Certain chemical groups and substituents may greatly affect complex formation. There is, for example, a correlation between solubility and complexing ability of drugs, yet nitro-and amino-groups may alter this relationship (Lach and Pauli 1966). In the case of *p*-nitrophenol, methyl groups in positions 2 and 6 have no significant influence on the stability of the complex, but even one methyl group in the 3-position lowers the stability of the complex by about two orders of magnitude. 3,5-Dimethyl-4-nitrophenol fails to form a complex at all (Szejtli 1982).

The stability of the complex is proportional to the hydrophobic character of the substituents; thus a methyl or ethyl substituent will increase the stability. Hydroxyl groups hinder complex formation, and their hydrophilic effects decrease in the order *ortho* > *meta* > *para*. In the case of amine groups it is important whether they are present in their neutral form or ionized form. Ionic species usually do not form stable complexes (Szejtli 1982).

The importance of optimum matching of the cavity size and ligand size in determining the strength of binding is highlighted by the work of Cromwell et al. (1985). They studied the standard free energy change, ΔG°, and standard enthalpy change, ΔH°, for the interaction of adamantanecarboxylate with three CDs of varying cavity size to characterize structure/energetic relationships for complex formation. β-CD forms the strongest complex with adamantanecarboxylate and the reaction enthalpy change is negative ($\Delta H^\circ = -4.85$ kcal/mol). They interpreted this favorable standard enthalpy change as indicating that the binding forces for this complex include a strong van der Waals interaction, due to the snug fit of adamantanecarboxylate into the β-CD cavity. The binding of adamantanecarboxylate to α-CD, with its smaller cavity, and to γ-CD, with its larger cavity, is poorer (140-fold lower binding constant for α-CD). They also found that the neutral carboxylic acid form of adamantanecarboxylate binds to CD better than does the carboxylate form.

A strong guest-size dependence is found for both the free energy change and enthalpy change for complex formation in a study of the effects of the variation in the size of alicyclic guests on CD inclusion complexation (Eftink et al. 1989). Thermodynamic parameters for the interaction of a congener series of alicyclic acids (e.g., adamantanecarboxylic acid) with α- and β-CDs in aqueous solution were determined. The side chains of these guests are roughly spherical and vary in carbon number from 11 to 5. With β-CD, it was found that 1:1 host:guest inclusion complexes were formed with all the guests at both low and high pH, with strong binding occurring at low pH, where the carboxylic acid forms of the guest predominate. With α-CD, 1:1 complexes are formed with the carboxylate forms of the guests, but 2:1 α-CD:guest complexes were formed, in a cooperative manner, with the carboxylic acid forms of the guests.

Although the neutral form of a drug generally forms a stronger complex with neutral CDs (α-, β-, γ-CD, and HP-β-CD), the effect of charge state of drug molecules on complexation is more complicated for anionic CDs such as SBE-β-CDs. Okimoto et al. (1995) reported that the anionic SBE-β-CD often exhibits 1:1 binding constants with neutral drugs that are comparable to or better than those observed for neutral HP-β-CD. The better binding was believed to be the result of the butyl micellar arms extending the hydrophobic cavity of the CD. For cationic drugs, SBE-β-CD was found to form much more stable complexes than HP-β-CD. For anionic drugs, however, the electrostatic repulsions may significantly affect the complexing ability of these molecules with SBE-β-CDs. The binding constant between the anionic warfarin molecule and SBE-β-CD, for example, is much lower than with HP-β-CD. There are cases, however, where the binding constants between anionic molecules and the anionic SBE-β-CD are almost equivalent to those observed for the neutral HP-β-CD, such as in the case of indomethacin and naproxen. These results suggest that the position of the charge in the drug and how it interacts with the charge in the CD may be important (Thompson 1997).

Although some correlation exists between the binding strength and a guest molecule's structural features or other physicochemical properties, the relationship is limited within certain groups of compounds. Despite some success in predicting binding constants of α-CD from the structures of guest molecules (Connors 1997), so far, no obvious correlation has been found between the physical