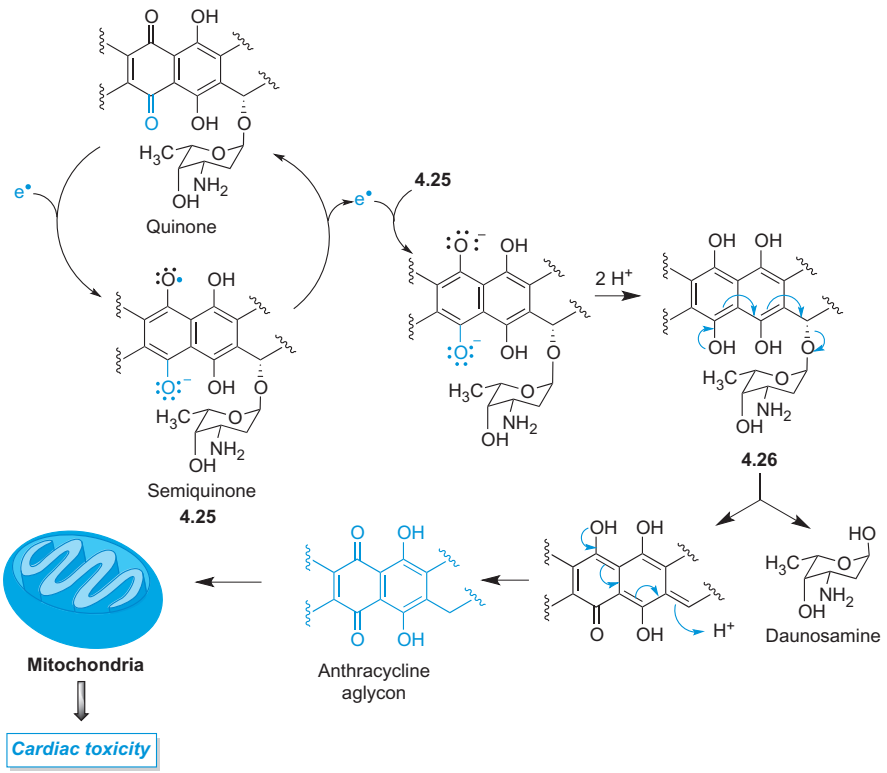

FIGURE 4.17

Elimination of the sugar moiety from anthracyclines and its role in anthracycline cardiotoxicity.

aglycons tend to accumulate in the inner mitochondrial membrane. The oxidative deterioration of mitochondrial functions due to the formation of radicals from these aglycons is one of the factors responsible for the cardiomyopathy associated with the use of anthacyclines.[20]

Another important chemical property of the anthracyclines relevant to their antitumor activity is their chelating ability, due to the presence of β-hydroxycarbonyl moieties in their structure, especially at the C-11 and C-12 positions.[32] Probably due to ionic interactions with the phosphate groups, the anthracycline–Fe^{3+} chelate binds to DNA much more tightly than the anthracycline itself and can then generate Fe^{2+} by reaction with superoxide anion. As previously mentioned, Fe^{2+} cations thus generated *in situ* can form hydroxyl radicals through their Fenton reaction with hydrogen peroxide (Figure 4.18). The high efficiency of DNA fragmentation by these hydroxyl radicals is reflected in the routine use of the Fenton reaction in DNA footprinting, a technique that fragments DNA indiscriminately and allows the determination of where DNA–protein interactions take place.[33]

Anthracyclines also induce a severe dysregulation of iron homeostasis, possibly mediated by the release of iron from intracellular stores. This helps to explain why the Fenton reaction takes place despite the fact that cells normally have very little or no free iron available,[34] and it is also very important in explaining the cumulative cardiotoxicity of the anthracyclines. The main target responsible for this dysregulation of iron homeostasis by the anthracyclines seems to be aconitase, a Krebs cycle enzyme