P. Chem

3/22/23
Wednesday

dissociation $PL \rightleftharpoons P + L$

$$K_D = \frac{([P]/[P]^\circ)([L]/[L]^\circ)}{([PL]/[PL]^\circ)}$$

numerically !

$$K_D^* = \frac{[PL]^\circ}{[P]^\circ [L]^\circ}$$

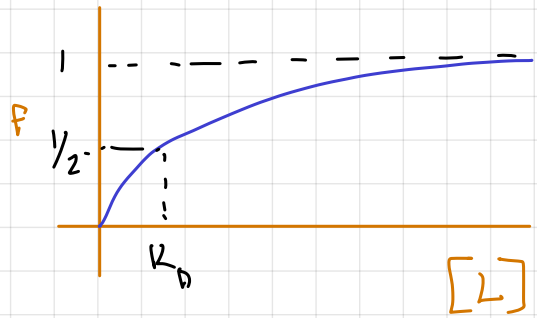
with $K_D^* = \frac{[P][L]}{[PL]}$ having units of M : mol/L

fraction occupied $f = \frac{[P][L]/K_D}{[P][L]/K_D + [P]} \cdot \frac{K_D/[P]}{K_D/[P]}$

$$f = \frac{[L]}{[L] + K_D}$$

$K_D = [L] \Rightarrow F = 1/2$

* used to determine K_D experimentally



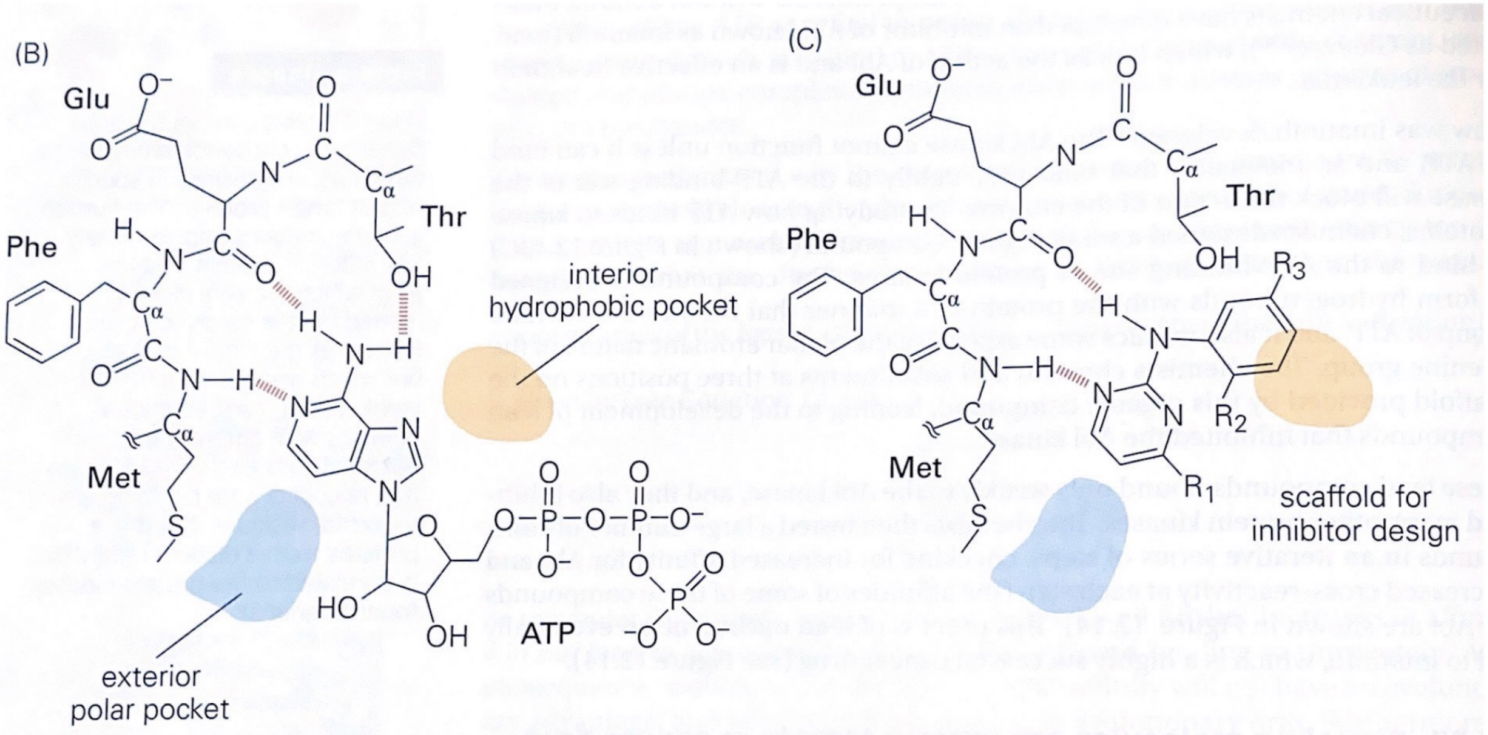
binding isothermal

affinity is specificity

usually K_D is not so different from the natural/physiological [L]

why?

- If mutations lower K_D, it doesn't change f much.
  - can stop the "off" state which is important for signaling
- If mutations raise K_D, protien could fail to bind ligand



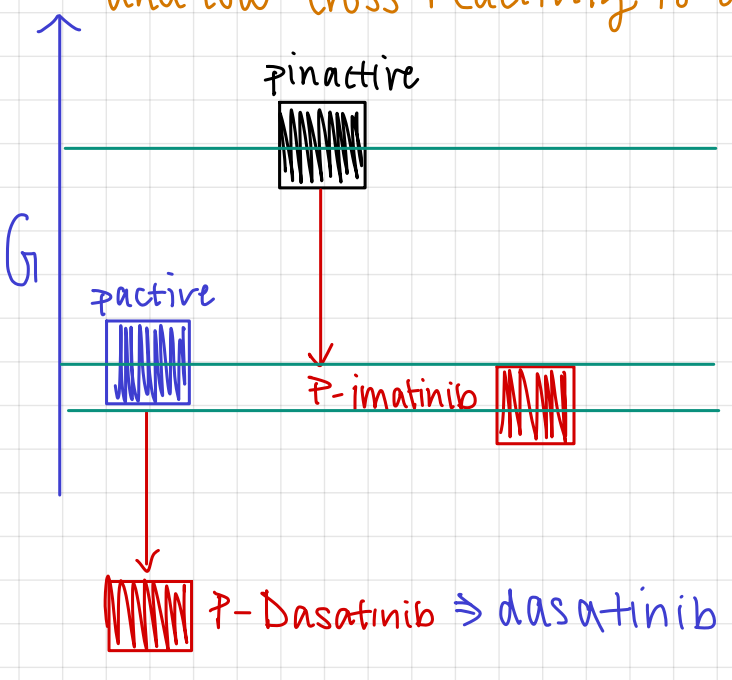
- drug development begins by identifying proteins that are critical to disease progression, and then focuses on design or discovery of molecules that inhibit the protein function

- The molecules that are first discovered to inhibit the target protein are called "lead compounds". Then these are refined.

example: imatinib → blocks Abl kinase to treat chronic mylogenous luekemia. Abl kinase catalyzes phosporylation of specific tyrosine residues that control signal transmissions between cells.

By studying how Abl kinase bonds ATP, chemists could design a scaffold to competitive inhibition

and low cross-reactivity to other kinases



P-Dasatinib ⇒ dasatinib bonds 350× stronger, but not as selective

*Protein Switching

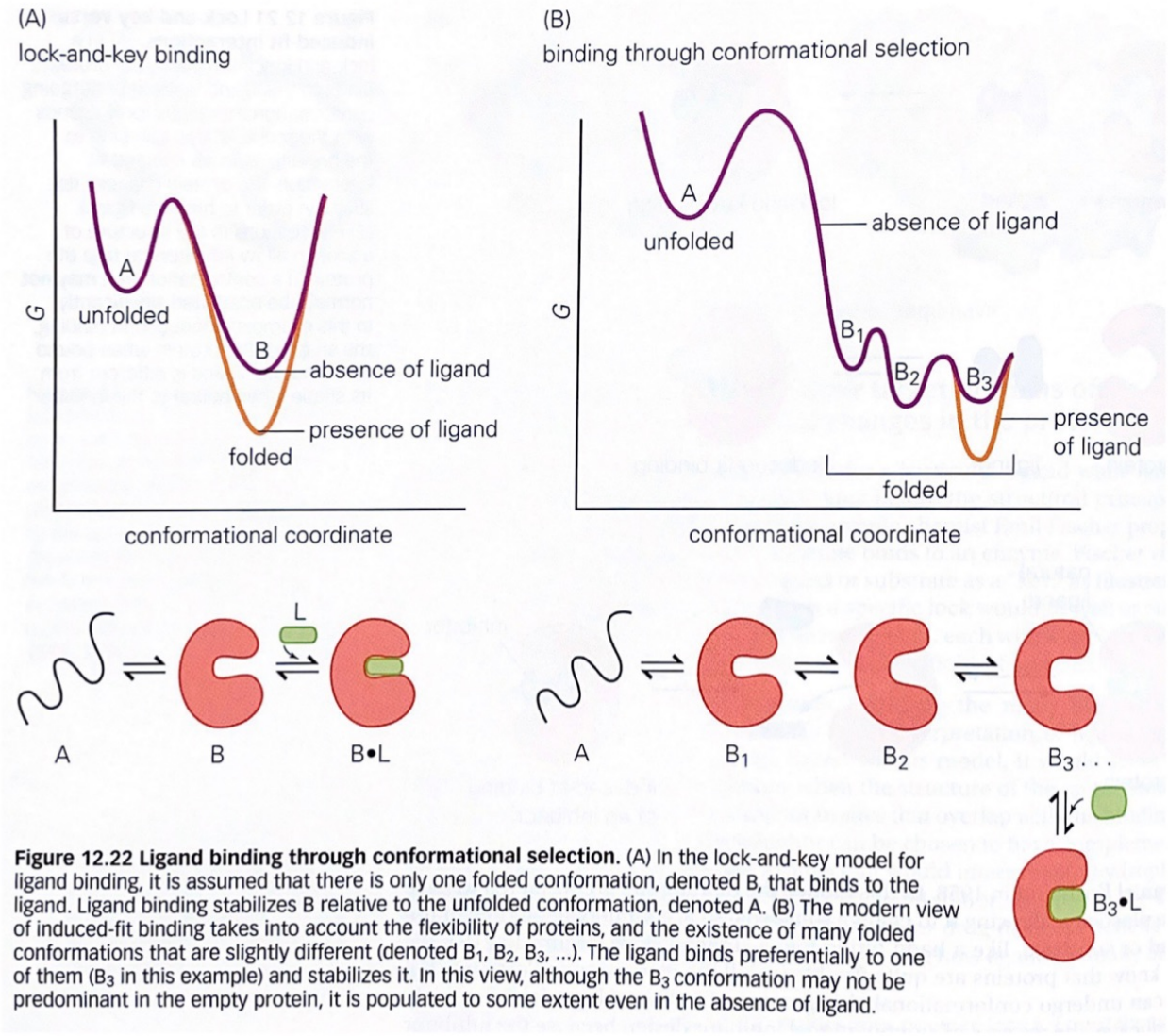


Figure 12.22 Ligand binding through conformational selection. (A) In the lock-and-key model for ligand binding, it is assumed that there is only one folded conformation, denoted B, that binds to the ligand. Ligand binding stabilizes B relative to the unfolded conformation, denoted A. (B) The modern view of induced-fit binding takes into account the flexibility of proteins, and the existence of many folded conformations that are slightly different (denoted B_1, B_2, B_3, ...). The ligand binds preferentially to one of them (B_3 in this example) and stabilizes it. In this view, although the B_3 conformation may not be predominant in the empty protein, it is populated to some extent even in the absence of ligand.

*Next class, back to Chapter 24