

FIGURE 6.20

Hydrogen bonds (HB) involved in the recognition of trabectedin by the DNA minor groove. The arrows are oriented from hydrogen donor to hydrogen acceptor groups.

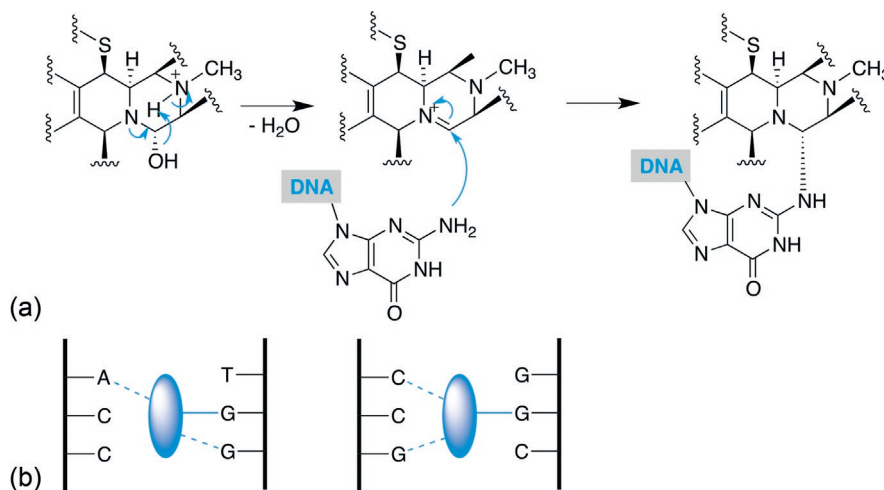


FIGURE 6.21

(a) DNA alkylation by trabectedin. (b) Interstrand "cross-linking" by trabectedin, involving a combination of covalent bonds and hydrogen binding.

at the 5'-AGC target sequence where the covalent linkage is less accessible to attack by a water molecule. In the case of trabectedin-AGT adducts, the complex is less stable and has more dynamic motion, leading to a higher conformational flexibility that renders it more accessible to solvation, with the consequent increase in the rate of the reverse reaction, as shown in Figure 6.22. In summary, the site selectivity of trabectedin depends on the rate of reversibility of the covalent adducts and not on the rate of the covalent bond-forming reaction.

The mechanism of action of trabectedin and related compounds is complex, and indeed they can be viewed as multitarget drugs.⁷² X-ray crystallography and NMR studies, supported by computational