

the conversion of CO_2 to H_2CO_3 at nearly 10^8 times the rate of the uncatalyzed reaction, while orotidine-5'-phosphate decarboxylase increases the rate of conversion of orotidine-5'-phosphate into uridine-5'-phosphate by 10^{17} over the nonenzymatic reaction.¹⁸ Also, like their non-biological counterparts, enzymes are unchanged by the catalytic process. Once the conversion from substrate to product is complete, the enzyme is free to encounter another substrate molecule and repeat the cycle until chemical equilibrium is reached.

An examination of the reaction mechanism of the cleavage of peptide bonds by serine protease (also known as serine endopeptidase) demonstrates the principles of enzyme reaction mechanisms (Figure 3.14). This enzyme employs a variety of hydrogen-bonding interactions and a key serine side chain to hydrolyze amide bonds in the peptide backbone of a protein. In the absence of a catalyst, hydrolysis of amide bonds requires extreme conditions, but serine protease can accomplish this reaction at an extremely high rate. Initial entry of a substrate into the active site is followed by the reaction of serine-195 with the substrate (a) to provide an enzyme–substrate complex intermediate (b). The formation of this intermediate is supported by the hydrogen-bonding interaction of other amino acids in the active site. Aspartic acid-102 and histidine-57 facilitate the deprotonation of serine-195 via hydrogen bonding, allowing it to react with the amide bond. The carbonyl of the amide substrate, on the other hand, is made more reactive through its interactions with serine-195 and glycine-193. The transient intermediate formed in this first step then reorganizes with loss of the amino-portion of the amide bond, leaving the former amide carbonyl bound to serine-195 as an ester (c). Although esters are less stable than amides, cleavage of esters is also slow in the absence of a catalyst. The serine-195 ester (c) reacts with a molecule of water with the assistance of the same active site amino acid side chains that supported the cleavage of the amide bond to form a second transient intermediate (d) that can rearrange to eject the C-terminal portion of the peptide substrate, leaving the enzyme ready for a new substrate (e).¹⁹

In some cases, enzymes require the presence of additional material, cofactors, in order to function properly (Figure 3.15). These cofactors or coenzymes can be a wide range of atoms and molecules. The matrix metalloproteinases,²⁰ which degrade collagen and gelatin, for example, require the presence of a zinc atom. In the absence of zinc, these enzymes will not function. Iron, magnesium, manganese, molybdenum, selenium, and copper have also been identified as required cofactors in a variety of enzymatic systems.²¹

Organic compounds also play a major role as coenzymes. Cytochrome P450 17A1,²² also referred to as 17- α -hydroxylase/ $\text{C}_{17,20}$ -lyase, for example, has a key role in the production of a number of biologically important