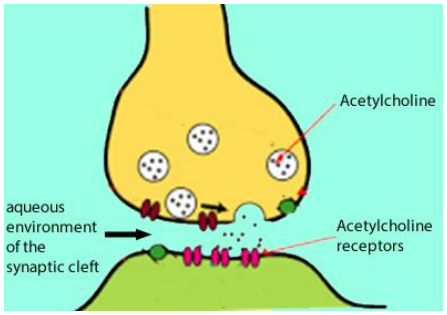
Worksheet – enzymes

1. Which of the following types of bonds can not take place between an enzyme's active site and a competitive inhibitor? Justify your answer.
   Dipole-dipole, Hydrogen bonding, disulfide bonds, van de Waals dispersion forces.

   Disulfide bonds are covalent and hence permanent. Competitive inhibitors do not form permanent bonds with the active site. All the other bonds are weak and temporary that are easily broken.

2. Myasthenia gravis is an autoimmune disorder where the body produces antibodies that block or destroy acetylcholine receptors on muscle cells. This results in reduced muscle stimulation and weakness. To counteract the reduced stimulation, acetylcholinesterase, the enzyme that breaks down the neurotransmitter, acetylcholine, is inhibited by a drug called pyridostigmine, in an attempt to increase the concentration of acetylcholine in the synaptic cleft. The selection of drug is crucial as an excess of acetylcholine lingering in the synaptic cleft can lead to excessive muscle stimulation, exacerbating the weakening of muscle responses.



The synaptic cleft is filled with extracellular fluid, which is primarily composed of water along with various ions, neurotransmitters, and other molecules.

Figure 1

Chemical structure of pyridostigmine

Figure 2

   a. Is pyridostigmine a competitive or non-competitive inhibitor of acetylcholinesterase? Justify your choice describing the impact of both a competitive and non-competitive inhibitors.

      Competitive inhibitor.

      A non-competitive inhibitor would irreversibly disable the enzyme leading to an increase in acetylcholine concentration in the synaptic cleft. This will result in the unwanted side effect of further weakening muscle response.

      A competitive inhibitor, on the other hand, will compete with acetylcholine for the active site of cholinesterase and reduce the rate of breakdown of the neurotransmitter. This will also cause an increase in acetylcholine in the synaptic cleft. However, unlike a non-competitive inhibitor, as soon as the concentration of acetylcholine increases the neurotransmitter will out-compete pyridostigmine for the active site and the rate of neurotransmitter breakdown will increase. This will prevent the concentration of neurotransmitter to increase in the synaptic cleft and avoid the side effect of further weakening muscle response.

b. Give one valid reason for the preparation of pyridostigmine as a bromide salt.
Increases the solubility of the compound in an aqueous environment.

c. A chemist proposed a reaction pathway for the synthesis of a new drug "C", shown in figure 3, to mimic pyridostigmine using two precursors. One precursor was the molecule shown in, figure 4. The MS of the other precursor is shown in figure 5 below.

i. What type of reaction takes place between molecules A and B?
esterification (condensation)

ii. What is the molar mass of molecule B? *89 g/mol*

iii. Calculate the atom economy for the reaction between molecules
A (111 g/mol) and B to produce molecule C 182 g/mol).

182 / (111 + 89) X 100 = 91%

Molecule C

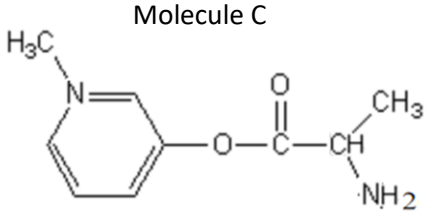


Figure 3

Molecule A

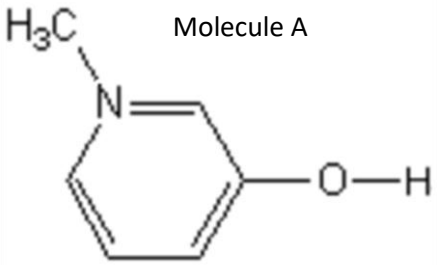


Figure 4

Molecule B

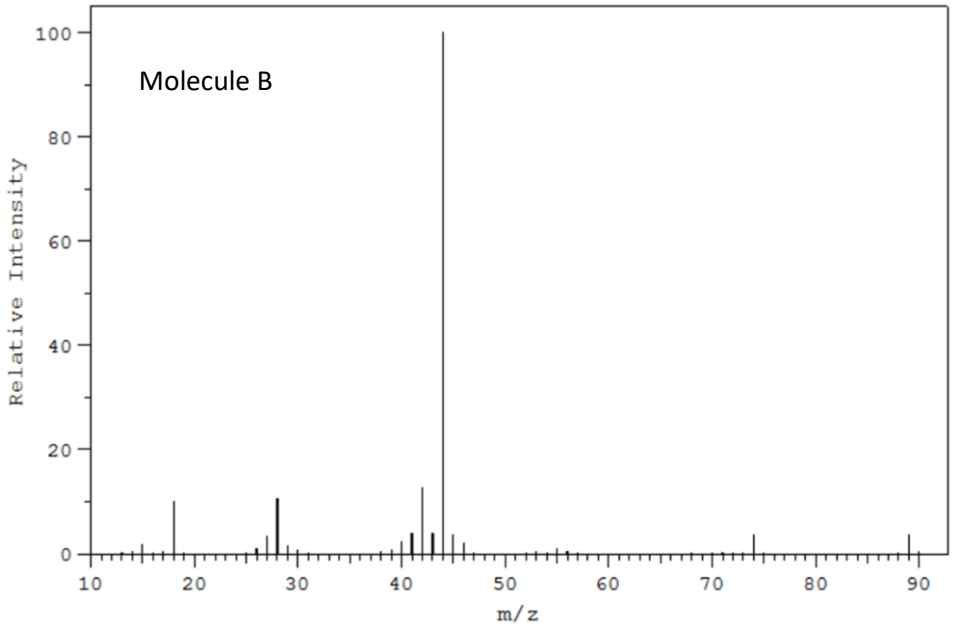


Figure 5

iv. Give the IUPC name of molecule B _____ *2-aminopropanoic acid*_

v. Give the semi-structural formula of the fragment that produced the base peak in the MS figure 5. _____ *$CH_3CH(NH_2)^+$*

vi. How many stereoisomers exist for molecule B _____*2*___

3. Figure 6 shows the energy profile of an uncatalyzed reaction.

a. Draw in the space provided in figure 6 how the energy profile will change when a catalyst is added.

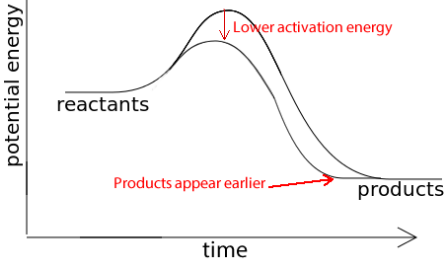


Figure 6

b. Consider the reactant and product particles shown in fig 7 as well as the two conformational states, A and B, of an enzyme.

i. Using the images in fig. 7 compare and contrast the lock-and-key and induced-fit models of enzyme substrate interactions. You may use diagrams to help your explanation.

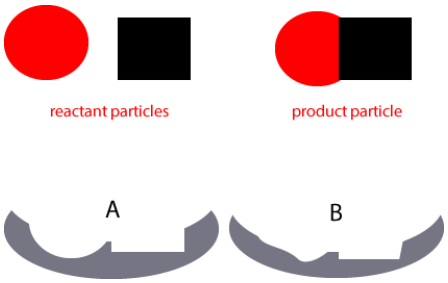


Figure 7

Any valid description that accurately compares and contrasts each model.
- Lock and key model involves a fixed complementary 3D shape of the active site on which the substrates fit perfectly.
- Induced fit model involves the active site,, not been complimentary in configuration to the substrates, but still having some capacity to accommodate the substrates. At whichpoint it undergoes conformational change to fit the substrates perfectly as if it were a lock and key model.

ii. Draw the enzyme-substrate complex in the box provided in fig 8.
The enzyme should now be complementary to the shapes of each reactant particle. Confirmational state A should now be shown.

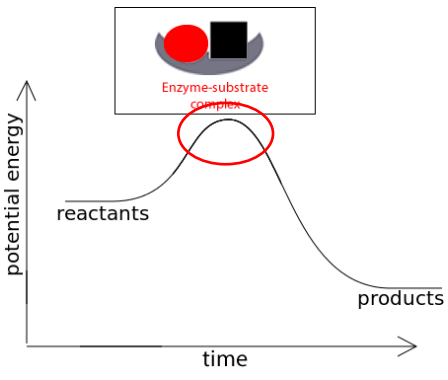


Figure 8

iii. Using figure 8, circle the point along the energy profile where the particles are the most unstable.
The enzyme substrate complex is the most energized and as such the most unstable particle.