Thermal Isomerisation of Methyl Linoleate Hydroperoxides. Evidence of Molecular Oxygen as a Leaving Group in a Radical Rearrangement

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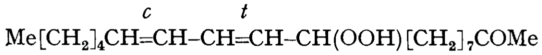
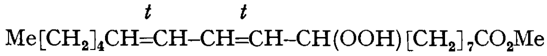
Summary Using an ^{18}O-enriched hydroperoxide, the pentadienyl hydroperoxides (**1**—**4**) were shown to undergo rearrangement in which the oxygen atoms of the hydroperoxy group exchanged with atmospheric oxygen.

THE study of the radical rearrangement of allylic[1] and pentadienyl[2] hydroperoxides [(**1**) and (**3**), derived from oxidations using lipoxygenases] has been handicapped by the instability of these hydroperoxides and the difficulties of preparing and quantitating different isomers. In this study, an h.p.l.c procedure[3] which resolves all four isomers of methyl linoleate hydroperoxide (**1**)—(**4**) and their derivatives under mild conditions was used to prepare and analyse the isomers. An ^{18}O-enriched hydroperoxide isomer ($R^{18}O^{18}OH$) of high isomeric purity was prepared for the first time for the study of the reaction which apparently involves the rearrangement of a group bearing an O–O bond. An enzymic procedure[4] was used that overcomes the difficulties caused by the loss of positional specificity which arises when lipoxygenase-catalysed reactions are carried out with a limited supply of oxygen.[5]



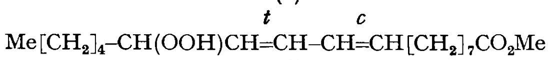
$$\mathrm{Me[CH_2]_4CH\overset{\mathit{c}}{=}CH{-}CH\overset{\mathit{t}}{=}CH{-}CH(OOH)[CH_2]_7COMe}$$

(**1**)



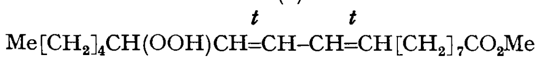
$$\mathrm{Me[CH_2]_4CH\overset{\mathit{t}}{=}CH{-}CH\overset{\mathit{t}}{=}CH{-}CH(OOH)[CH_2]_7CO_2Me}$$

(**2**)



$$\mathrm{Me[CH_2]_4{-}CH(OOH)CH\overset{\mathit{t}}{=}CH{-}CH\overset{\mathit{c}}{=}CH[CH_2]_7CO_2Me}$$

(**3**)

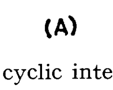


$$\mathrm{Me[CH_2]_4CH(OOH)CH\overset{\mathit{t}}{=}CH{-}CH\overset{\mathit{t}}{=}CH[CH_2]_7CO_2Me}$$

(**4**)

c = *cis*, *t* = *trans*

The methyl linoleate hydroperoxide isomers (**1**)—(**4**) were stable when kept as dilute ethereal solutions at −20 °C but underwent isomerisation at higher temperatures. Heating, in air, at 40 °C for 16 h in hexane resulted in 50—60% conversion of a single isomer into the other isomers with > 90% recovery of the mixture as (**1**)—(**4**). The reaction was non-selective; any single isomer resulted in a mixture of all four isomers. Isomerisation was faster in non-polar solvents (% conversion of an isomer decreased in different solvents in the order hexane > CCl_4 > toluene > $CHCl_3$ > ethanol). It was accelerated by the addition of metal salts and was completely inhibited by 200 p.p.m. of the antioxidant 2,6-di-t-butyl-4-methyl phenol. A free-radical chain mechanism with which the above observations are consistent has been suggested for the analogous 1,3-rearrangement of allylic hydroperoxides.[1] This involves the abstraction of H from a hydroperoxide (ROOH) to form a hydroperoxy radical (ROO·) which is the species that undergoes rearrangement (ROO· → R′OO·). Abstraction of hydrogen from another hydroperoxide molecule would yield the product as well as propagate the chain (R′OO· + ROOH → R′OOH + ROO·). However, the suggested[1] involvement of cyclic peroxidic intermediates (A) for the 1,3-rearrangement of peroxy radicals has not been observed and the corresponding cyclic intermediates are unlikely to be formed in the present case of a 1,5 rearrangement in which the double bonds are in a *cis–trans* or a *trans–trans* configuration. Using ^{18}O-labelled methyl linoleate hydroperoxide, we examined the alternative possibility that, during isomerisation, the carbon–oxygen bond of the COO· group is broken in a distinct step.

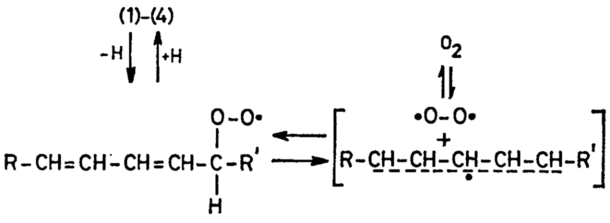


(A)

A sample of ^{18}O-labelled (**1**) was prepared enzymically[4] [89% isomeric purity, $R^{18}O^{18}OH$ to $R^{16}O^{16}OH$ ratio of 90·1 : 9·9; $^{18}O_2$ (> 99%) was used for the preparation; the high percentage of ^{16}O-hydroperoxide is a result of dissolved

$^{16}O_2$ in the enzyme extracts and of exchange with the atmosphere (see below) during the work-up of the hydroperoxide]. Incubation of the hydroperoxide in hexane at 40 °C for 16 h afforded a mixture of isomers (97% yield) with the composition (**1**), 37·5; (**2**) 27·1; (**3**), 6·7; and (**4**), 28·7% and the following ^{18}O-enrichment for the individual isomers: (**1**), 81·8; (**2**), 54·2; (**3**) 56·4; and (**4**), 53·9%. There is thus a loss of ^{18}O-label that is greater for the rearranged isomers which showed similar losses. The $^{18}O_2$: $^{16}O^{18}O$: $^{16}O_2$ ratio in the gases (total volume 0·88 ml) above an isomerised sample (total loss of $^{18}O_2$ 2·64 μmol) was 0·330 : 0·004 : 1 (the corresponding ratio for a control sample was 0·008 : 0·004 : 1). The gaseous $^{18}O_2$ accounted for 73 ± 5% of the loss from the hydroperoxides. Total recovery of $^{18}O_2$ was not determined owing to the unknown solubility of oxygen in hexane under the condition of the experiment (rapid freezing to −77 °C). The almost quantitative recovery of the hydroperoxides and the absence of an appreciable increase in $^{16}O^{18}O$ oxygen in the gases indicate that the formation and subsequent decomposition of a tetroxide to oxygen and other compounds, a reaction postulated for termination steps involving *t*-alkyl–aryl peroxy radicals,[6] is unimportant in the isomerisation of (**1**)—(**4**).

The isomerisation of methyl linoleate hydroperoxides is therefore accompanied by the exchange of the oxygen atoms of the hydroperoxy group with atmospheric oxygen. This arises through the decomposition of the intermediate peroxy-pentadienyl radical, to form, in a spin-allowed reaction, a pentadienyl radical and ground state molecular oxygen which exchanges with atmospheric oxygen (see Scheme). Reaction (or recombination) of molecular oxygen with the pentadienyl radical is then a step common to the pathways of both isomerisation and autoxidation and yields both 9-OOH [(**1**) and (**2**)] and 13-OOH [(**3**) and (**4**)] isomers. The proposed mechanism for the rearrangement of peroxypentadienyl radicals is analogous to that suggested[7] for the 1,5 radical rearrangement of pentadienyl ammonioamidates. In the present case it is a neutral molecule rather than a radical that undergoes migration and is, as far as we are aware, the first example of the involvement of molecular oxygen as a leaving group in a rearrangement reaction.



SCHEME. R and R′ = C_5H_{11} or $C_7H_{14}CO_2Me$

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