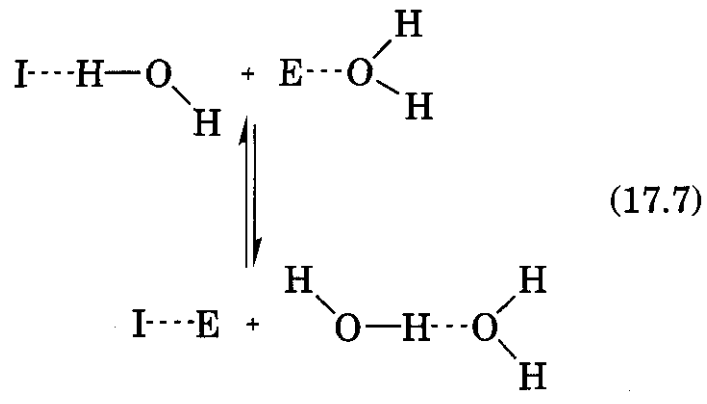
pounds and water. The optimal distance between the atoms is the sum of each of their van der Waals radii, so these forces come into play only when there is good complementarity between enzyme and inhibitor. Although van der Waals forces are quite weak, usually around 0.5-1.0 kcal/mol for an individual atom-atom interaction, they are additive and can make an important contribution to inhibitor binding.

2.1.3 Hydrophobic Interactions. Hydrophobic interactions may be described as entropy-based forces. When a nonpolar compound is dissolved in water, the strong water-water interactions around the solute lead to an effective "ordering" of the structure of the solvent. This is entropically unfavorable; that is, there is negative entropy of dissolution. When a nonpolar inhibitor binds to a nonpolar region of an enzyme, all the ordered water molecules become less ordered as they associate with bulk solvent, leading to an increase in entropy. According to Equation 17.4 any increase in entropy will lead to a decrease in free energy and, through Equation 17.3, stabilization of the enzyme-inhibitor complex. It has been calculated that a single methylene-methylene interaction releases about 0.7 kcdmol of free energy. Even though this figure is not high, given that enzymes and inhibitors usually have large regions of hydrophobic surface, this type of bonding may also play a significant role in inhibitor binding.

2.1.4 Hydrogen Bonds. A hydrogen bond occurs when a proton is shared between two electronegative atoms (i.e., —X—H· · ·Y). Electron density is pulled from the hydrogen by X, giving the hydrogen a partial positive charge that is strongly attracted to the nonbonded electrons of Y. The bond is usually asymmetric, with one of the heteroatoms, the hydrogen bond donor, having a normal covalent bond distance to the proton. The other heteroatom, the hydrogen bond acceptor, is usually at a distance somewhat shorter than the van der Waals contact distance and, for optimal hydrogen bonding, the atoms should be arranged linearly. A hydrogen bond is a special type of dipole-dipole interaction and, as we have seen, although these forces can be quite significant in nonpolar solvents, water greatly diminishes their magnitude. The energy of the amide-amide N H . ·O hydrogen bond is about 5 kcdmol, and is typical for hydrogen bonds (60).

It should be remembered that, for a hydrogen bond to form between an enzyme and an inhibitor, any hydrogen bonds between the inhibitor and water, as well as those between the enzyme and water, must be broken (Equation 17.7).



(17.7)

Overall, the total number of hydrogen bonds remains constant and, provided that the hydrogen bonds between the inhibitor and enzyme are not significantly more favorable than those between water and the inhibitor or those between water and the enzyme, the net change in enthalpy is usually insignificant. On the other hand, formation of the enzyme-inhibitor complex usually leads to an overall increase of entropy because the inhibitor remains bound to the enzyme and the formerly bound water molecules are released.

2.1.5 Cation-π Bonding. Recently it has become apparent that there is another important noncovalent binding force that may be exploited when designing enzyme inhibitors. Cations, from simple ions such as Li^+ to more complex organic molecules such as acetylcholine, are strongly attracted to the electron-rich (π) face of benzene and other aromatic compounds (61, 62). Cation-T bonds, as well as other amino-aromatic interactions, are common in structures in the protein data bank (63), and it has been estimated that more than 25% of tryptophan residues are involved in interactions of this type (64). The finding that the cationic group of acetylcholine was bound primarily by aromatic residues, most especially by a tryptophan residue, not by the ex-