stress situations derived from exposure to toxic agents, damage due to radiation, and a variety of diseases, resulting in adaptive responses associated with local oxidative stress.

Oxidative stress can be defined as a situation of imbalance between the production of radical species and antioxidant defense systems in the cell. Oxidative stress can cause damage to all kinds of biomolecules, including lipids, proteins, and DNA. For this reason, the mechanism of action of several kinds of antitumor agents is based, at least partly, on the production of hydroxyl radicals and other ROS and the subsequent damages that they cause on biological molecules by a number of mechanisms that are summarized in this section.[1,2] Most of these mechanisms have been discovered during the course of studies on the anthracyclines.[3] On the other hand, there is an increasing body of evidence showing that ROS can directly interact with crucial signaling molecules essential for cell proliferation and survival and can therefore be viewed as critical for cellular signaling.[4]

2.1 MEMBRANE PHOSPHOLIPID PEROXIDATION

Cell membranes are one of the biological structures more sensitive to damage by radicals because of the presence in them of polyunsaturated fatty acids (PUFAs) containing methylene groups that are simultaneously adjacent to two double bonds. The C–H units in these methylenes are particularly suitable points of attack by hydroxyl and other radicals because of the stabilization of the resulting carbon radical by double resonance (Figure 4.4).

The reaction of these polyunsaturated side chains with oxygen radicals leads to *phospholipid peroxidation* and subsequent membrane injury. This process is initiated by the attack of a hydroxyl radical to one of the previously mentioned bis-allylic positions existing in the fatty acid side chains, leading to the generation of an alkyl radical **4.1**. Superoxide radical is not sufficiently reactive to initiate lipid peroxidation, and in any case its negative charge precludes its transport across the highly lipophillic cell membrane. Carbon radical **4.1** reacts rapidly with a molecule of oxygen, which is sufficiently hydrophobic to access the interior of the membranes, generating a peroxyl radical (R–O–O$^{\cdot}$, **4.2**), which can abstract a new hydrogen atom from a doubly allylic C–H bond in the adjacent fatty acid side chain. This leads to a hydroperoxide **4.3** and a new radical **4.1**, allowing a self-maintained radical process that extends to an expanding area of the membrane, as long as there is sufficient oxygen (propagation

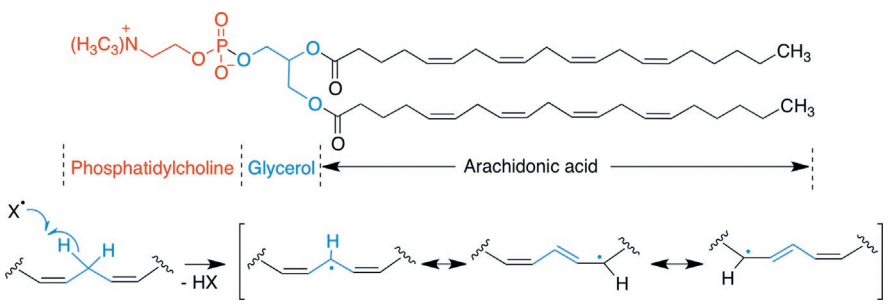

FIGURE 4.4

Radical generation in membrane phospholipids.