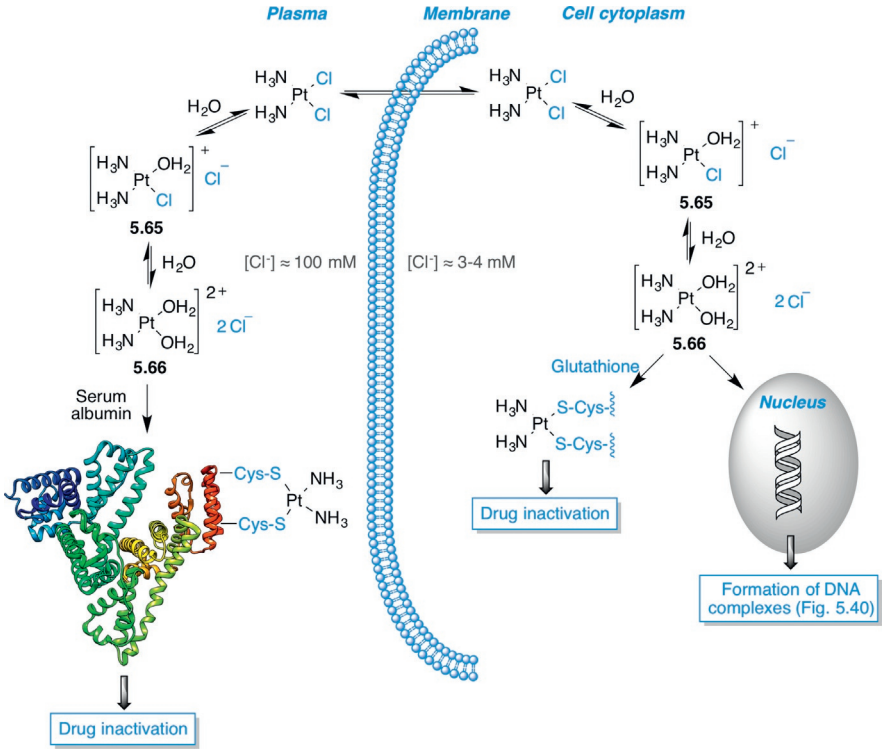

FIGURE 5.39

Intracellular bioactivation of cisplatin.

groups of cysteine residues present in serum albumin and other proteins is estimated to deactivate up to 98% of the drug after its intravenous administration (Figure 5.39).[88]

The active complexes **5.65** and **5.66** enter the nucleus and become attracted by the negatively charged DNA. This electrostatic interaction is followed by complexation with nitrogen atoms of purine bases, normally the N-7 atoms of two vicinal guanine units,[89] that displace the two water molecules leading to intrastrand cross-linking. This reaction deforms the DNA tertiary conformation, as shown by X-ray crystallography, and causes its unwinding at the complexation site (Figure 5.40).[90] As a consequence, high-mobility-group proteins become attached to DNA by intercalation of a phenylalanine unit at the unwound DNA damage site along the widened minor groove, preventing DNA replication.[91] Although, strictly speaking, Pt coordination with DNA bases cannot be considered an alkylation reaction, cisplatin and its analogs are normally studied among the alkylating agents because of the electrophilicity of the active species.

The cisplatin-induced cross-linking can also take place between two opposing DNA strands. In this case, the portion of the DNA double helix close to the coordinating deoxyguanosines is unwound and bent toward the minor groove, together with the *cis*-diammineplatinum (II) fragment, and the complementary deoxycytidines are displaced to an extrahelical arrangement (Figure 5.41).[92]