



FIGURE 4.5

Phospholipid peroxidation by hydroxyl radicals.

phase). If traces of cations such as  $\text{Fe}^{2+}$  are present, they can generate new oxygen radicals ( $\text{RO}\cdot$  and  $\text{HO}\cdot$ ) from hydroperoxides **4.3** through Fenton chemistry, contributing to the extension of the peroxidation process (Figure 4.5).

## 2.2 MALONDIALDEHYDE GENERATION AND ITS CONSEQUENCES

Peroxy radicals **4.2** can also evolve to cyclic endoperoxides by attack onto a neighboring carbon-carbon double bond in the same chain in a process resembling the one catalyzed by cyclooxygenase, as shown in Figure 4.6 for the case of a molecule of arachidonic acid. Peroxy radicals **4.2** may lead to lipid peroxidation, as previously mentioned (see Section 2.1). Alternatively, they can cyclize to radical **4.4**, which then undergoes a new cyclization, coupled with the addition a second oxygen molecule and subsequent reduction of the hydroperoxyl radical thus generated, to give **4.5**. Together with other products, these intermediates generate malondialdehyde (MDA) through a retro Diels-Alder mechanism.

MDA can link covalently to amino groups in proteins, especially at Lys residues, resulting in intra- and intermolecular protein cross-links (Figure 4.7a). It may also react with DNA bases and cause mutagenic lesions, consisting of large insertions and deletions at GC base pairs, by reaction with guanine amino groups to give the oxopropenyl derivatives **4.6**, which are finally cyclized to