pyrimidopurine derivatives **4.7**, known as M_1dG adducts (Figure 4.7b).[5] The implication of MDA-induced DNA damage in the antitumor effects of radical-generating drugs such as the anthracyclines has been clearly established.[6] In proliferating cells, the formation of M_1dG adducts is accompanied by cell cycle arrest and inhibition of cyclin-associated kinase activities. It has been proven that antitumor compounds of the anthracyclin group, at low concentrations, increase MDA-dependent DNA oxopropenylation several-fold,[7] establishing a potential link between antitumor drug-dependent generation of ROS, induction of lipid peroxidation, and DNA damage.[8]

In addition to MDA, a number of acrolein derivatives are generated by homolytic cleavage of hydroperoxides derived from PUFAs. These electrophilic species also give DNA adducts, with potential mutagenic consequences.[9]

2.3 DNA STRAND CLEAVAGE

In mammalian cells, the DNA both in the nucleus and in the mitochondria has to be maintained throughout the entire life of the cell. These genomes and their precursor nucleotides are highly exposed to ROS, which are inevitably generated as a result of the respiratory function in mitochondria. Oxidative stress by hydroxyl radical causes direct DNA damage, mainly by strand cleavage, and also causes damage by oxidation of pyrimidine and purine bases.[10]

Because of the negative charge of its phosphate groups, DNA acts as an anion and is therefore capable of binding many cations, including those required for Fenton chemistry such as Fe^{2+} and Cu^{+}. In addition, deoxyribose also has good iron binding properties. This allows “site-specific” hydroxyl radical generation that cannot be countered by radical scavengers. Perhaps for this reason, antitumor compounds that act by DNA strand cleavage are also normally chelating agents.

The main products of DNA strand scission, which have been studied mainly in connection with the mechanism of action of the antitumor drug bleomycin, are free DNA bases and *N*-(3-oxopropenyl) bases, which are accompanied by 5′-phosphate-modified DNA fragments and 3′-phosphoglycolate DNA derivatives (see Figure 4.9). The formation of *N*-(3-oxopropenyl) bases requires additional oxygen,[11] whereas that of free bases does not,[12] as shown by isotope studies with $^{18}O_2$ and $H_2{}^{18}O$.

This process starts by the radical-induced abstraction of a proton from any position of the deoxyribose moiety and can lead to a large number of products. For instance, oxidation at C-4 leads to carbon radical **4.8**, stabilized by resonance with the ring oxygen. Addition of an oxygen molecule gives the sugar peroxyl radicals **4.9**, which are transformed into hydroperoxide **4.10** by incorporation of one proton and one electron. If their source is the desoxyribose unit of another DNA molecule, the radical process becomes self-maintained, as shown in Figure 4.8.

One possible degradation pathway for the hydroperoxides that explains some of the products observed in the presence of additional oxygen involves a ring expansion through a modified Crigee rearrangement, where isotope studies with $^{18}O_2$ and $H_2{}^{18}O$ prove that hydroxide is released from **4.10**.[7] The stabilized cation **4.11** resulting from the rearrangement undergoes an elimination reaction to **4.12**, which is subsequently decomposed to the observed fragments **4.13**, **4.16**, and **4.17**. The last two species come from **4.14** and **4.15** by the mechanism shown in Figure 4.9.

Fragments **4.17** are known as base propenals and can serve as precursors to the mutagenic M_1dG adducts previously discussed as arising from MDA, as shown in Figure 4.10.[13]

The liberation of DNA bases in this pathway can be explained by the mechanism shown in Figure 4.11, in which the 4′-radical **4.8** evolves to the oxonium cation **4.18** by one-electron oxidation.