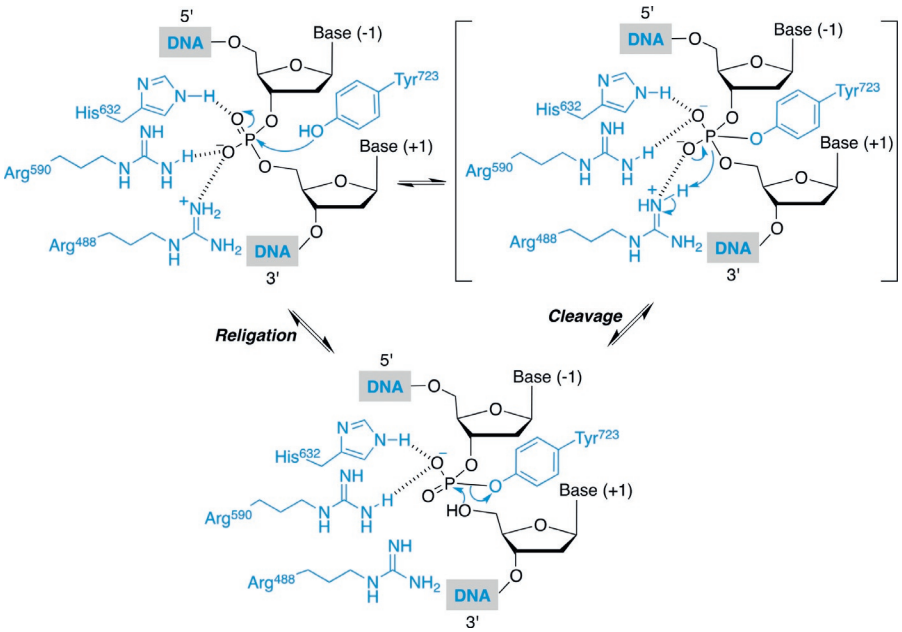

FIGURE 7.9

The catalytic cycle of topoisomerase Ib.

The cytotoxicity of Top1 inhibitors is due to trapping of cleavable complexes (Top1cc) rather than to the inhibition of Top1 catalytic activity, because the cleavable complexes lead to DNA damage by DNA replication and transcription. This trapping takes place during apoptosis induced by anticancer drugs such as Top1 inhibitors, the Top2 inhibitors etoposide, doxorubicin, and amsacrine, and the tubulin inhibitors vinblastine and taxol, being considered a general process of programmed cell death caused by alterations of the DNA structure induced by caspases and reactive oxygen species.[56]

4.2 TOPOISOMERASE II MECHANISM

Eukariotic Top2 is a homodimeric enzyme that makes a transient DNA double-strand break, where the tyrosines from the active sites of both monomers attack the phosphodiester bond to the 5′ side of the phosphate, leading to a covalent 5′-phosphotyrosyl linkage in each strand. This mechanism is shown in Figure 7.11, in comparison to the one previously described for Top1.

These breaks between the strands are not directly opposite to each other; instead, they are separated by a four-base pair overhang, generating a space through which another region of intact DNA can be passed (Figure 7.12). In other words, in the case of Top2 enzymes, a full DNA duplex, known as the T (transported) strand, goes through the double-strand break made by the enzyme homodimers.

The full catalytic cycle of Top2 is complex and is summarized in Figure 7.13, together with the names of drugs that have steps of this cycle as targets.[57] The enzyme assumes two different