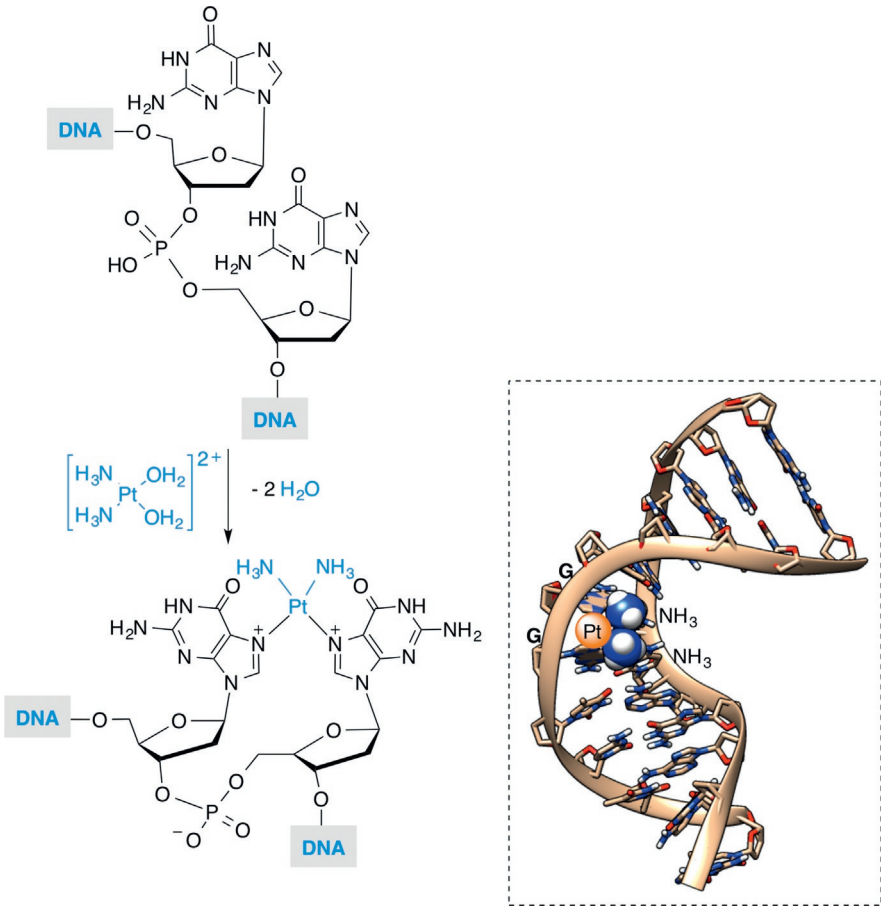

FIGURE 5.40

Reaction between DNA and cisplatin, leading to intrastrand cross-linking. The three-dimensional complex was generated from Protein Data Bank reference 1A84 and displayed with Chimera 1.8.1.

An additional mechanism for prevention of DNA transcription is replacement of Zn by Pt in the zinc-finger protein transcription factor. The existence of the zinc cation is essential to coordinate amino acids of the protein, usually cysteine and histidine, packing together the DNA binding domains into a dense structure. Replacing the zinc ion with platinum disrupts this conformation and binds the zinc finger permanently to DNA–polymerase-α, which is a transcription enzyme vital for cell replication (Figure 5.42). Platinum–DNA adducts also activate other cellular processes that mediate the cytotoxicity of these anticancer drugs.[93] Additional cytotoxicity mechanisms that have been proposed include the interactions of Pt complexes with the cell membrane[94] or with regulatory proteins.[95]

Due to the very high toxicity of cisplatin and the existence of intrinsic or acquired drug-resistance problems, thousands of analogs have been prepared in an effort to improve its selectivity and