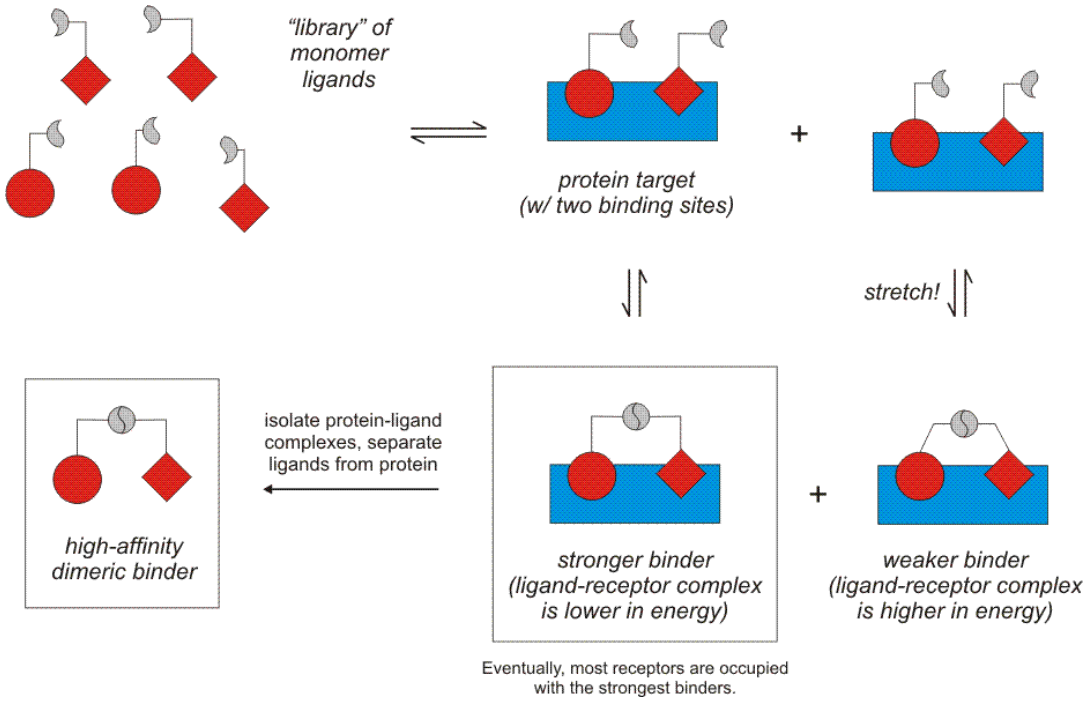
Chemistry 4011/8011 Friday, October 27

Problem Set 6
Due: *In class, Friday, November 3*

1. Jean-Marie Lehn has proposed "dynamic combinatorial libraries" as potential sources for pharmaceutically active agents that bind to biological targets in multiple places.[1] In Lehn's scheme, pharmaceutical lead molecules that bind singly to targets are modified with linkers that allow them to spontaneously dimerize or multimerize. The target binding site(s) then, in effect, selects for molecules that contain multiple binding elements and that show enhanced target affinity because of the additive binding enthalpy and "chelating" effect of these elements.



   For example, K. C. Nicolaou and coworkers have used this concept to optimize the binding of tethered, modified vancomycin dimers to vancomycin's biological target, a peptide critical for bacterial cell-wall synthesis. In this way, Nicolaou's group created new drug candidates with stronger target affinities than vancomycin monomer alone.[2]

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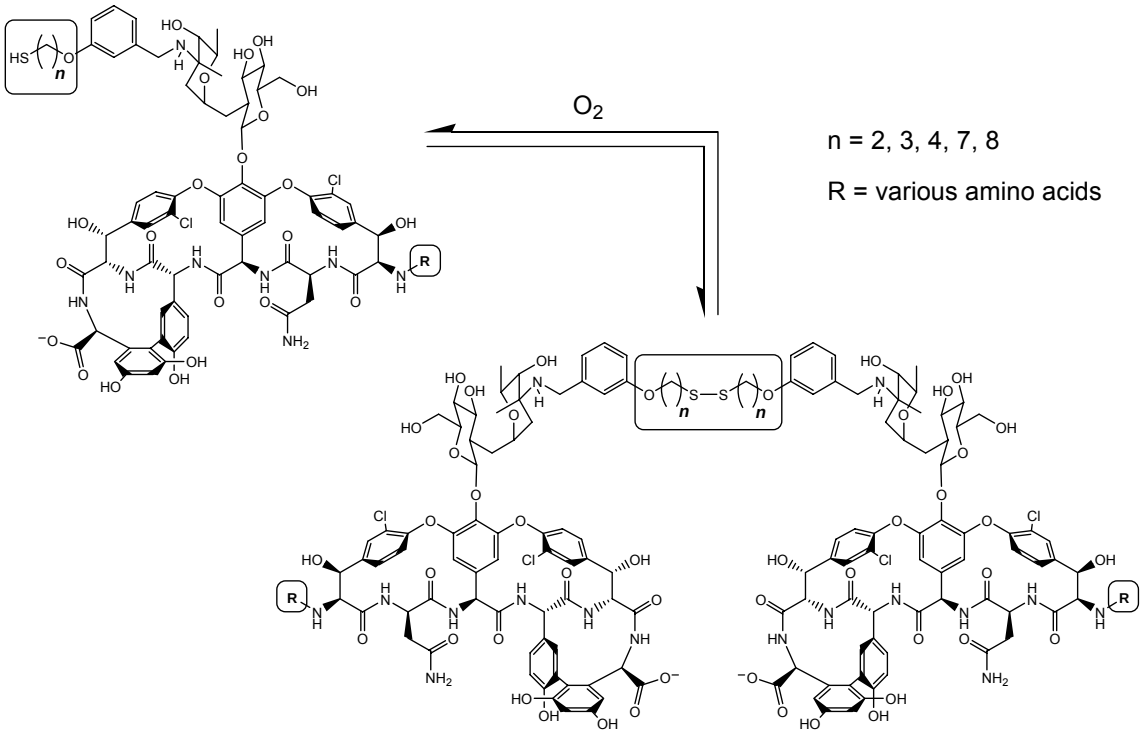
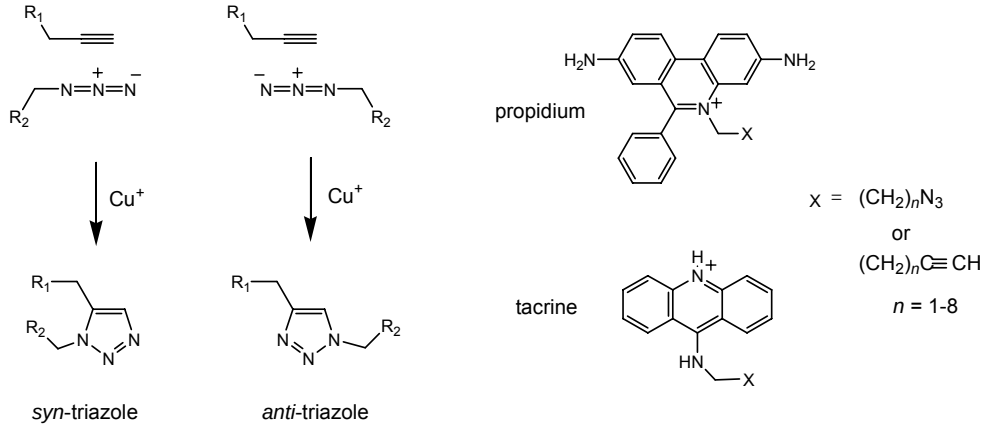
[1] Ramström, O.; Lehn, J.-M. *Nature Reviews Drug Discovery* **2002**, *1*, 26-36.
[2] Nicolaou, K. C.; Hughes, R.; Cho, S. Y.; Winssinger, N.; Smethurst, C.; Labischinski, H.; Endermann, R. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3823-3828.

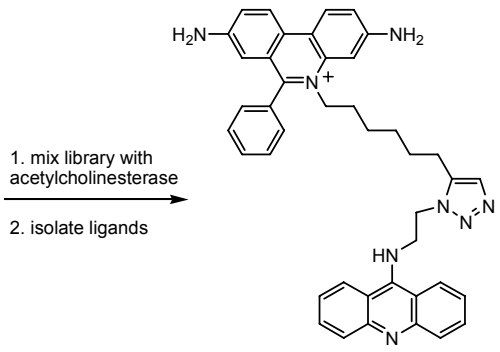


Here, mixing monomers that had different *n* and R resulted in the selection of a dimer with *n* = 3, R = LeuNMe by the biological target. (In this case, unlike the cartoon on the previous page, the two halves of the optimized dimer were the same.)

Barry Sharpless and coworkers have developed new linking chemistry ("click chemistry")[3] that they have applied to connect two compounds, propidium and tacrine, that bind acetylcholinesterase in different locations with the goal of selecting for stronger binders.[4]

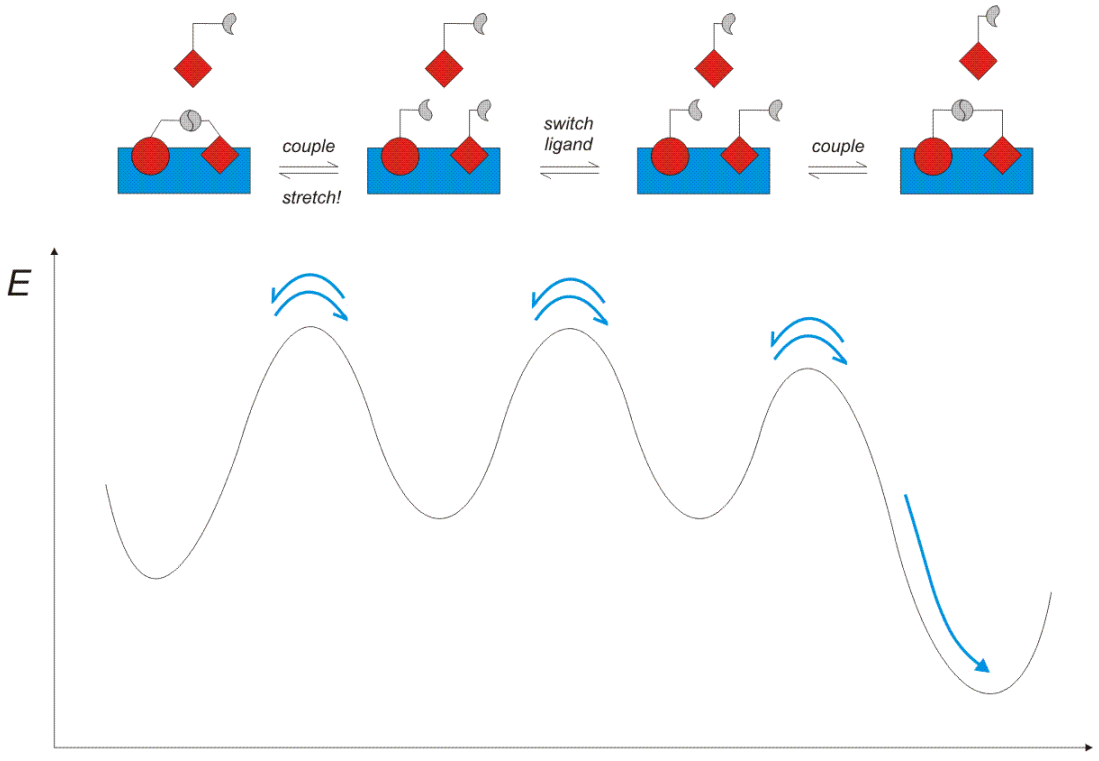


[3] Review: Breinbauer, R.; Köhn, M. *ChemBioChem* **2003**, *4*, 1147-1149.
[4] Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radić, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1053-1057.



Like Lehn's system, the selected molecule has two parts that are designed to bind in two places to the acetylcholinesterase target, and binding affinity of the heterodimer ligand is higher than the component monomers alone. While this approach works towards the same goals as Lehn's, the system is *not* inherently designed to optimize target binding.

a) An energy diagram for Nicolaou's selection might look something like this:



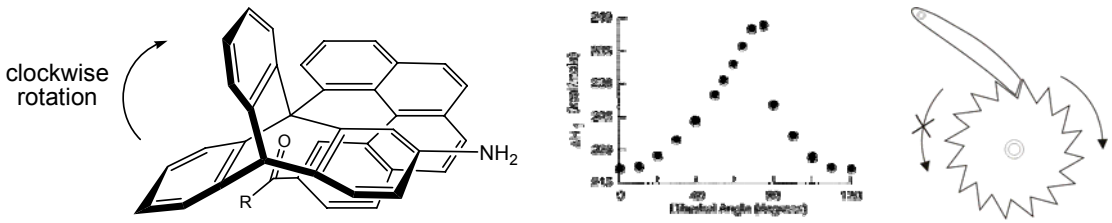
In this diagram, the selection "chooses" the dimer that isn't stretched because the total energy of the ligand-receptor complex is lower. This diagram, however, does not accurately depict the selection in Sharpless' system. Draw a potential energy diagram and cartoon that more accurately reflects the

energetics of Sharpless' ligand selection, as described in their *Angewandte Chemie* paper.

b) Although Nicolaou's selection will always choose the optimum ligand for binding, Sharpless' system will *not* necessarily choose the best binder. (In the particular case described in the paper, the dimer with the lowest binding concentration K_d was in fact chosen. But this did not have to be the case.) Under what energetic circumstances might Sharpless' strategy select for sub-optimal ligands from the pool of candidates? For example, if the stronger binder had tacrine and propidium connected to each other via a *syn*-triazole, under what circumstances might an *anti*-triazole be selected instead? Answer this problem by pointing out particular features of the diagram you drew in part (a).

(To answer this problem, you are probably going to want to read the cited articles, available online through Walter library's E-Journal page, http://www.lib.umn.edu/articles/ej.phtml. I've created links to some of the articles on the course website.)

2. T. Ross Kelly and coworkers have synthesized a set of trypticene-based molecules that they envision functioning like "molecular ratchets".[5] These molecules contain a chiral helicene moiety that is designed to act like a pawl against a toothed gear, and molecular modeling calculations indicate a potential energy profile for rotation that looks like the asymmetric tooth of a gear.



In principle, this might be used like a motor to mechanically turn something (very very small), and you might imagine that the trypticene rotates preferentially in one direction. However, despite your experience that gear like the one I drew above rotates in only one direction, this will not be true for Kelly's ratchet.[6]

a) Kelly's ratchet has three states, where the amine group is pointed at 120° (shown above), 240°, and 0°. The 120° state is the lowest-energy state,

[5] Review: Sestelo, J. P.; Kelly, T. R. *Appl. Phys. A* **2002**, *75*, 337-343.
[6] In fact, according to the Second Law of Thermodynamics, it isn't true for any "Brownian" ratchet. Read Richard Feynman's lectures on the subject, or see http://en.wikipedia.org/wiki/Brownian_ratchet for more info.

because of interactions between the stacked, electron-rich aniline and electron-poor phenone groups, and the 240° state is the highest-energy state, because of steric interactions between the amine and R. These same steric interactions make the reaction barrier between the 120° and 240° states very high. For this problem, assume that:

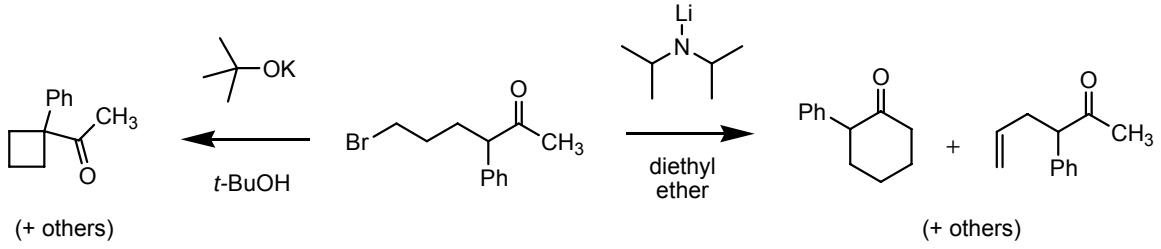
$\Delta H(240°\rightarrow 0°) =$ -4 kcal/mol;
$\Delta H(120°\rightarrow 240°) =$ +8 kcal/mol;
$\Delta H^{\ddagger}(120°\rightarrow 240°) =$ 32 kcal/mol;
$\Delta H^{\ddagger}(240°\rightarrow 0°) =$ 22 kcal/mol;
$\Delta H^{\ddagger}(0°\rightarrow 120°) =$ 22 kcal/mol.

Draw a potential energy diagram for complete rotation of the trypticene ratchet.

b) To turn the gear I drew one complete (360) rotation, you would have to turn it clockwise—it doesn't go counterclockwise. Under normal thermal motion, however, Kelly's molecular ratchet does NOT preferentially make complete (360°) rotations in the clockwise direction—it goes both ways. Why is Kelly's molecular ratchet different from a macroscopic gear?

c) What external influence might produce preferential clockwise (or counterclockwise) rotation in Kelly's ratchet? (Much leeway here, you can re-design the system any way you like, and you can be vague. But don't propose anything nonphysical. So, please, don't suggest that a tiny munchkin hand will turn the trypticene.)[7]

3. When the bromophenylketone shown below is treated with strong base, enolate ions are generated which can undergo intramolecular reactions with the bromine functionality. However, the products observed depend upon which base and which solvent are used.



Only products which are *selectively* observed for each base are shown in the reaction above—the two reaction conditions yield many products in common.

[7] For some ideas, see: Siegel, J. *Science* **2005**, *310*, 63-64.

Explain the selective products, both in terms of reaction mechanisms (electron pushing) and, more importantly, in terms of reaction kinetics and thermodynamics.

Problems to try on your own:

MPOC, Chapter 7: Problems 13, 17.