



FIGURE 3.11 (a) Human glyoxalase 1, an enzyme responsible for the production of S-D-lactoylglutathione from the hemithioacetal of methylglyoxal and reduced glutathione, occurs as a dimer of two 183 amino acid residue proteins. An X-ray crystal structure of a monomeric unit bound to S-hexylglutathione is shown. (b) A magnified image of the active site of human glyoxalase 1 bound to S-hexylglutathione is shown. The catalytic site contains a zinc atom that is critical to enzymatic activity (RCSB 1BH5).

between a substrate and the enzyme, while hydrophobic interaction can occur between nonpolar amino acid side chains and nonpolar regions of a substrate molecule. Hydrogen bonds can also be formed between the substrate and the active site amino acids, either through their side chains (e.g., arginine, asparagine, etc.) or with the amide back bone of the protein. Compounds that cannot meet the strict criteria required for binding at the active site of an enzyme cannot be substrates for the enzyme.

The question of how enzymes accelerate chemical reactions has been considered by scientists for over 100 years. Perhaps the earliest hypothesis on enzymatic mechanisms was present by Emil Fischer in 1894. His “lock and key” model (Figure 3.12) proposed that enzymes and substrates must have complementary geometric shapes that exactly fit each other in order for an enzyme to function on a given molecule.¹⁴ Fischer’s theory was modified independently by Brown¹⁵ and Henri,¹⁶ each of whom suggested that enzymatic reactions occurred through an enzyme–substrate complex (Figure 3.12(a)). The theory was further modified in 1958 by Daniel Koshland with the addition of the concept of “induced fit.” This additional aspect of enzyme mechanistic theory suggested that the binding of a substrate to the active site could induce conformational changes to the enzyme itself. These conformational changes could increase the catalytic activity of the enzyme by moving key residues into the proper orientation to catalyze the desired reaction (Figure 3.12(b)).¹⁷

Although they are far more complex when compared to simple acid catalysts that might be used to prepare an ester from an alcohol and a carboxylic acid, the principal features that define a catalyst are still the same.