Stereochemical Aspects of Fatty Acid Oxidation: Hydroperoxide Isomerases[†]

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Lipoxygenases catalyze dioxygenation of polyunsaturated fatty acids to produce fatty-acid hydroperoxides. The reaction involves initial stereospecific abstraction of a hydrogen atom from a bis-allylic methylene group followed by antarafacial attack by dioxygen at one of the terminal carbon atoms of the pentadienyl radical. 8(R)-Dioxygenase, recently discovered in the fungus Gaeumannomyces graminis, catalyzes formation of 8-hydroperoxy derivatives of linoleic and oleic acids by abstracting one hydrogen from C-8 and inserting dioxygen at the same carbon atom. Isotope-labeling studies show that the configuration at C-8 is inverted during this process.

The fungus Saprolegnia parasitica, a fish parasite, contains an ω6-lipoxygenase and an epoxy alcohol synthase. The latter enzyme catalyzes isomerization of fatty acid hydroperoxides into α,β- and γ,δ-epoxy alcohols. Experiments with ^{18}O-labelled hydroperoxides demonstrate that the hydroperoxide → epoxy alcohol conversion consists of intramolecular transfer of the terminal hydroperoxide oxygen to either of the two conjugated double bonds. The reactions proceed with retention of geometrical configuration, i.e. epoxidation of the α,β (E) and γ,δ (Z) double bonds of the parent fatty acid hydroperoxide gives rise to trans and cis epoxides, respectively.

G. graminis, as well as the marine red alga Gracilariopsis lemaneiformis, contain vicinal diol synthases that catalyze isomerization of fatty-acid hydroperoxides into vicinal dihydroxy fatty acids. Studies using ^{18}O-labelled hydroperoxides show that the hydroperoxide → diol conversions occur by intramolecular transfer of the terminal hydroperoxide oxygen to the vicinal methylene group. Experiments with stereospecifically deuteriated fatty-acid hydroperoxides demonstrate that the intramolecular hydroxylations catalyzed by the two vicinal diol synthases proceed with retention of absolute configuration of the carbon hydroxylated.

Lipoxygenases catalyze dioxygenation of polyunsaturated fatty acids to produce hydroperoxides having one pair of conjugated E/Z double bonds.[1] Fatty-acid hydroperoxides having non-conjugated double bonds are produced in the presence of 8(R)-dioxygenase, a recently discovered enzyme which catalyzes allylic dioxygenation of e.g. linoleic and oleic acids.[2] Hydroperoxides can also be obtained from polyunsaturated fatty acids by pseudoenzymatic oxygenation in the presence of myoglobin and other heme proteins,[3,4] by autoxidation[5] and by non-radical oxygenation upon exposure to singlet molecular oxygen.[6]

Because of the relatively low dissociation energy of the O–O bond of the hydroperoxy group (ca. 44 kcal mol^{-1}), hydroperoxides undergo a variety of reactions,[7] including thermal decompositions and metal-ion- and acid-catalyzed rearrangements. In addition, specific enzymes catalyze the further metabolism of fatty-acid hydroperoxides generated in animal and plant tissues. During recent years work in our laboratory has been concerned with hydroperoxide metabolism in plants and fungi. Figure 1 summarizes enzyme-catalyzed transformations of hydroperoxides discovered by us and other workers. Allene oxide synthase catalyzes dehydration of hydroperoxides into unstable allene oxide derivatives.[8,9] This enzyme has a functional role in plants in the biosynthesis of jasmonic acid, an important plant hormone.[10] Dehydration of hydroperoxides may also be catalyzed by divinyl ether syn-

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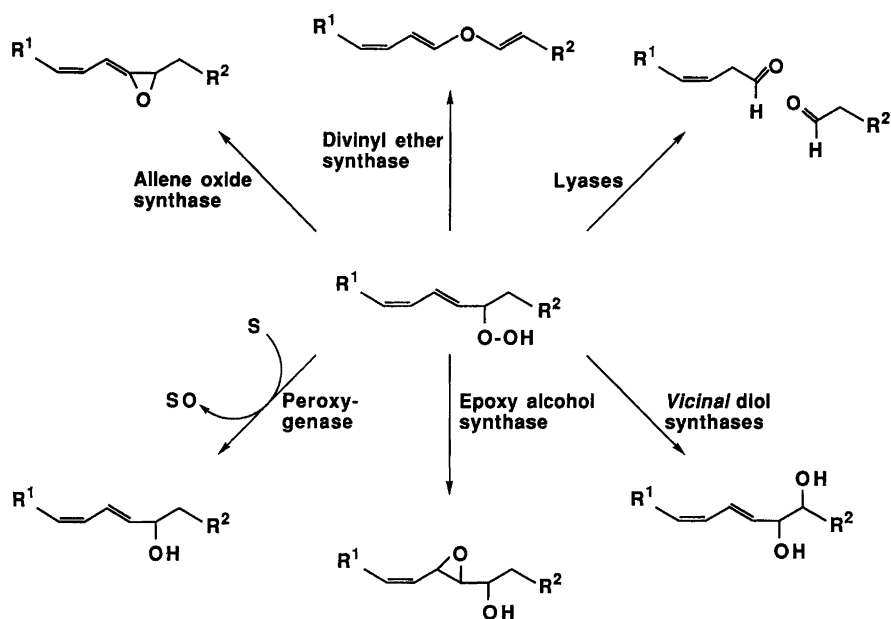
Fig. 1. Enzymatic transformations of linoleic acid 9(S)- and 13(S)-hydroperoxides in plants and fungi. 9(S)-Hydroperoxy-10(E),12(Z)-octadecadienoic acid, $R^1 = (CH_2)_4$–CH_3, $R^2 = (CH_2)_6$–COOH; 13(S)-hydroperoxy-9(Z),11(E)-octadecadienoic acid, $R^1 = (CH_2)_7$–COOH, $R^2 = (CH_2)_3$–CH_3.

thase, in which case a carbon–carbon bond is cleaved. The enzyme, which is present in potato tubers, is responsible for the biosynthesis of the divinyl ether derivatives colneleic and colnelenic acids from the 9-hydroperoxides of linoleic and α-linolenic acids, respectively.[11] Lyases constitute a group of enzymes that catalyze chain cleavage of hydroperoxides and formation of two short-chain aldehyde fragments.[12] The aldehydes can be further metabolized by reduction into alcohols, and, in the case of β,γ-unsaturated aldehydes, by isomerization of the double bond to produce the corresponding α,β-unsaturated compounds. The mixture of aldehydes and alcohols thus produced is responsible for the odour of green leaves (cf. the odour of cut grass). Reduction of the hydroperoxide group into the corresponding alcohol occurs in the presence of the enzyme peroxygenase.[13] A co-substrate which accepts the terminal hydroperoxide oxygen is necessary for this reaction. Hitherto identified co-substrates include certain aromatic compounds, which are hydroxylated,[13] sulfides, which are converted to sulfoxides,[14] and cis- unsaturated fatty acids, which are epoxidized.[15,16] Finally, hydroperoxide isomerases, the topic of the present review, catalyze rearrangement of fatty-acid hydroperoxides without a net change of state of oxidation. Two classes of hydroperoxide isomerases, i.e. epoxy alcohol synthase and vicinal diol synthases, have been recognized so far in tissues of plants and fungi.

Epoxy alcohol synthase

The primitive fungus *Saprolegnia parasitica*, a fish parasite, contains an enzyme system for sequential degrada-

tion of polyunsaturated fatty acids into allylic epoxy alcohols.[17,18] Two enzymes were responsible for the transformation, i.e. an ω6-lipoxygenase and an epoxy alcohol synthase. The first-mentioned enzyme catalyzed oxygenation of arachidonic acid into 15(S)-hydroperoxy-5(Z),8(Z),11(Z),13(E)-eicosatetraenoic acid, while the latter enzyme catalyzed conversion of the hydroperoxide into a mixture of the two epoxy alcohols 13(R),14(R)-epoxy-15(S)-hydroxy-5(Z),8(Z),11(Z)-eicosatrienoic acid and 11(S),12(R)-epoxy-15(S)-hydroxy-5(Z),8(Z),13(E)-eicosatrienoic acid. In the same way, linoleic acid was oxygenated to 13(S)-hydroperoxy-9(Z),11(E)-octadecadienoic acid (1), which was isomerized into the α,β-epoxy alcohol 11(R),12(R)-epoxy-13(S)-hydroxy-9(Z)-octadecenoic acid (2) and the γ,δ-epoxy alcohol 9(S),10(R)-epoxy-13(S)-hydroxy-11(E)-octadecenoic acid (3)[19] (Fig. 2). Studies using various isomeric fatty acid hydroperoxides as substrates showed that the epoxidation proceeded with retention of geometrical configuration, i.e. epoxidations of the α,β(E) and γ,δ(Z) double bonds yielded *trans* and *cis* epoxides, respectively. Furthermore, experiments with chemically prepared unnatural hydroperoxides, such as linoleic acid 13(R)-hydroperoxide, showed that the configuration of the epoxide group introduced did not have any relation to the configuration of the hydroperoxide group of the substrate but was solely dictated by the epoxy alcohol synthase. Thus a consistent pattern of absolute configurations of epoxy alcohols was observed, i.e. α(R),β(R) for the α,β-epoxy alcohols and γ(R),δ(S) for the γ,δ-epoxy alcohols.

Incubation of $^{18}O_2$-labelled arachidonic acid 15(S)-hydroperoxide with epoxy alcohol synthase resulted in the formation of epoxy alcohols that retained both atoms of
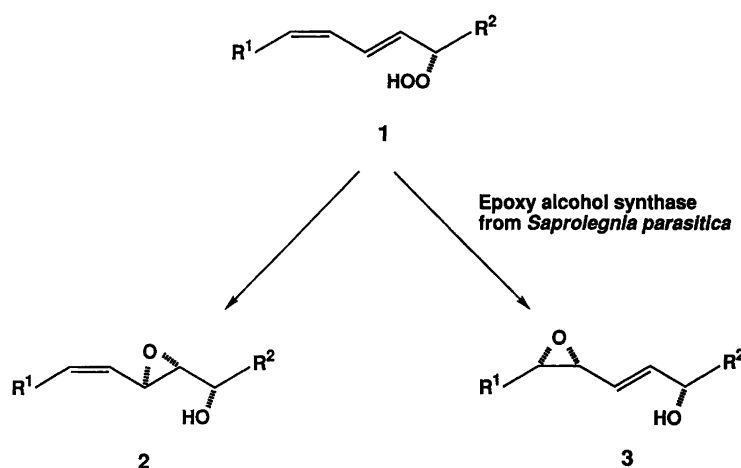
Fig. 2. Biosynthesis of epoxy alcohols in *Saprolegnia parasitica*. **1**, 13(S)-Hydroperoxy-9(Z),11(E)-octadecadienoic acid; **2**, 11(R),12(R)-epoxy-13(S)-hydroxy-9(Z)-octadecenoic acid; **3**, 9(S),10(R)-epoxy-13(S)-hydroxy-11(E)-octadecenoic acid. $R^1 = (CH_2)_7-COOH$, $R^2 = (CH_2)_4-CH_3$.

^{18}O. Furthermore, incubation of mixtures of $^{18}O_2$-labelled and unlabelled hydroperoxide resulted in the formation of two isotopic species of epoxy alcohols, i.e. doubly ^{18}O-labelled and unlabelled. The amounts of singly ^{18}O-labelled epoxy alcohols were negligible. This result showed that the terminal hydroperoxide oxygen was utilized by the synthase for intramolecular epoxidation of either of the two conjugated double bonds of the hydroperoxide. As shown in Fig. 3, it is proposed that the enzymatic hydroperoxide (**1**) → epoxy alcohol (**3**) transformation involves initial formation of enzyme-bound hydroxy acid (**4**) plus oxidized enzyme, followed by transfer of oxygen to either the (E) double bond or the (Z) double bond of the enzyme-bound hydroxy acid. It seems likely that the oxygen-binding ligand ('X' in Fig. 3) is a transition metal, possibly heme iron.

Conversion of hydroperoxides into epoxy alcohols in the presence of vanadyl acetylacetonate was examined as a chemical model for epoxy alcohol synthase of *S. para-*

sitica.[20] In these studies, treatment of the methyl ester of linoleic acid 13(S)-hydroperoxide with a catalytic amount of vanadyl acetylacetonate in hexane afforded a 1:1 mixture of diastereomeric α,β-epoxy alcohols in high yield, i.e. methyl 11(R),12(R)-epoxy-13(S)-hydroxy-9(Z)-octadecenoate (methyl ester of **2**; *threo* epoxy alcohol; 42% yield) and methyl 11(S),12(S)-epoxy-13(S)-hydroxy-9(Z)-octadecenoate (*erythro* epoxy alcohol; 42% yield). Formation of γ,δ-epoxy alcohol, corresponding to **3**, was not observed. ^{18}O studies revealed that epoxy alcohol formation in this system occurred by intermolecular epoxidation.

Epoxy alcohols such as **2** and **3** (Fig. 2), both of which contain an allylic epoxide group, are rapidly hydrolyzed at weakly acidic pH. For example, their half lives in water at pH 3 at 23 °C were 1–2 min.[17] The resulting product was a mixture of isomeric trihydroxy derivatives. Methods for regio- and stereochemical analysis of such trihydroxy acids have been developed.[21] Applying these tech-
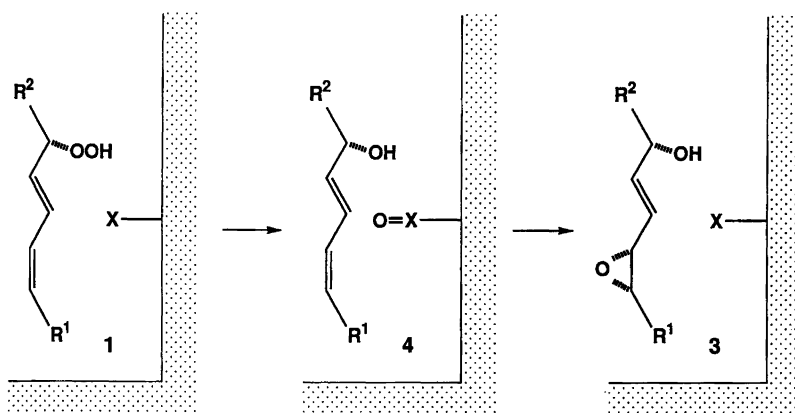
Fig. 3. Proposed mechanism of formation of epoxy alcohols by *vicinal* diol synthase from *Saprolegnia parasitica*. **1**, 13(S)-Hydroperoxy-9(Z),11(E)-octadecadienoic acid; **4**, 13(S)-hydroxy-9(Z),11(E)-octadecadienoic acid; **3**, 9(S),10(R)-epoxy-13(S)-hydroxy-11(E)-octadecenoic acid. $R^1 = (CH_2)_7-COOH$, $R^2 = (CH_2)_4-CH_3$.
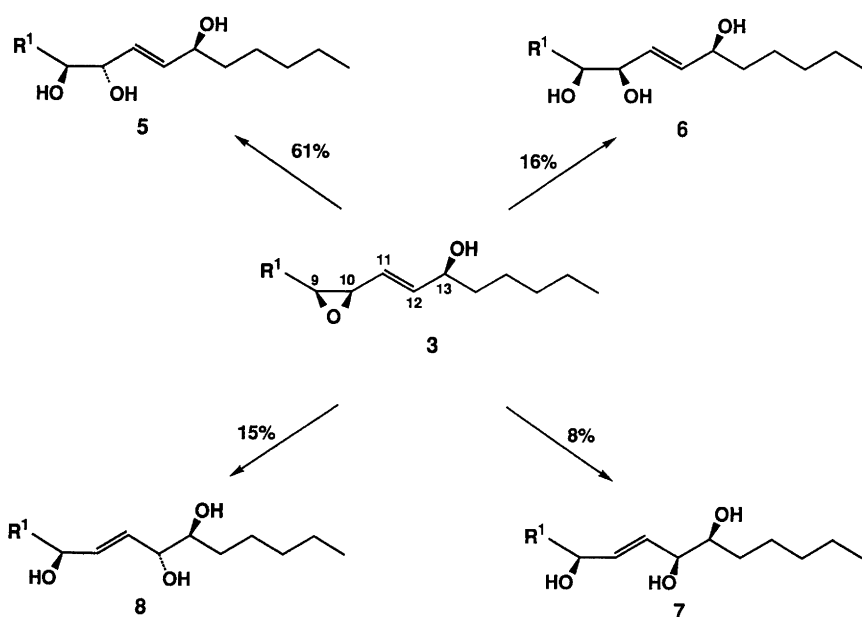
Fig. 4. Hydrolysis of epoxy alcohol **3** into isomeric trihydroxyoctadecenoic acids. **3**, 9(S),10(R)-Epoxy-13(S)-hydroxy-11(E)-octadecenoic acid; **5**, 9(S),10(S),13(S)-trihydroxy-11(E)-octadecenoic acid; **6**, 9(S),10(R),13(S)-trihydroxy-11(E)-octadecenoic acid; **7**, 9(S),12(S),13(S)-trihydroxy-10(E)-octadecenoic acid; **8**, 9(S),12(R),13(S)-trihydroxy-10(E)-octadecenoic acid. $R^1 = (CH_2)_7$–COOH.

niques to trihydroxy acids formed from epoxy alcohol **3** demonstrated that hydrolysis mainly (61%) occurred at the allylic epoxide carbon (C-10) with inversion of configuration. In addition, hydrolysis occurred by solvent attack at C-10 with retention of configuration (16%) as well as by attack at C-12 with isomerization of the double bond into the Δ^{10} position and opening of the epoxide function (Fig. 4). Interestingly, solvent attack at C-12 did not occur to the same extent from the two sides of the plane of the Δ^{11} double bond. It may be speculated that water molecules above the plane of the double bond (Fig. 4) were less reactive in attacking C-12 because of hydrogen bonding to the C-13 hydroxyl group. Epoxy alcohols can also be hydrolyzed enzymatically. Thus, we have recently identified an epoxy alcohol hydrolase from oat seed that catalyzes regio- and stereospecific hydrolysis of epoxy alcohol **3** to produce trihydroxyocta-decenoic acid **5** as the only product.[22]

Vicinal diol synthases

Vicinal *diol synthase from* Gracilariopsis lemaneiformis. Two *vicinal* dihydroxy fatty acids, i.e. 12(R),13(S)-di-hydroxy-5(Z),8(Z),10(E),14(Z)-eicosatetraenoic acid and 12(R),13(S)-dihydroxy-5(Z),8(Z),10(E),14(Z),17(Z)-eicosapentaenoic acid, related to arachidonic acid and eicosapentaenoic acid, respectively, have been isolated from the marine red alga *Gracilariopsis lemaneiformis.*[23] Experiments with an acetone powder preparation[24] and with fractionated homogenates of the alga[25] have clarified the mode of formation of these diols. Two enzyme ac-

tivities were involved, i.e. an arachidonic acid 12-lipoxy-genase and a *vicinal* diol synthase.

The lipoxygenase was a 84–89 kDa protein that catalyzed oxygenation of arachidonic acid into arachidonic acid 12(S)-hydroperoxide. Other polyunsaturated fatty acids were also oxygenated, e.g. 6,9,12-octadecatrienoic acid (**9**) to provide the corresponding 10(S)-hydroperoxy-derivative (**10**) (Fig. 5). The stereochemistry of the algal lipoxygenase reaction, as determined by experiments using stereospecifically deuteriated **9**, consisted of abstraction of the *pro-R* hydrogen from C-8 and insertion of oxygen at C-10 to provide the 10(S)-hydroperoxide **10** (Fig. 5). Thus there was an antarafacial relationship between hydrogen abstraction and oxygen insertion, in agreement with previous results obtained with plant and animal lipoxygenases.[1] In fact, the steric course of oxygenation catalyzed by algal 12-lipoxygenase was identical to that catalyzed by arachidonic acid 12-lipoxygenase from human platelets.[26] Interestingly, in contrast to mammalian 12-lipoxygenases, the algal enzyme required Na^+ for its catalytic activity. Thus, the activity of desalted algal 12-lipoxygenase was only ca. 5% of that of enzyme assayed in the presence of 0.8–1 M NaCl. Li^+ and Mg^{2+} had about 50 and 10%, respectively, of the stimulatory activity compared to that of Na^+, whereas other uni- and divalent cations were inactive.

The *vicinal* diol synthase was equally distributed between the soluble fraction and the 105 000 g particulate fraction of homogenate of *G. lemaneiformis*. Upon gel filtration, the soluble synthase separated into two peaks of enzyme activity, corresponding to proteins having molecular weights of 40–45 and >220 kDa. These two
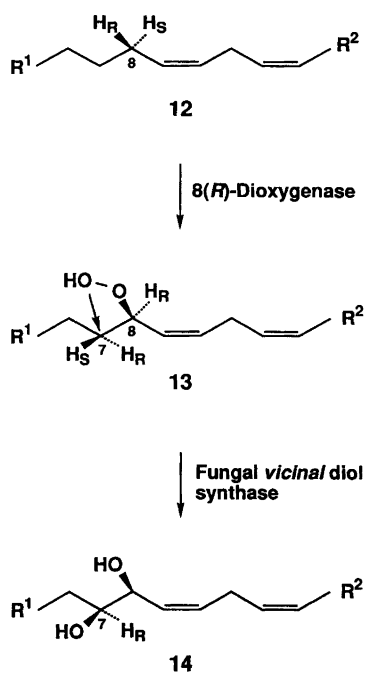
Fig. 5. Steric courses of lipoxygenase and *vicinal* diol synthase reactions in *Gracilariopsis lemaneiformis*. **9**, 6,9,12-Octadecatrienoic acid; **10**, 10(*S*)-hydroperoxy-6(*Z*),8(*E*),12(*Z*)-octadecatrienoic acid; **11**, 10(*R*),11(*S*)-dihydroxy-6(*Z*),8(*E*),12(*Z*)-octadecatrienoic acid.

forms of the synthase (probably monomeric and polymeric forms), as well as the particle-bound synthase, catalyzed the same reaction, i.e. conversion of arachidonic acid 12(*S*)-hydroperoxide into 12(*R*),13(*S*)-dihydroxy-5(*Z*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoic acid. 10(*S*)-Hydroperoxy-6(*Z*),8(*E*),12(*Z*)-octadecatrienoic acid (**10**) was isomerized in an analogous way to provide 10(*R*),11(*S*)-dihydroxy-6(*Z*),8(*E*),12(*Z*)-octadecatrienoic acid (**11**) (Fig. 5). Additionally, the enzyme catalyzed isomerization of linoleic acid 9(*S*)- and 13(*S*)-hydroperoxides into 8(*S*),9(*R*)-dihydroxyoctadecadienoic acid and 13(*R*),14(*S*)-dihydroxyoctadecadienoic acid, respectively. The 'unnatural' hydroperoxide, linoleic acid 13(*R*)-hydroperoxide, was also isomerized and provided 13(*S*),14(*S*)-dihydroxyoctadecadienoic acid. On the other hand, the two monounsaturated hydroperoxides 9-hydroperoxy-10(*E*)-octadecenoic acid and 10-hydroperoxy-8(*E*)-octadecenoic acid did not serve as substrates for the synthase.[27] From these results it was obvious that the *vicinal* diol synthase-catalyzed reaction occurred with a large number of fatty acid hydroperoxides possessing the 1-hydroperoxy-2(*E*),4(*Z*)-pentadiene moiety. Notably, the absolute configuration of the hydroxyl group introduced was invariably '*S*', regardless of the position and configuration of the hydroperoxy group of the substrate.

Experiments with ^{18}O-labelled linoleic acid 13(*S*)-hydroperoxide demonstrated that the hydroperoxide → diol conversion was strictly intramolecular. Further experiments with **10**, stereospecifically deuteriated at C-11, showed that the *vicinal* diol synthase-catalyzed hydroxylation occurred with stereospecific elimination of the

pro-S hydrogen from the methylene group α to the hydroperoxy group. Thus, the intramolecular hydroxylation catalyzed by *vicinal* diol synthase proceeded with retention of absolute configuration (Fig. 5).

The mechanism proposed for the transformation catalyzed by algal *vicinal* diol synthase was analogous to that catalyzed by epoxy alcohol synthase (Fig. 3), i.e. initial formation of enzyme-bound hydroxy acid plus oxidized enzyme followed by oxygen rebound to produce dihydroxy acid and the native enzyme as shown in eqn. (1).

Hydroperoxy acid + Enz-X → [Hydroxy acid····Enz-X = O] →

Dihydroxy acid + Enz-X   (1)

Vicinal *diol synthase from* Gaeumannomyces graminis. The fungus *Gaeumannomyces graminis* is a cereal parasite which causes the so-called 'take-all' disease of wheat. In an early study, it was observed that preparations of this fungus catalyzed hydroxylation of arachidonic acid into a mixture of 18- and 19-hydroxyarachidonic acids.[28] More recently, fatty-acid oxygenation in *G. graminis* was re-examined using linoleic acid and other C_{18} fatty acids as substrates.[2,29] When incubated with cell-free preparations of mycelia of the fungus, linoleic acid (**12**) was converted into 8(*R*)-hydroxylinoleic acid and 7(*S*),8(*S*)-dihydroxylinoleic acid (**14**) as the main products. In addition, smaller amounts of 8(*R*)-hydroperoxylinoleic acid (**13**) were isolated (Fig. 6). Studies on the mode of formation of **13** and **14** revealed the presence in *G. graminis* of a novel fatty acid dioxygenase, provisionally designated linoleic acid 8(*R*)-dioxygenase, as well as a *vicinal* diol synthase. The two enzyme activities were separable by differential centrifugation of the mycelial homogenate; however, their molecular properties have not yet been determined.

The 8(*R*)-dioxygenase catalyzed oxygenation of linoleic acid into 8(*R*)-hydroperoxylinoleic acid, a reaction which consisted of hydrogen abstraction at C-8 and insertion of dioxygen at the same carbon atom. Oleic and α-linolenic acids were similarly oxygenated into 8-hydroperoxy derivatives. The 8(*R*)-dioxygenase-catalyzed reaction differed from the lipoxygenase reaction in several respects, the most striking one being the fact that the 8(*R*)-dioxygenase reaction involved abstraction of an allylic hydrogen (C–H bond dissociation energy, ca. 88 kcal mol^{-1}) rather than a bis-allylic hydrogen (C–H bond dissociation energy, 75–80 kcal mol^{-1}). Experiments with **12**, stereospecifically deuteriated at C-8, demonstrated that the *pro-S* hydrogen was selectively eliminated during the conversion,[30] i.e. the oxygenation proceeded with inversion of absolute configuration at C-8 (Fig. 6).

The *vicinal* diol synthase of *G. graminis* catalyzed isomerization of 8(*R*)-hydroperoxylinoleic acid into 7(*S*),8(*S*)-dihydroxylinoleic acid. 8-Hydroperoxyoleic acid and 8-hydroperoxy-α-linolenic acid were converted in an analogous way into 7,8-diol derivatives. [18]O studies demonstrated that the conversion was strictly intramo-

Fig. 6. Steric courses of 8(R)-dioxygenase and vicinal diol synthase reactions in Gaeumannomyces graminis. 12, Linoleic acid; 13, 8(R)-hydroperoxylinoleic acid; 14, 7(S),8(S)-dihydroxylinoleic acid. $R^1 = (CH_2)_4-COOH$, $R^2 = (CH_2)_4-CH_3$.

lecular,[2] and experiments with 13, stereospecifically deuteriated at C-7, revealed that the hydroxylation at C-7 occurred with retention of absolute configuration[30] (Fig. 6). Vicinal diol synthases from the fungus G. graminis and the red alga G. lemaneiformis both catalyzed conversion of hydroperoxides into vicinal diols by intramolecular hydroxylation of the methylene group α to the hydroperoxide; however, that the two enzymes were not identical was indicated by, e.g., the finding that the algal enzyme did not catalyze conversion of monounsaturated hydroperoxides.

Conclusion

Epoxy alcohol synthase from S. parasitica and vicinal diol synthases from G. lemaneiformis and G. graminis are hydroperoxide-metabolizing enzymes which have formal similarities to cytochrome P-450 in catalyzing double-bond epoxidation with retention of geometrical configuration, and hydroxylation at aliphatic carbon occurring with retention of absolute configuration. Future research is needed in order to establish whether the epoxy alcohol synthase and the vicinal diol synthases of the present review are P-450 proteins. It is noteworthy that two important prostaglandin endoperoxide-metabolizing enzymes in mammalian tissue, i.e. thromboxane A synthase[31] and prostaglandin I synthase,[32] as well as a fatty-acid hydroperoxide-metabolizing enzyme in plant tissue, i.e. allene oxide synthase,[9] belong to the cytochrome

P-450 family. In addition, peroxygenase[13] and fatty-acid hydroperoxide lyase[33] have been found to be heme proteins.

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