C1: Irreversible Covalent Inhibition

Given what you already know about protein structure, it should be easy to figure how to inhibit an enzyme. Since structure mediates function, anything that would significantly change the structure of an enzyme would inhibit the activity of the enzyme. Hence extremes of pH and high temperature, all of which can denature the enzyme, would inhibit the enzyme in an irreversible fashion, unless it could refold properly. Alternatively we could add a small molecule which interacts noncovalently with the enzyme to either change its conformation or directly prevent substrate binding. Finally, we could covalently modify certain side chains, that if they are essential to enzymatic activity, would irreversibly inhibit the enzyme.

We discussed previously the types of reagents that would chemically modify specific side chains that might be critical for enzymatic activity. For example, iodoacetamide might abolish enzyme activity if a Cys side chain is required for activity. These reagents will usually modify several side chains, however, and determining which is critical for binding or catalytic conversion of the substrate can be difficult. One way would be to protect the active site with a saturating quantities of a ligand which binds reversibly at the active site. Then the chemical modification can be performed at varying reaction times. The critical side chain would be protected from the chemical modification, but the extent of protection would depend on the Kd, concentration of the protecting ligand, and the length of the reaction.

more TBA

The rest of the chapter will deal with reversible, noncovalent inhibition

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