# 2 Molecular Recognition

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## 2.1 INTRODUCTION

Molecular recognition is the foundation for the function of virtually any biological system. It relies on the existence of favorable interactions between two (or more) molecules which could be a neurotransmitter molecule and its protein receptor or an enzyme and its substrate. Recognition of one molecule by another is driven by energetics. If two molecules attract each other, the total free energy of the two molecules and their surroundings will be lower compared to the situation where the two molecules are far apart. Therefore, based on "the lowest potential energy principle," the two molecules will tend to stick together in a noncovalent complex. Understanding the basic principles of noncovalent interactions is essential to understand how biological systems work at the molecular level, and it is a prerequisite for understanding how drugs interact with their target macromolecules and how they obtain selectivity or even specificity. It is also the foundation of "structure-based drug design," a discipline where medicinal chemists seek to optimize the strength of molecular interactions exploiting the knowledge of the three-dimensional structure of the host molecule combined with an understanding of energetic contributions to binding from different parts of the molecules (see Chapter 4).

Molecular recognition is often highly selective and the first attempt to understand this selectivity was made in 1894 by Emil Fisher. Fisher formulated the "lock-and-key principle" (Figure 2.1a) to explain why certain enzymes would only degrade certain substrates. The principle in this hypothesis is that the substrate has to fit like a key in a lock to trigger an enzymatic reaction. The lock-and-key principle was also applied in the broader context of medicinal chemistry, and it makes perfect sense that a drug has to bind to its receptor in order to exert an action—"if it doesn't bind it doesn't work."

* Deceased.