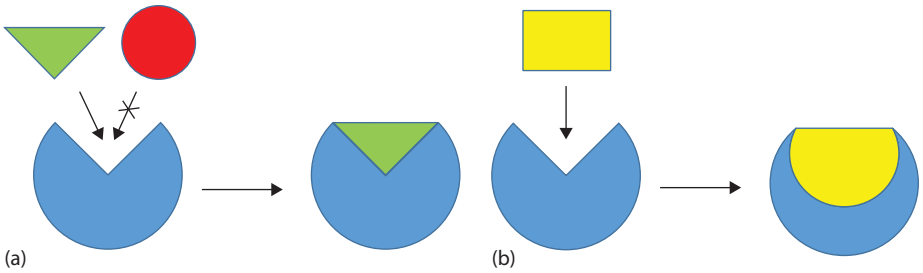

FIGURE 2.1 (a) Lock and key and (b) induced fit hypothesis.

However, one of the limitations of the lock-and-key principle as a general model was its inability to explain why certain inhibitors could block enzyme activity without affecting binding of the substrate and why some enzymes were extremely specific toward their substrate while others were not. To accommodate these scenarios, Daniel E. Koshland in 1958 introduced the "induced fit theory," which is illustrated in Figure 2.1b. In the induced fit model which is often referred to as the "hand in glove" model, the substrate and the enzyme are mutually allowed to adapt to each other upon binding just like the glove changes its conformation when a hand slips into it. The model is in perfect agreement with the notion that small molecules are flexible and can change conformation by rotation around single bonds. Likewise, proteins such as enzymes and receptors are flexible and can adapt to small molecule ligands by changing amino acid side chain conformations or by movement of the protein backbone. Today, the three-dimensional structures of a huge number of proteins have been determined by X-ray crystallography in the presence of different drug molecules. These structures support the induced fit hypothesis which today is generally accepted.

The understanding of molecular recognition and specificity in drug binding has been greatly aided by X-ray crystallographic structures of macromolecules in complex with various ligands. Combined with an understanding of the attractive and repulsive physical forces acting between the two interacting molecules, one can understand molecular recognition and learn how to optimize molecules toward better affinity and specificity. The aim of this chapter is to understand, in terms of basic physical chemistry and examples, the nature and magnitude of molecular interactions. This is one of the most fundamental aspects of medicinal chemistry and will provide a framework for many of the other chapters in this book where affinity, selectivity, and structure–affinity relationships are being discussed.

Throughout this book, protein X-ray structures are referred to by a four-letter code which is the same identifier that is used in the protein data bank (PDB), a repository for experimentally determined structures of protein and protein–ligand complexes. All the structures can be accessed from the web page www.rcsb.org or via apps for mobile devices, e.g., "Pymol" from App Store or "RCSB PDB Mobile" from App Store and Google Play. The apps can be downloaded free of charge, and once installed, you can tap in the four-letter pdb code and the app will automatically download and display a three-dimensional model of the protein complex so you can explore the fascinating world of protein structures on your own.

2.2 DETERMINATION OF AFFINITY

The affinity of a ligand for its receptor is defined as the equilibrium (i.e., the difference in free energy, ΔG) between the bound ligand–protein complex on one side and the "free" unbound ligand and unbound protein on the other as illustrated in Figure 2.2. This means that it is a basic thermodynamic equilibrium that underlies the principles of molecular recognition.