A non-radical mechanism for the rearrangement of linoleic acid dihydroperoxides

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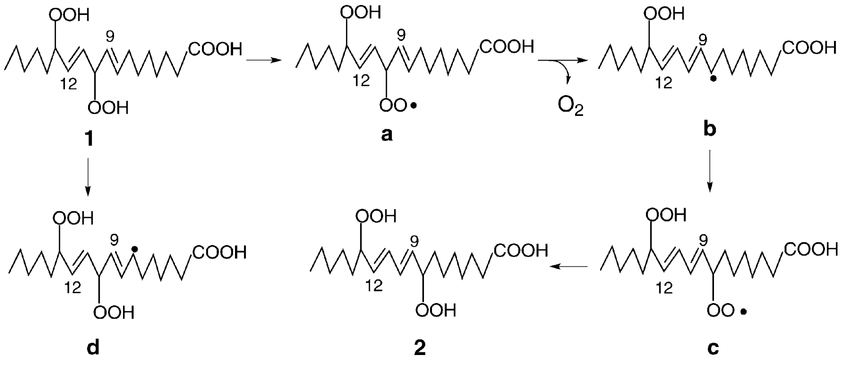
A non-radical mechanism for the rearrangement of the 10,13-dihydroperoxide of linoleic acid to the 8,13-dihydroperoxide is proposed, and different pathways for the formation of 4-hydroperoxy-2-nonenal *via* a dioxetanyl radical are speculated (the mechanism of formation of 4-hydroperoxy-2-nonenal is of great interest since it is a precursor of the highly bioactive 4-hydroxy-2-nonenal and 4-oxo-2-nonenal).

Lipid hydroperoxides may undergo conversion to alkoxyl radicals whose β-scission simultaneously affords aldehydes and carbon-centered radicals. However, formation of some important aldehydes such as hexanal, 9-oxononanoic acid and 4-hydroperoxy-2-nonenal (4-HPNE) by such alkoxyl radical reactions is unlikely since it requires the simultaneous formation of vinyl radicals, a highly energetically unfavourable process.[1] On the other hand, there is evidence that peroxyl radical reactions are important in the formation of such products. Two suggested mechanisms by which peroxyl radicals might participate in aldehyde formation are (i) cross-molecular addition of peroxyl radicals followed by further hydroperoxidation and generation of alkoxyl radicals whose β-scission affords oxygen-stabilized carbon-centred radicals,[2] and (ii) the cyclization of lipid peroxyl radicals to form dioxetanyl radicals which are susceptible to thermolysis.[3,4]

Interestingly, Schneider *et al.* recently found that in the absence of added metal ions at 37 °C, the 13-hydroperoxide of linoleic acid (13-LA-OOH) was converted to aldehydic products such as 4-HPNE while the 10,13-dihydroperoxide (10,13-LA-OOH, **1** in Scheme 1) basically underwent rearrangement to the 8,13-dihydroperoxide (8,13-LA-OOH, **2**).[5] Their proposal that this rearrangement occurred *via* the facile β-fragmentation of peroxyl radical **a** to afford the conjugated double bond system in radicals **b** and **c** as well as compound **2** (Scheme 1) seems to rule out aldehyde formation by cyclization of both peroxyl radical **a** and the more stable peroxyl radical **c**.



Scheme 1

This contradicts the fact that, using 3-hydroperoxy-2,3-dimethyl-1-butene as a model of unsaturated fatty acids, product formation according to the peroxycylization theory has been demonstrated.[3] That peroxyl anions have been used to prepare some dioxetanes[6] further supports the feasibility of peroxyl radical cyclization.

We consider that although the β-fragmentation of bisallylic peroxyl radicals such as **a** is indeed facile, the conversion of dihydroperoxide **1** to peroxyl radical **a** may not have been significant under the experimental conditions of the mentioned study since in the absence of metal ion catalysts, hydroperoxy groups are rather stable.[2,7] Moreover, since the homolytic bond dissociation energy at 25 °C is 85 kcal mol^{-1} for both $CH_2{=}CHCH_2$–H and CH_3CH_2OO–H,[8,9] conditions that enable the generation of **a** should equally enable abstraction of H-7 from **1**, leading to formation of radical **d** and propagation of radical reactions other than the observed rearrangement. In addition, radical **b** should also undergo some conversion to the conjugated 12,13-dihydroperoxide (12,13-LA-OOH), which was not detected. Notably, the conversion of 9,12-LA-OOH (which is analogous to **1**) to aldehydic products in the presence of metal ions has been reported.[10] Thus it is likely that the rearrangement of **1** to **2** occurred by a non-radical mechanism.

Our proposed mechanism for the non-radical rearrangement (Scheme 2) begins in a similar manner to the known

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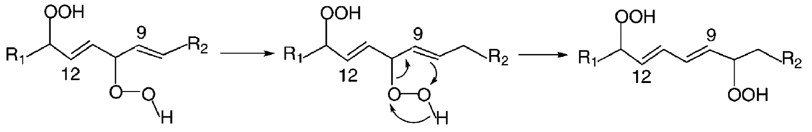
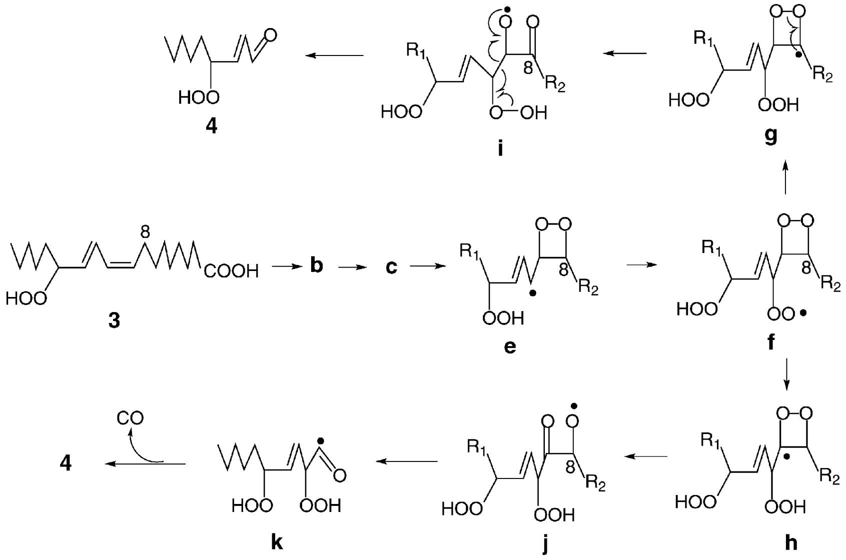


Scheme 2



Scheme 3

reaction of hydroperoxides with alkenes to form epoxides.[11] Thus, coordination of the C8–C9 π bond with the 10-hydroperoxy group's electrophilic oxygen leads to heterolytic C–O cleavage (which should be favorable due to formation of a conjugated double bond system) and a facile hydrogen migration to the second oxygen of the hydroperoxy group, probably by a concerted mechanism. The lack of formation of the 12,13-dihydroperoxy isomer may be due to interactions between the 13-hydroperoxy group and the C11–C12 π bond interfering with coordination of the 10-hydroperoxy group to this π bond.

On the other hand, easier initiation of radical reactions and formation of aldehydes from 13-LA-OOH (**3** in Scheme 3) may be rationalized by the fact that abstraction of H-8 from this compound gives radical **b** which is more resonance-stabilized than radical **d**.† Peroxyl radical **c** may then be considered to be a key intermediate in the formation of 4-HPNE. This might involve an intermolecular addition to another molecule of **3**. Alternatively, if **c** cyclizes to form dioxetanyl radical **e**, we suppose that the latter will be readily converted to dioxetane peroxyl radical **f**. It is known that aliphatic peroxyl radicals may undergo self abstraction of hydrogen atoms.[12,13] For radical **f**, self abstraction of H-8 or H-9 should be favourable since radicals **g** and **h** thus generated are oxygen-stabilized. Radical **g** may rearrange to alkoxyl radical **i**, whose β-scission directly affords 4-HPNE **4**. Similarly, β-scission of alkoxyl radical **j** obtained from **h** affords α-hydroperoxy carbonyl radical **k**, whose expected facile decarbonylation affords 4-HPNE **4**. In addition, thermolysis of the dioxetane group in **f** will produce an aldehydic peroxyl radical whose self abstraction of the carbonyl hydrogen also generates radical **k** and 4-HPNE **4**.

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† The significant generation of **b** during the oxidation of **3** is supported by the fact that 8,13-LA-OOH **2** is an important product of the oxidation of **3**,[14] since the conversion of **3** to **2** is expected to occur *via* radicals **b** and **c** (Scheme 3) followed by hydrogen abstraction by the latter.

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