Inhibition of Enzyme Catalysed Reactions

- **Inhibition of enzyme** action involve the decrease/stoppage of enzymatic action owing to forces as well as chemical compounds, which damage, transform or block the enzymatic active sites.
- **Based upon reversibility**, enzyme inhibition can be classified into two types: (1) Reversible and (2) irreversible.
- **Reversible inhibition (RI)** is not of permanent nature and take place when an inhibitor depicts non-covalent association at the active site and, thus inhibiting one of the substrates from binding. This inhibition is overcome as a result of enhanced concentration of substrate, dilution or dialysis. The utmost common type of RI detected in a single substrate enzyme reaction is competitive inhibition (CI) in which the inhibitor combines/associate at the same site as the substrate and, thereby competes with the same binding site.
- **Irreversible inhibition** is of permanent nature and occurs if an inhibitor first combines at the active site followed by reaction to an active site group that results in the formation of a covalent bond. It is unable to overcome by enhanced concentration of substrate, dilution as well as dialysis. For instance, heavy metals as well as iodoacetamide bind to enzymatic –SH groups and, thereby upset/disrupt enzymatic conformation.
- **Based upon competitiveness**, enzyme inhibition can be classified into three types: (a) Competitive inhibition, (b) Noncompetitive inhibition as well as (c) Uncompetitive inhibition

- **(a) Competitive inhibition:** In this case, the enzymatic active site is blocked/inhibited owing to the presence of a substance, which look like the substrate in its molecular structure. As a result, the concerned enzymes are not able to take part towards catalysing the transformation of the substrate to product and, thus enzymatic activity undergo inhibition. This inhibition is overcome as a result of enhanced concentration of substrate, dilution or dialysis. For instance, malonate, a competitive inhibitor, competes with substrate "succinate" towards succinate dehydrogenase (enzyme). Here, the malonate closely resemble succinate in its molecular structure and thus, result in competitive inhibition.

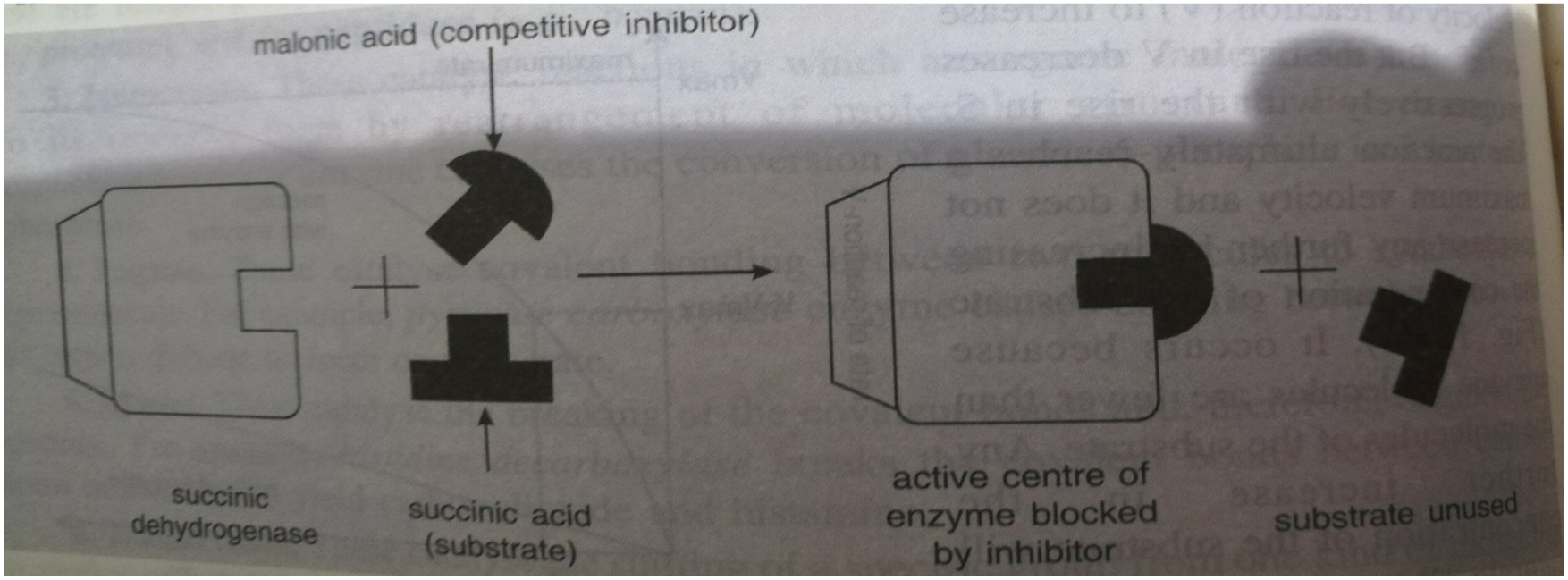


Fig. 1. Competitive inhibition of enzymatic action (Verma and Pandey 2006)

(a) Competitive inhibition

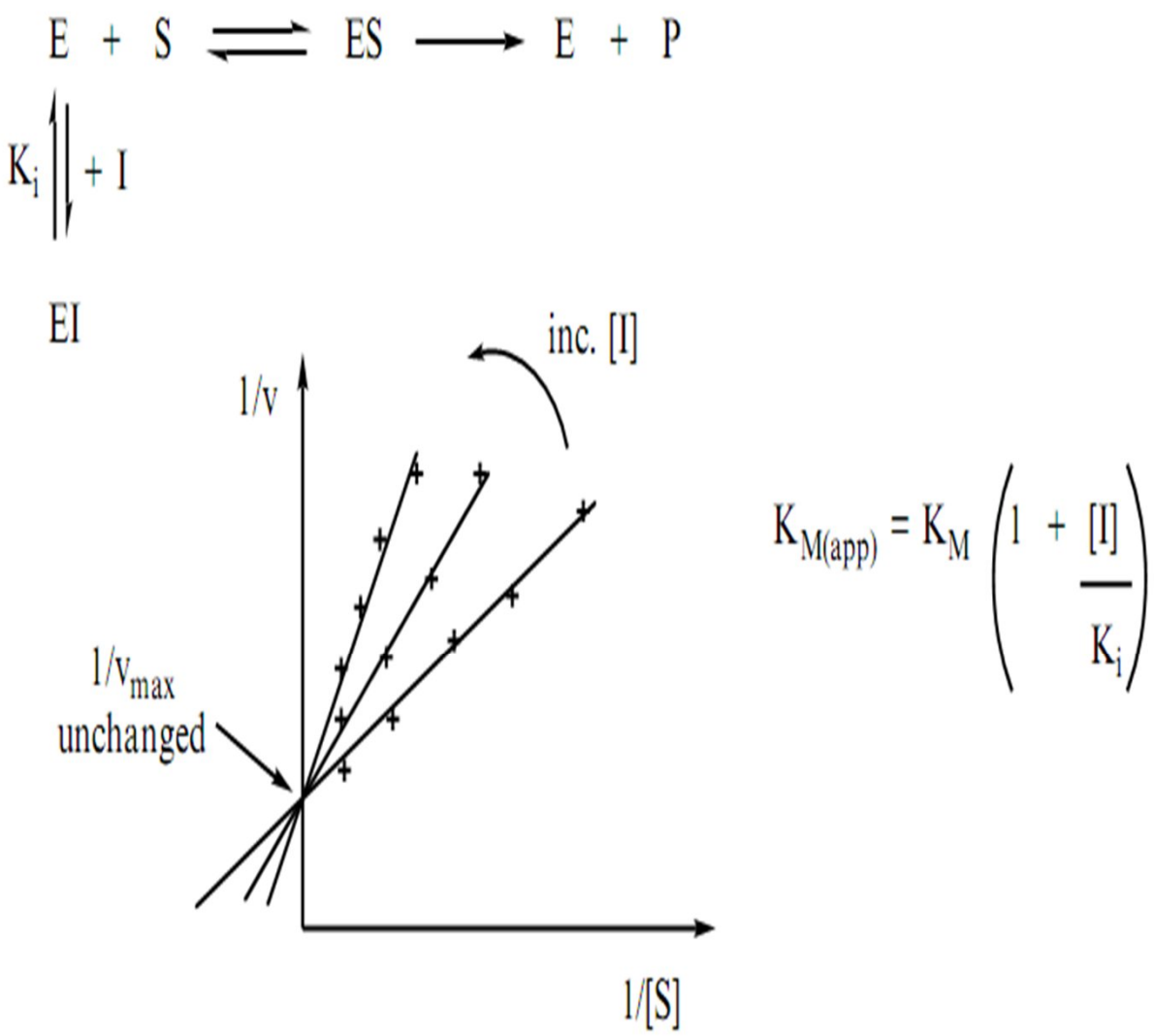
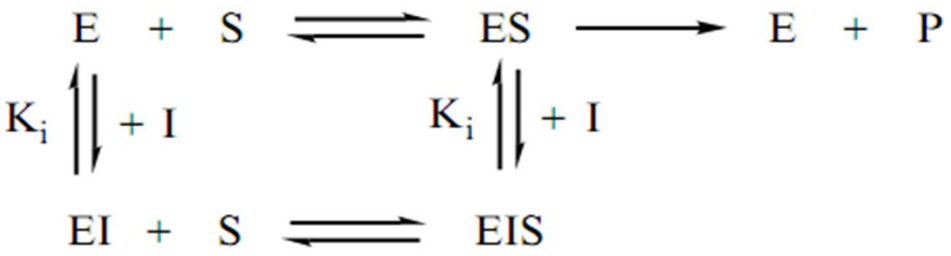


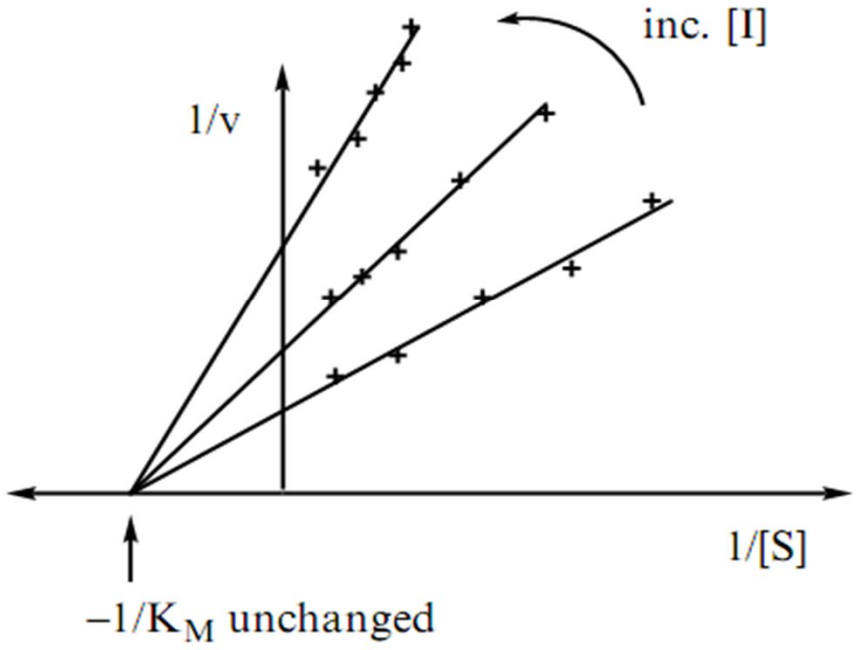
Fig. 2. Competitive inhibition (Bugg 2004)

- As shown in above Fig. 2., if the rate of the enzymatic reaction is measured at varying substrate concentrations but fixed inhibitor concentrations, apparent K_M values ((K_M)app) can be measured at varying inhibitor concentrations. When plotted on a Lineweaver–Burk plot, a series of straight lines are attained, intersecting on the y-axis. Therefore the v_{max} is unaffected by competitive inhibition, since at high substrate concentrations the substrate can competitively displace the inhibitor (Bugg 2004).

- **(b) Non-competitive inhibition** involves those inhibitors, which do not having any structural resemblance to that of substrate. Therefore, such inhibitors are not involved in blocking the substrate binding site, nevertheless other enzymatic site. In this type of inhibition, enzyme binds with substrate but no products are formed. For instance, cyanide binds with the copper ions of a respiratory enzyme "cytochrome oxidase". Such phenomenon ultimately results in the inhibition of cellular respiration followed by death in case cyanide combines with all the available enzymes. Similarly, Iodoacetamide binds in irreversible manner to –SH group of enzymes that ultimately lead to non-competitive inhibition (Bugg 2004; Verma and Pandey 2006).

(b) Non-competitive inhibition





$$v_{max(app)} = v_{max} \Big/ \left(1 + \frac{[I]}{K_i}\right)$$

Fig. 2. Non-competitive inhibition (Bugg 2004)

- **Allosteric inhibition or feed back inhibition:** Some enzymes depicts two different sites, i.e., active substrate binding site as well as modifier site (known as allosteric site). When a modifier binds with allosteric site of an enzyme, then it may influence the conformation of the enzymatic active site and, thereby blocking/inhibiting its catalytic activity.

- The enzymes having allosteric site for binding with modifiers are known as allosteric enzymes.

- Most of the enzymes present in metabolic route (a chain of reaction) are allosteric enzymes. In such enzymes, the another enzymatic product of the chain behave as a modulator substance that either increases or decreases their activity. Such kind of inhibition in enzymatic reactions mediated through the end product is called feedback inhibition.

- For instance, glycolysis involves hexokinase enzyme that responsible for the transformation of glucose molecule into glucose-6-phosphate. The excess end product formation of the same reaction, i.e., glucose-6-phosphate results in allosteric inhibition of hexokinase.

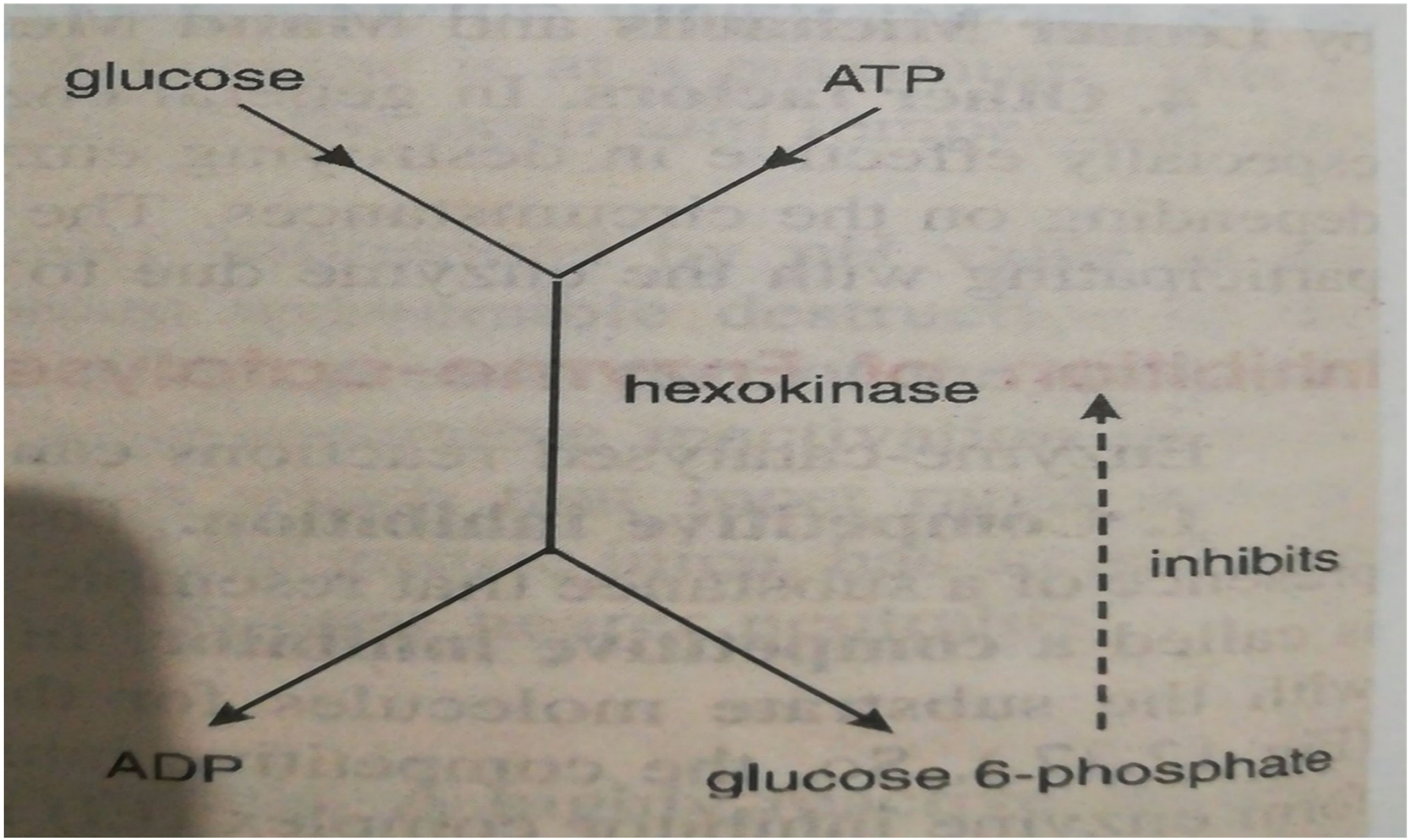


Fig. 2. Feed back inhibition of hexokinase (an allosteric enzyme) (Verma and Pandey 2006)

- **Denaturation of proteins:** As enzymes are composed of proteins, therefore at high temperature, they undergo denaturation followed by inhibition in their activity. This inhibition of enzymatic activity in fact owing to the loss of native protein configuration (Verma and Pandey 2006).
- An enhancement in temperature results in enhancement in bond length amongst different amino acid residues. After a certain limit, the bonds can break, which result in disruption of physical configuration of enzyme, thereby unable to catalyse the reaction (Verma and Pandey 2006).
- **Resources for aforementioned notes:**

1. **Verma, P.S.; Pandey, B.P. (2006) Biology, S. Chand & Company Ltd., New Delhi, India, pp. 681-683.**
2. **Bhatti, K. (2015) Companion Biology, S. Dinesh & Co., India, pp. 1328-1345.**
3. **Bugg, T. D.H. (2012) Introduction to Enzyme and Coenzyme Chemistry, Blackwell Publishing Ltd, UK.**