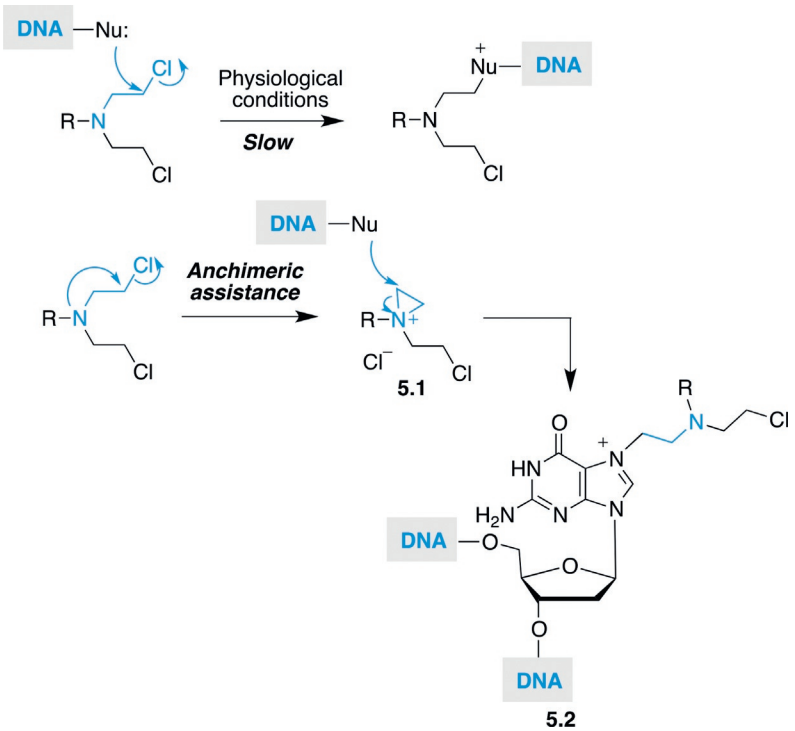
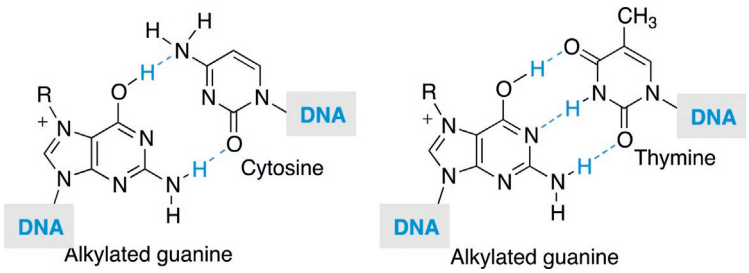


FIGURE 5.2

Mechanism of DNA alkylation by nitrogen mustards.

As a consequence, hydrogen bonding with cytosine is weakened because only two bonds can be established at best, whereas pairing of the 6-hydroxy species with thymine leads to a more stable complex (three hydrogen bonds). The normal pairing is altered to guanine–thymine, leading to mutations.



Another consequence of guanine alkylation is an increase in the electrophilicity of positions adjacent or conjugated to the positive charge at N-7, which leads to several hydrolytic reactions that alter the DNA structure. Thus, cleavage of the heteroside bond in structure **5.2**, although slow,[9] induces DNA depurination to give **5.3**. This structure is in equilibrium with the open form **5.4**, which has a good leaving