	Av. 25.5.[a]	Av. 82.6(5.3)	42
	Gas	361	77(33)	80.4(4.2)	44
	Benzene	310	$2.6(3) \times 10^5$	44 (Calcd)	45
	Hexane	298	$1.4(1) \times 10^5$		14

[a]Individual values differ by not more than a factor of 10.

6 Computational studies

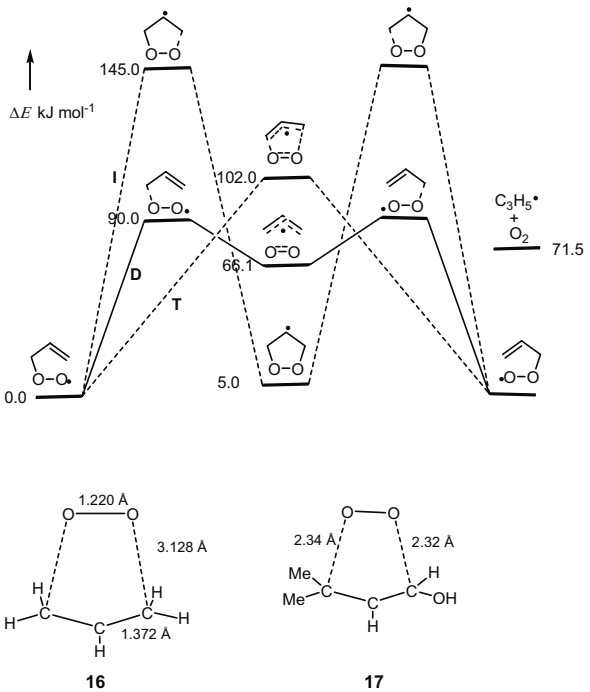
In 1993, Boyd and Porter investigated the mechanism of the Schenck rearrangement of the allylperoxyl radical at the MP2 or MP3/6-31G(d,p)//HF/6-31G(d) level.[39] They showed that reaction via a cyclic intermediate involved almost 170 kJ mol^{-1}, whereas fragmentation into an allyl radical and triplet oxygen required only 90 kJ mol^{-1}, but they were not able to locate a route through a cyclic transition state.

Olivella and Solé[46] located all three pathways [cyclic intermediate (**I**), cyclic transition state (**T**) and dissociated pair (**D**)] for the rearrangement at the RCCSD(T)/6-311 + G(3df,2p) level, and found barriers for cyclisation of 145 kJ mol^{-1}, and for the cyclic transition state of 102 kJ mol^{-1}, but that for dissociation into a loose allyl radical/$^3O_2$ complex to be 90.0 kJ mol^{-1}. Their energy diagram is reproduced in Scheme 4. The complex had an energy of 66.1 kJ mol^{-1} above that of the allylperoxyl radical, with a binding energy of 5.4 kJ mol^{-1} and the geometry shown in **16**. The allyl-peroxyl bond dissociation energy was thus 71.5 kJ mol^{-1}. A charge of only 0.026 e was calculated to be transferred from the allyl radical to the oxygen in the complex, indicating that the interaction is chiefly due to dispersion forces.

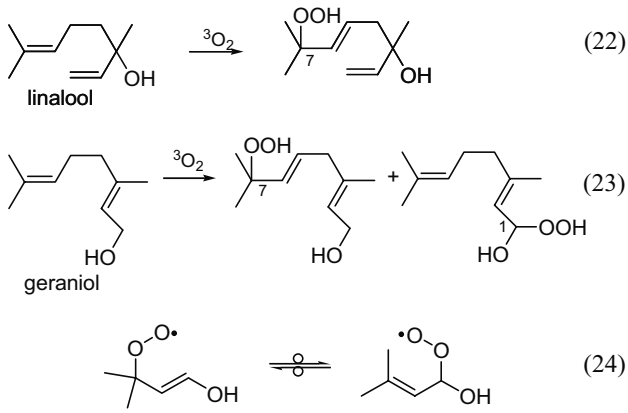
Lee and Bozzelli carried out similar calculations at the B3LYP/6-31G(d,p) density functional level[47] and found the allyl-peroxyl bond dissociation energy to be 84 kJ mol^{-1}.

Linalool[48] and geraniol[49] are widely used commercial fragrances which may undergo autoxidation to give allylic hydroperoxides [Equations (22) and (23)] which can lead to allergic contact determatitis and which have been subjected to computational studies.

Bäcktorp *et al*. carried out computations at the B3LYP/6-311 + G(2d,p) level on 3-methyl-2-buten-1-ol as a model for the hydroxyallyl group of geraniol[49] and concluded that for the Schenck rearrangement of the allylperoxyl radical, [Equation (24)], the transition state with the geometry shown in **17** involved a lower activation energy than that required for the dissociative mechanism.



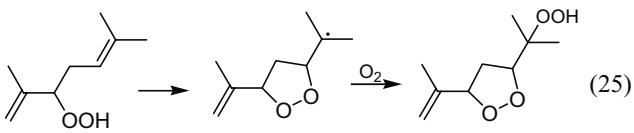
Scheme 4 Three computed reaction pathways for the Schenck rearrangement, involving and intermediate (I), a transition state (T) or dissociation (D). Reproduced with permission from ref. 46.



7 Alternative reactions

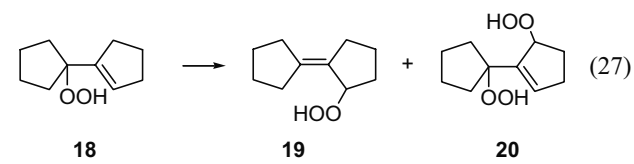
As alternatives to the Schenck or Smith rearrangements, allylperoxyl radicals may add intramolecularly to a double bond or abstract a hydrogen atom.

Intramolecular addition to a suitably positioned C=C double bond usually leads to 5- or 6-*exo*-cyclisation[1] Examples are given in Equations (25)[50] and (26).[51]

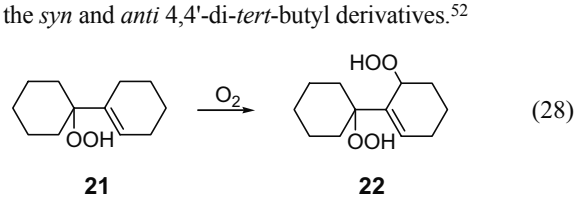


Courtneidge has identified diene and triene systems in which both rearrangement and cyclisation of allylperoxyl radicals can be observed (Scheme 5).[31] The Schenck rearrangements were suggested to be about two orders of magnitude slower than the 5-*exo* ring closures, which Porter estimated to have a rate constant of *ca* 8 × 10^2 s^{-1} at 30 °C;[38] this is in accord with the values listed in Table 2.

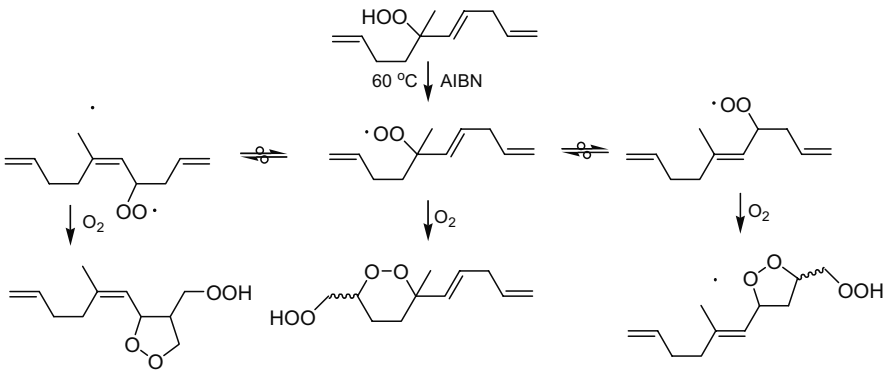
If oxygen is present, allylic hydroperoxides may show an alternative reaction. In the absence of air, the cyclopentenyl hydroperoxide **18** of Table 1, entry 12, rearranges cleanly to **19,** but in air in 48 h it gives **19** (27%) together with the dihydroperoxide **20**.



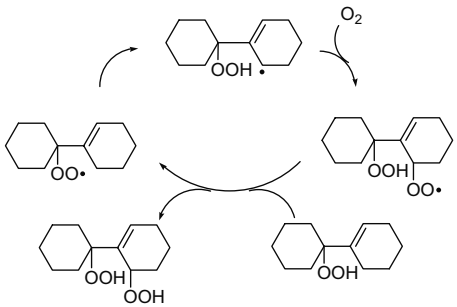
Similarly the cyclohexyl analogue (**21**) in $CDCl_3$ under nitrogen at room temperature shows no rearrangement during 2 months, nor at 40 °C in the absence or presence of AIBN as an initiator, but, under air or oxygen, it is rapidly converted into the dihydroperoxide **22**,[6] and the same behaviour is observed with the *syn* and *anti* 4,4'-di-*tert*-butyl derivatives.[52]



It appears that the allylperoxyl radical abstracts a hydrogen atom from the 6-position of the neighbouring ring to give an allylic radical which picks up dioxygen to give a peroxyl radical, which propagates the chain (Scheme 6).



Scheme 5 Rearrangement and cyclisation by allylperoxyl radicals.



Scheme 6 Intramolecular abstraction of hydrogen by an allylperoxyl radical.

8 The Smith rearrangement

Relatively few examples of the Smith rearrangement are recognised (Table 3) because they have to take place at a chiral centre to be apparent; even in those few examples, the identification often involves the assumption that the Schenck rearrangement, and sometimes also the $^1O_2$ ene synthesis, yield only one isomer.

At 40 °C, the 7α-hydroperoxide from cholesterol in $CDCl_3$ (Table 3, entry 5) rearranged to give 20% of the 7β epimer in 48 h. The reaction is slower than the Schenck rearrangement of the 5α-hydroperoxide and is inhibited by 4-methyl-2,6-di-*tert*-butylphenol. When the reaction was carried out under $^{18}O_2$ for 3.5 h, the 7β product contained 73% ^{18}O, but the 7α reactant remained isotopically normal. The maximum amount of rearrangement which has been reported is about 30%, but the equilibrium position is not known.[24] Autoxidation of cholesterol is reported to give 7-hydroperoxycholesterol with a 1 : 2 α/β ratio.[54]

When the 5β-hydroperoxide from valencene (Table 3, entry 4) was allowed to stand in chloroform under $^{18}O_2$ for 90 h, the principal product was the isotopically normal 8β–hydroperoxide, together with some 10% of the 8α–hydroperoxide which contained >55% ^{18}O, and presumably resulted from the Smith rearrangement of the 8β product.[6]

The optical purity of the hydroperoxides from methyl oleate degrades over time. This might be ascribed to incomplete stereospecificity in the Schenck rearrangement, but also might be due to Smith epimerisation.[21]

This evidence indicates that the Smith rearrangement is again a radical chain reaction but it involves a greater exchange of dioxygen with the atmosphere than does the Schenck rearrangement. It appears that dissociation into allyl and $^3O_2$ fragments occurs but the separation between the fragments is now larger, allowing more extensive oxygen exchange with the atmosphere, and diffusion of the dioxygen to the opposite face of the sp^2 carbon radical centre.

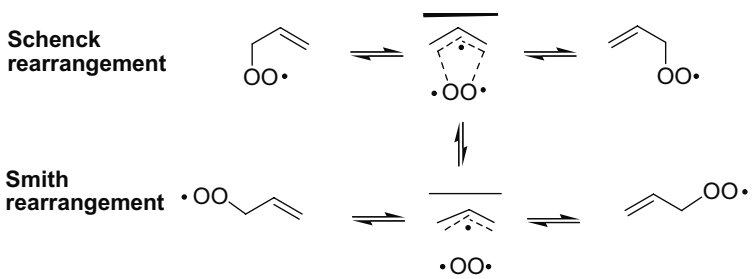
9 Conclusion

The Schenck and Smith rearrangements are both a consequence of the reversibility of the reaction of allyl radicals with triplet dioxygen, and differ mechanistically in the degree of separation of the two components as shown diagrammatically in Scheme 7.

As autoxidation involves the same colligation of an allyl radical and oxygen, it might be expected to give the same distribution of allylic isomers and, as far as can be judged, this seems to be the case. For example the autoxidation of cholesterol gives 7α- and 7β-hydroperoxides in the ratio of 1 : 2,[54] whereas the Schenck rearrangement followed by the incomplete Smith rearrangement of the 5α-hydroperoxide gives the 7α- and 7β-hydroperoxides in the ratio of about 7 : 3.

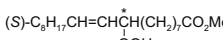
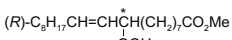
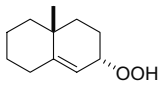
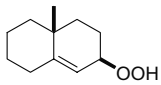
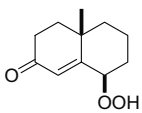
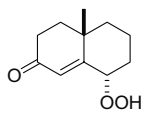
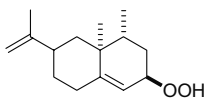
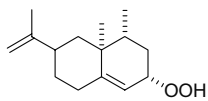
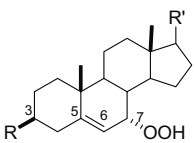
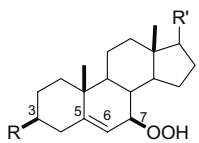
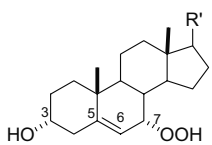
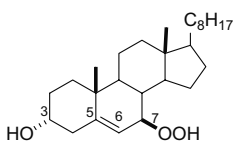
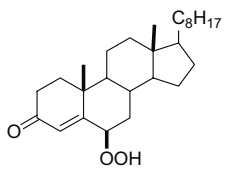
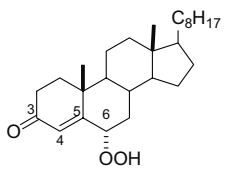
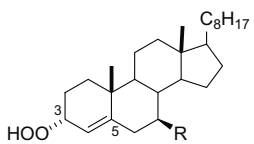
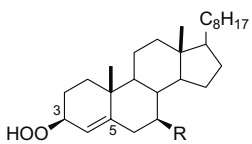
It is difficult, however, to ensure that the Schenck and Smith rearrangements do not take place during autoxidation and, indeed, they may be inseparable from it if autoxidation and the rearrangements proceed through the same allyl radical-dioxygen intermediates: the rearrangements maybe an integral part of any autoxidation of an allylic substrate.

It would be interesting to attempt to intercept the dioxygen during the rearrangement of a hydroperoxide such as cyclohex-2-enyl hydroperoxide, using a scavenger that does not react with the hydroperoxide or the peroxyl radical.



Scheme 7 The related mechanisms of the Schenck and Smith rearrangements.

Table 3 Examples of the Smith rearrangement

Entry	Allylic isomer **B**	Allylic isomer **C**	Comments	Ref.
1			At 22 °C, the *S*-hydroperoxide of >99% *ee*, gives 1.5 ± 0.5% of the *R* enantiomer. At 50 °C, 3 ± 0.5% is formed.	35
2			After 259 h in $CDCl_3$, *ca* 5% of **C** is formed from **B**.	15
3			After 150 h at room temperature in $CHCl_3$, the equilibrium composition appears to be *ca* 1.8:1	53
4			The concentration of **C** in a mixture of **A, B** and **C**, in $CDCl_3$, increases during 90 h in the presence of TBHN.	16
5			In $CDCl_3$ at 40 °C, 20% of **B** is converted into **C** in 3.5 h. In EtOAc at 40 °C, the yield of **C** is 25–30%.	24
6	R = OH, R' = C_8H_{17}	R = OH, R' = C_8H_{17}	In EtOAc, epimerisation is 25–30% complete in 48 h. Under $^{18}O_2$, 73-83% ^{18}O is incorporated into the product. The reaction is inhibited by BHT.	5 24
7	R = OCH_3, R' = C_8H_{17}	R = OCH_3 R' = C_8H_{17}	For all four of these compounds, singlet oxygenation of the 5-ene gives principally the 7α-OOH-5-ene, presumably through successive Schenk then Smith rearrangements of the 5αOOH-6-ene.	24
8	R = $OSiMe_3$, R' = C_8H_{17}	R = $OSiMe_3$, R' = C_8H_{17}		
9	R = OCOMe, R' = C_8H_{17}	R = OCOMe, R' = C_8H_{17}		
10	R = OCOPh, R' = C_8H_{17}	R = OCOPh, R' = C_8H_{17}		
11	R = $=CH_2$, R' = C_8H_{17}	R = $=CH_2$, R' = C_8H_{17}	The equilibrium position appears to be *ca* 70% **B** and 30% **C**.	33 27
12			Singlet dioxygenation of epicholesterol gives only the 7β-hydroperoxide.	6
13			In $CDCl_3$, the ratio of the concentrations of **B** and **C** at equilibrium is *ca* 1:1.5. The rearrangement is inhibited by BHT.	53
14			A mixture of 29% of the 5-OOH **A** and 37% of the 3α- and 7.5% of the 3β-OOH, after 48 h in $CHCl_3$, gave the 3α- and 3β-OOH in the ratio of 8:1.	26

Benzene, which forms as strong a complex as does the allyl radical with $^3O_2$,[46] does not appear to affect the rearrangement, but a fluorocarbon, which forms a stronger complex, might accomplish this.

It should be borne in mind that the evidence for the mechanism involving a solvent-caged intermediate pair relates as yet only to (acyclic, linear) oleic acid derivatives. The computed energy level **T** for the route involving a cyclic transition state for the allylperoxyl radical is not far above that (**D**) involving dissociation (Scheme 2),[46] and for the 1, 1-dimethyl-3-hydroxyallylperoxyl radical [Equation (24) and Formula **16**], these energy levels appeared to be interchanged.[49] The possibility remains that the route **T** may still have a part to play in Schenck rearrangements of allylperoxyl radicals with a more complex structure.

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