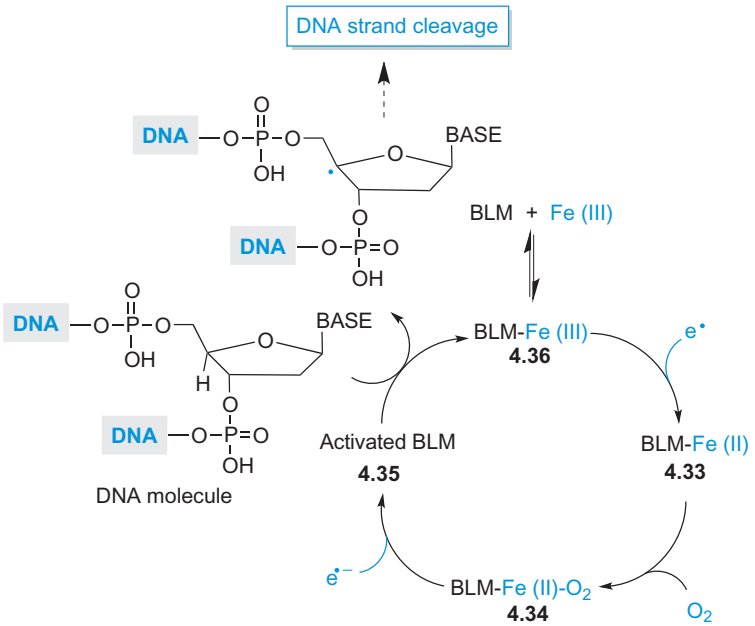

FIGURE 4.28

Redox cycling of bleomycin.

Alternatively, the O–O bond in **4.37** could be homolytically cleaved, giving the bleomycin–Fe(IV)=O species **4.39** and a hydroxyl radical, any of which can abstract the DNA 4′-hydrogen (Figure 4.30). A concerted reaction of **4.37** with DNA with concomitant O–O bond homolysis to give **4.39** is also possible.[88]

The bleomycin molecule can be viewed as finely tuned for its function, and its various structural portions act synergistically to effect efficient DNA cleavage, with the roles summarized in Figure 4.31.[89] The bleomycin–iron complex is formed at the metal binding domain, comprising the β-aminoalanine–pyrimidine–β-hydroxyhistidine moiety. This portion of the molecule contains five nitrogen atoms at a distance suitable to form a stable chelate with Fe(II), leaving a sixth coordination valence available for a molecule of oxygen. The mode of interaction of the bleomycins with DNA involves two types of interactions, one of which is electrostatic binding of the cationic or protonated amino side chain with DNA phosphate groups, as proven by the observation that non-basic side chains, although more easily transported into the cells, are much less active. The role of the bisthiazole system in DNA interaction has also been thoroughly studied, and two binding modes seem possible, namely intercalation and binding into the minor groove. Because DNA strand scission starts by abstraction of the deoxyribose 4′-hydrogen, which lies in the minor groove, it seems likely that bleomycin binds there, but intercalation has also been proven by the lengthening of linear DNA or the uncoiling of circular DNA.[90] Bleomycin shows selectivity toward 5′-GC-3′ and 5′-GT-3′ sequences because of hydrogen bonding recognition of either the bithiazole unit or the aminopyrimidine function.[91,92] Finally, the sugar moiety may be responsible for the uptake of the drug into