The Mechanisms of the Rearrangements of Allylic Hydroperoxides

Athelstan L. J. Beckwith,[a] Alwyn G. Davies,[b] Ian G. E. Davison,[b] Allan Maccoll,[b] and Margaret H. Mruzek[b]

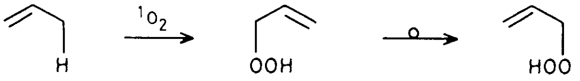
[a] *Research School of Chemistry, Australian National University, Canberra, A.C.T. 2601 Australia*
[b] *Chemistry Department, University College London, 20 Gordon Street, London WC1H 0AJ, U.K.*

The suprafacial rearrangement of 3β-hydroxy-5α-hydroperoxy-Δ^6-cholestene to the 7α-hydroperoxy-Δ^5 isomer does not involve exchange of O_2 with the atmosphere, suggesting that it proceeds by a non-dissociative mechanism; on the other hand, the slower subsequent rearrangement of the 7α-Δ^5-hydroperoxide to the 7β-Δ^5-hydroperoxide is susceptible to exchange, and follows a dissociative mechanism.

Unsaturated compounds react with singlet oxygen to give allyl hydroperoxides (**1**). In non-polar solvents, these hydroperoxides may then undergo allylic rearrangement to give the isomeric hydroperoxides (**2**) (Scheme 1) with structures similar to those of the products of the reaction of the unsaturated compounds with triplet oxygen.[1,2] These rearrangements are subject to inhibition by phenols and to acceleration by light and by sources of free radicals, and are accepted to follow a radical chain mechanism involving intermediate allylperoxyl radicals (**3**) and (**4**), as shown in Scheme 2.

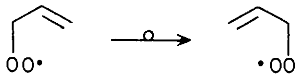
We are concerned here with the structures of the allylperoxyl radicals and the mechanisms of their rearrangements, and we report an ^{18}O isotope study of the rearrangement of the cholesterol-derived 5α-Δ^6-hydroperoxide (**5**) to the 7α-Δ^5-hydroperoxide (**6**) and thence to the 7β-Δ^5-hydroperoxide (**7**) (Scheme 3).

Brill[2] and Porter[3] have provided convincing evidence against the intermediacy of a cyclic carbon-centred radical (**8**). Brill[2] suggested that the allylperoxyl radicals (**3**) and (**4**) were not separate and distinct species, but that they had the common structure (**9**) in which the unpaired electron is located in an antibonding orbital on oxygen. We find, however, that photolysis of (**5**) in chloroform at 223 K shows a singlet e.s.r. spectrum, *g* 2.0150, typical of a tertiary peroxyl radical, whereas (**6**) under the same conditions shows a doublet *a*(1H) 2.49 G (G = 10^{-4} T), *g* 2.0143, typical of a secondary alkylperoxyl radical. The isomeric radicals (**3**) and (**4**) derived



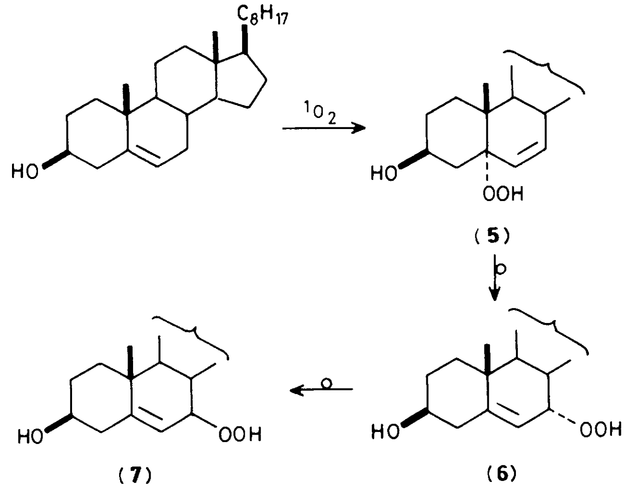
(**1**) (**2**)

Scheme 1

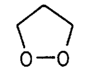


(**3**) (**4**)

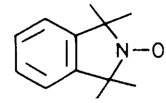
Scheme 2

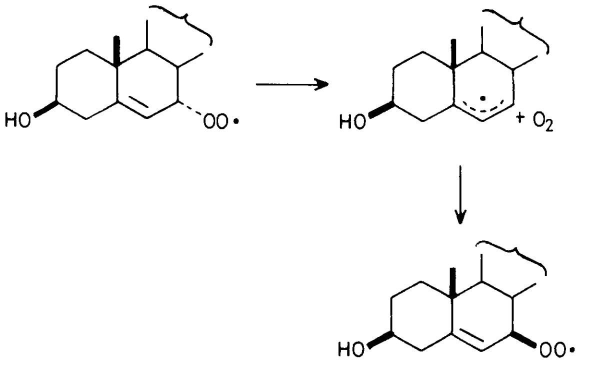


Scheme 3


(8)


(9)


(10)



Scheme 4

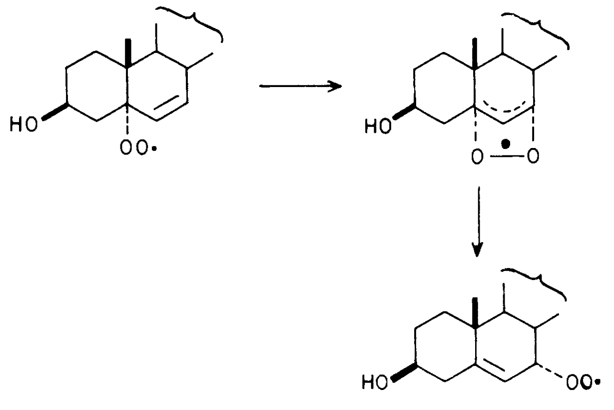
from the hydroperoxides (**5**) and (**6**) therefore exist as a distinct acyclic species.

The hydroperoxide (**5**) in chloroform was allowed to rearrange partially (*ca.* 3.5 h) to (**6**) under an atmosphere of 99% $^{18}\mathrm{O}_2$. The mixed hydroperoxides were immediately reduced with triphenylphosphine, and the corresponding alcohols which were formed were separated by preparative h.p.l.c. and analysed by ^{1}H n.m.r. (400 MHz) and mass spectrometry (electron impact at 20 eV). Neither the 5α-Δ^6-alcohol derived from residual (**5**), nor the 7α-Δ^5-alcohol derived from the product (**6**) had acquired the ^{18}O label, but a trace of the 7β-Δ^5-alcohol was also isolated and this was found to contain 82 and 83% ^{18}O in duplicate experiments.[4]

The isotopically normal 7α-Δ^5-hydroperoxide (**6**) was therefore dissolved in chloroform under $^{18}\mathrm{O}_2$, and after *ca.* 3.5 h the hydroperoxides were reduced with triphenylphosphine and the resulting alcohols were separated by h.p.l.c. The 7α-Δ^5-alcohol derived from (**6**) was still isotopically normal, but the epimeric 7β-Δ^5-alcohol was enriched with ^{18}O to the extent of 73%.

These results were confirmed by mass spectroscopic analysis of the dioxygen in the gas phase and of the triphenylphosphine oxide obtained from the reduction.

The rate of the rearrangement (**5**) → (**6**) or of (**6**) → (**7**), *in vacuo*, was unaffected by the presence of the nitroxyl radical (**10**) (10 mol %) which reacts with allylic radicals at close to the diffusion-controlled rate.[5]



Scheme 5

We conclude that the epimerization (**6**) → (**7**), which is susceptible to isotope exchange, proceeds by dissociation of the allylperoxyl radical into the free allyl radical and oxygen (Scheme 4).[†] Presumably recombination of the solvent-caged allyl radical and O_2 is too fast for the nitroxyl radical to interfere.

The suprafacial rearrangement (**5**) → (**6**), on the other hand, which is not susceptible to oxygen isotope exchange, cannot involve kinetically free allyl radical and oxygen, and the evidence is compatible with the reaction proceeding through a cyclic transition state as represented in Scheme 5.[‡]

These results suggest a further examination of the analogous pentadienylic rearrangement of linoleate hydroperoxides, which Chan has shown to involve geometrical isomerization, and isotope exchange with an oxygen atmosphere.[7] It is possible that the exchange could occur during a reaction equivalent to our epimerization (Scheme 4), and that the pentadienylic rearrangement itself could proceed without exchange, by a non-dissociative mechanism.

Note added in proof: In a recent parallel study[8] of the allylic rearrangement of hydroperoxides derived from oleic acid, Porter *et al.* have similarly concluded that the reaction proceeds *via* a five membered ring transition state.

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[†] In the gas phase, the dissociation of the allylperoxyl radical ($C_3H_7O_2\cdot \rightarrow C_3H_7\cdot + O_2$) shows Arrhenius parameters A (1.6 ± 0.8) × 10^{10} s^{-1} and E_a 53.3 ± 1.6 kJ mol^{-1}.[6]

[‡] The maximum degree of dissociation which the results permit would appear to be a charge transfer complex between the allylic radical and oxygen.