Models of Enzyme Inhibition

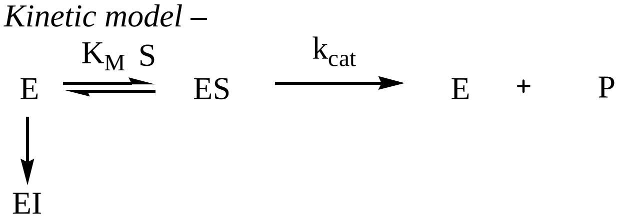
Some general notes

This is a quick description of the four basic models of inhibition, and how I think about them. These models are somewhat simplified, and make a handful of really important to think about assumptions (one that is common to all of the reversible models is that inhibited enzyme is not productive). I hope this helps to clarify the topic. This is a rough, 11 at night, draft, and I'd be happy to correct any errors, or try to clarify sections that you find unclear, so let me know.

Irreversible inhibition

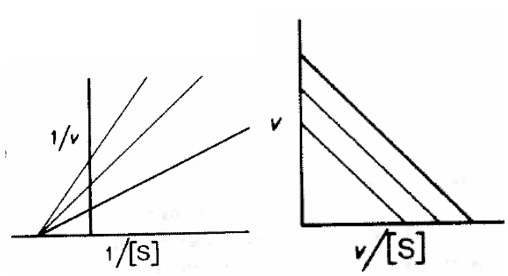
Mode of action – The enzyme binds the inhibitor, which irreversibly kills it (mind you, this can also be accomplished by mechanical means such as heat).

Kinetic model –



Effect – Since you are effectively destroying enzyme, this results in a decrease in $[E]_o$, resulting in a decrease in v_{max}, and therefore an apparent decrease in k_{cat}.

Graphical results –

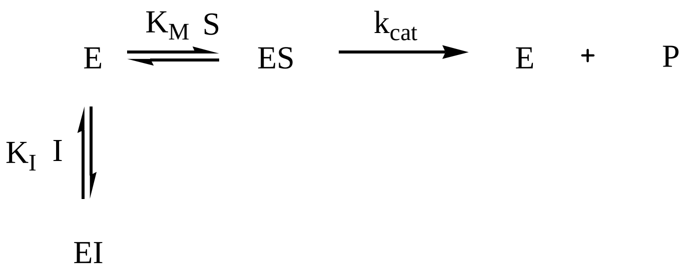


Attempting to dialyze away the inhibitor is not effective, as it is covalently bound to the enzyme. You also hear of this type of inhibitor called a "suicide inhibitor". There are many examples of drugs that are irreversible inhibitors.

Competitive inhibition

Mode of action – In competitive inhibition the inhibitor and the substrate compete for free enzyme, but each preclude the binding of the other. This implies that they both bind to the active site, which is generally but not always true.

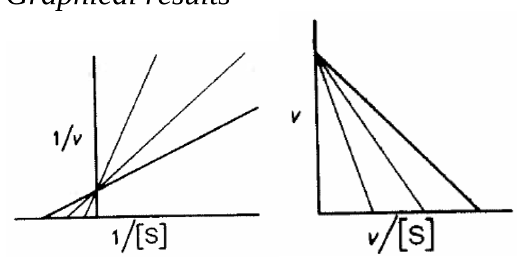
Kinetic model:



Effect – By drawing off, in a reversible fashion, free enzyme from the left of the equilibrium, you are shifting the equilibrium away from ES. This appears to increase the K_M.

Rate equation – $$v = \frac{k_{cat}[E]_o[S]}{[S] + K_M\left(1 + \frac{[I]}{K_I}\right)}$$

Graphical results –

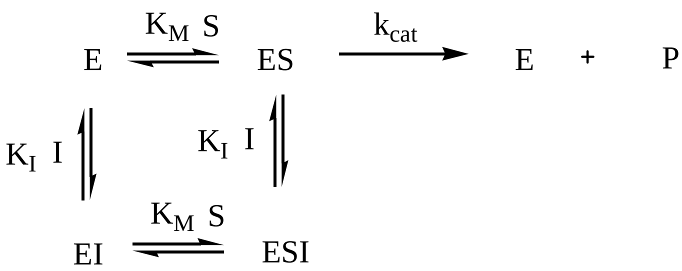


Dialyzing away the inhibitor restores active enzyme (this is true of all reversible models of inhibition). Most drugs are competitive inhibitors of enzymes.

Noncompetitive inhibition

Mode of action – In noncompetitive inhibition substrate binding and inhibitor binding are completely independent of each other, but the ternary complex (ESI) is not productive.

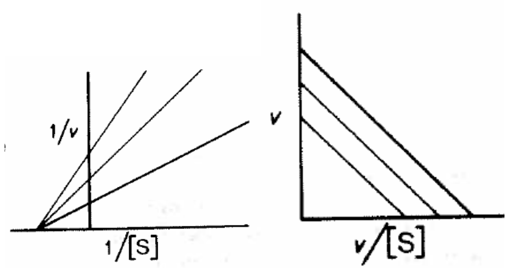
Kinetic model:



Effect – In noncompetitive inhibition the equilibrium between enzyme without substrate and enzyme with substrate is unchanged, but some of each of those happens to have inhibitor. Since the ternary complex can't make product, this appears the same as removing some enzyme from the pool. This decreases v_{max}, and therefore apparently decreases k_{cat}.

Rate law – $v = \dfrac{[E]_o[S]k_{cat}/(1+[I]/K_I)}{[S]+K_M}$

Graphical results:

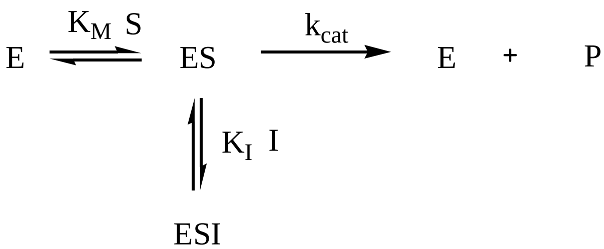


Dialysis restores enzyme activity, as it does for all reversible modes of inhibition. Note that this is the easiest way to determine the difference between this and irreversible inhibition.

Uncompetitive inhibition

Mode of action – This one is a bit odd, in that the inhibitor can only bind to the enzyme-substrate complex, reversibly forming a nonproductive ternary complex.

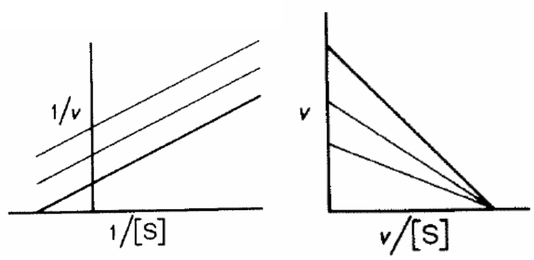
Kinetic model:



Effect – Fitting in with its weird nature, uncompetitive inhibition shifts the equilibrium to the right the same way that competitive inhibition shifts it to the left, apparently *decreasing* the K_M (that's right folks, it looks like it is binding the substrate more tightly). It is also pulling down the pool of enzyme-substrate complex to form the nonproductive ternary complex, decreasing k_{cat}. Carefully study the relationship between this rate equation and those for the other two modes of reversible inhibition shown above, it's pretty nifty.

Rate law – $v = \dfrac{[E]_o[S]k_{cat}/(1+[I]/K_I)}{[S]+K_M/(1+[I]/K_I)}$

Graphical results:



Again, dialysis restores activity. I think this one is kind of nifty.

Mixed inhibition

Mode of action – This one is a pain in the tush. Binding substrate effects the ability of the enzyme to bind substrate, but doesn't make it zero. Binding inhibitor effects the ability to bind substrate, but doesn't make it zero. The k_{cat} and K_M both apparently change, and your slopes and intercepts are all over the place. It would take a professor significantly more evil than me to make you interpret this one on a test, and that's saying something...