Etoposide (VP-16-213)[154] is used mainly to treat testicular cancer that does not respond to other treatment and as a first-line treatment for small cell lung cancers, but it is also used to treat chorionic carcinomas, Kaposi's sarcoma, lymphomas, and malignant melanomas. A phosphate prodrug of etoposide (Etopophos®) has been used for antibody-directed enzyme prodrug therapy and is discussed in Section 2.4 of Chapter 13.

Initial nuclear magnetic resonance and binding studies of the binary enzyme–etoposide complex coupled with DNA functional studies (DNA cleavage) in the ternary complex suggested that the binding of etoposide to Top2 involved mainly interactions with the A, B, and E rings, whereas interactions with DNA in the ternary complex were due primarily to the D ring, with a contribution from the sugar moiety. Recently, the crystal structure of a large fragment of human Top2b complexed to DNA and to etoposide has been published (Figure 7.24). This study showed the rather different set of interactions depicted in Figure 7.25.[155] In agreement with this mode of binding, removal of the C-4 glycoside has little effect on induced DNA cleavage, and in fact, this group can be replaced by a polyamino side chain (see later discussion of TOP-53 and F14512).

Teniposide (Vumon®) is used less frequently, especially to treat lymphomas. DNA religation inhibition by etoposide seems to be due to inhibition of the release of ADP from the hydrolysis of ATP[156] and to its activation through oxidation–reduction reactions to produce derivatives that bind directly to DNA. It has been shown that the *O*-demethylated metabolite of etoposide **7.10**, which has the same potency as the parent drug, is subsequently oxidized to an *ortho*-quinone metabolite **7.12**, which is also a potent inhibitor of the Top2–DNA cleavable complex.[157] It has been proposed that the presence of free radical intermediates such as semiquinone **7.11** contributes to DNA strand breakage, which seems to be supported by the fact that the 4′-OH group of etoposide is essential for its activity as shown by the inactivity of its 4′-OMe derivative. On the other hand, etoposide is a substrate of myeloperoxidase, an enzyme with tyrosinase activity that catalyzes a one-electron oxidation to form the phenoxyl radical **7.13** (Figure 7.26). However, the formation of radicals **7.11** and

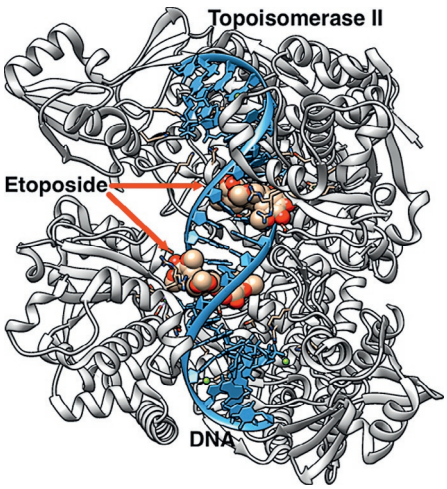

FIGURE 7.24

Structure of the ternary complex formed between human topoisomerase IIβ, DNA, and etoposide.