spermine and other polyamines by neutrophile-generated ROS.[75] Although mitoxantrone can be reductively activated to a semiquinone free radical, this process has a low efficiency and the compound undergoes less redox cycling *in vitro* than the anthracyclines.[76] The formation of adducts of formaldehyde-activated mitoxantrone occurs preferently at CpG and CpA sequences, and it is stimulated by cytosine methylation.[77] Thus, the reaction of mitoxantrone with formaldehyde leads to the hydroxymethyl derivative **4.30**, which forms a covalent bond with a guanine amino group to give the covalent adduct **4.32**, presumably through iminium cation **4.31** as an intermediate. The involvement of a single covalent bond has been proved by mass spectrometry, and further stabilization of the complex by hydrogen bonding has been suggested on the basis of molecular modeling studies (Figure 4.25).[78] PIM1 kinase has been identified as a new target for mitoxanthrone that might contribute to its anticancer activity.[79]

Heteroanalogs of mitoxantrone, such as pixantrone, act primarily as topoisomerase II inhibitors and are discussed in Chapter 7.

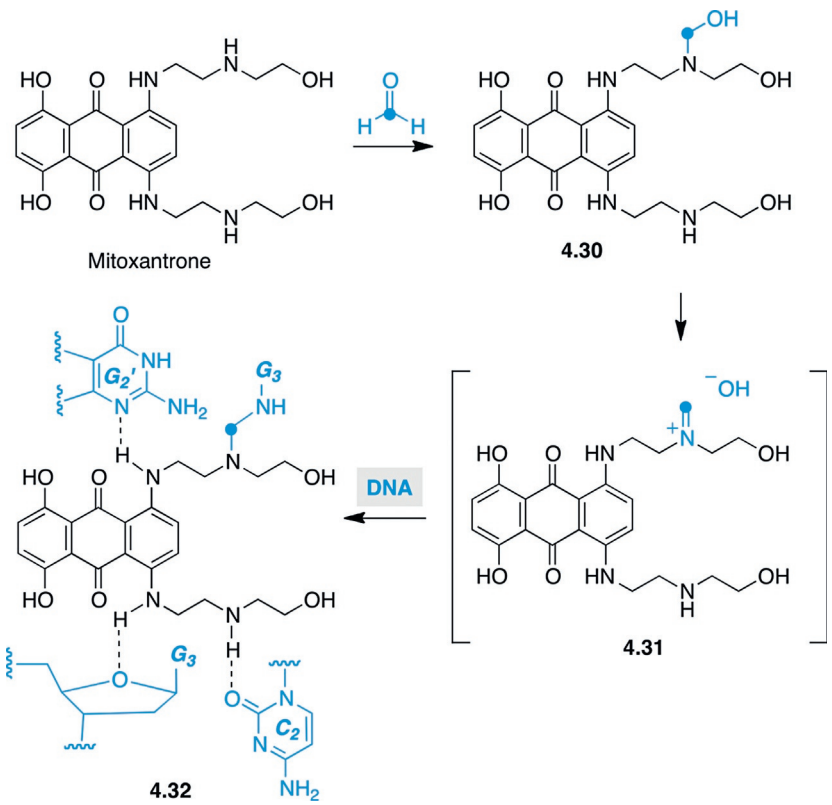

FIGURE 4.25

Adducts of DNA with formaldehyde-activated mitoxantrone.