How do enzymes catalyse biological reactions?

A catalyst is a substance which can alter the rate of a reaction without itself altering. Most biological catalysts are enzymes and are formed from the specific 3D structures of proteins, however RNA can also act as an enzyme although these are much less common and less versatile. So proteins are discussed here. Enzymes are able to provide a lower energy pathway for reactions and therefore able to increase reaction rates by factors of at least a million.

Most reactions do not occur spontaneously and require either an input of energy or a catalyst to proceed. For a reaction to happen the reacting molecules must be given enough energy for collisions to result in product formation. This is the activation energy and it is where reactants are in their transition state.

Enzymes provide an alternative reaction pathway which allows the activation energy to be lowered i.e. $\Delta G^\ddagger$ is much lower for the catalysed reaction.

Enzymes form complexes with their substrates in reversible reactions to create an enzyme-substrate complex. This complex can go on to form the products of the reaction or return to form the substrate and enzyme again.

Enzyme + Substrate $\leftrightarrow$ Enzyme substrate complex $\leftrightarrow$ Enzyme + Product

The induced fit model of enzyme activity suggests that the enzyme and substrate are not an exact complementary fit as first put forward by the lock and key theory. Instead they form weak non-covalent interactions (encounter complex) and then by rearrangement complementarity is increased to form the transition state.

Lock and key theory
Induced fit theory

The transition state provides the optimal conditions for the making and breaking of bonds. By stabilising the transition state, the enzyme catalyses the reaction. The binary of the substrate glycyltyrosine to carboxypeptidase shows the large structural changes that can occur when forming the enzyme-substrate complex, the phenolic hydroxyl group of tyrosine 248 moves 12 Å (around a quarter of a diameter of the proton) to accommodate the substrate. This also has the effect of creating a micro-environment where water is excluded from the active site.

The enzyme-substrate complexes increase the local effective concentration of reactants, increasing the rate of reaction. Enzymes also bind more tightly in the transition state, and this allows the products to be released quickly and effectively, and the enzyme can be reused.

Another crucial factor of the catalytic activity of enzymes is the specificity of the active site, which determines which pathway reactions will take. The substrate is bound to the active site by weak attractions such as electrostatic attractions, hydrogen bonds, van der Waals forces, and hydrophobic interactions. The specificity is determined by the amino acid residues within the active site. These often come from different parts of the primary structure. Most active sites have a 3D structure and form clefts of crevices, which create microenvironments for reactions to take place.

There are many different types of enzymes such as oxidoreductases and transferases, and each has a specific shape. It is therefore also common that catalysis mechanisms take place in many different ways.

Acid/base catalysis occurs where the enzyme donates or accepts an electron to the product. This can occur simultaneously when residues carrying out the catalysis are prevented from combining by the protein framework of the enzyme. The histidine residues (12 and 119) in ribonuclease act as proton donors and acceptors in catalysing the formation of cyclic phosphate intermediate and the following hydrolysis.

Proximity effects in catalysts are used to stabilise intermediates, this occurs through electrostatic interactions between negatively and positively charged side groups and substrate.
Covalent catalysis results in the formation of a covalently bonded intermediate for example when p-nitrophenyl acetate bonds with chymotrypsin, an acetyl enzyme intermediate is formed by covalent bonding. The enzyme is later regenerated forming acetate as a product.

Geometrical factors increase strain on the substrate and thereby causing catalysis. Lysozyme for example bonds to 6 sugar residues, the favourable binding to 5 of the rings allows a strain to be placed on the 4th ring. This ring is forced into a half chair configuration and subsequently the bond is cleared.

Nucleophilic attack on catalysts can be shown in the lysozyme mechanism. Here Asp52 side chain displaces the oxygen of the glycosidic bond by the nucleophilic attack of carbon 1 on the 4th ring of peptidoglycan.

Other complexes also arise which affect catalysis. Molecular tunnels allow a substrate to be passed between different active sites in one enzyme. Compartmentalisation of enzymes into organelles for example segregates particular substrates for catalysts and increases concentration locally. Almost all enzymes are specifically placed within a cell in eukaryotic organisms and some form multienzyme complexes so that the product from one enzyme is passed directly to another which limits diffusion time. These complexes and arrangements within the cell all serve to increase the rate and efficiency at which the enzymes work.

Although many different catalytic mechanisms are carried out by enzymes and they are specific to one substrate only, the main function is the same, all enzymes provide a specific active site which can form a stable transition state with the substrate. This stable transition state lowers the activation energy and allows the reaction to take place, at a rate which would otherwise be impossible in most biological systems.

Comment:

The student had identified the following areas based on feedback from the previous essay, which it was aimed to address:

- Linking evidence to claims and ideas more clearly
- Structure of essay- linking paragraphs & finding key points
- Concise writing
- Wider use of language
- Better academic style/formal language
- Use of relevant diagrams

Supervisor comments overall:

This is a big improvement on your last essay! You have used better academic language, written more concisely, have included some examples and have included a couple of diagrams. In order to improve it further you need to think about the following:
1. The essay needs to be more specifically directed at answering the question – which requires a better introduction and conclusion as well as more effective linking of the paragraphs. The key features of enzymes – high specificity and high catalytic activity with low substrate concentrations in physiological conditions (at pH 7 and 37°C) do not really come across. Maybe this should be the focus of the introduction?

2. You could make better use of examples – I have indicated some places in which you could do this.

3. You could include some evidence – e.g. the effect of pH on lysozyme activity provides evidence for the activity of Glu35 and Asp52 as proton donors and acceptors. Or the fact that denatured enzymes are not catalytically active which shows the essential contribution of the 3-D structure.

4. You should include more diagrams e.g. of parts of the catalytic mechanism.

5. You have not introduced all of the catalytic mechanisms:
   (i) Metal ion catalysis
   (ii) Use of prosthetic groups and co-factors to provide additional functionality
   (iii) Transition state stabilisation

6. I don’t think that you have mentioned that enzymes do not alter the position of equilibrium for a reaction.

7. Finally maybe in the conclusions you could have introduced the concept that many enzymes have additional binding sites for other molecules (allosteric enzymes) which allows control of catalysis to be exerted.