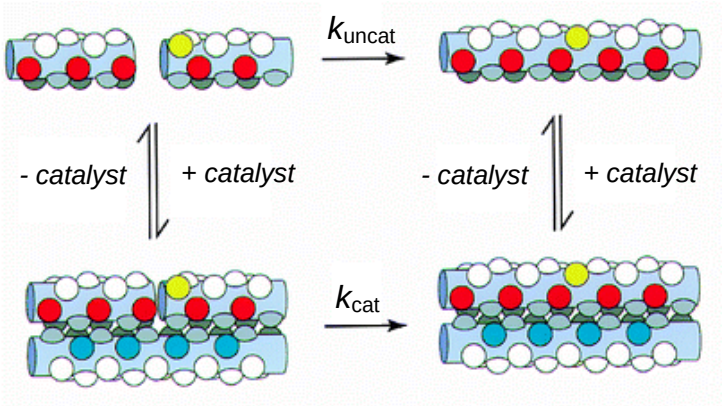
Chemistry 4011/8011 Friday, December 1

Problem Set 9
Due: *In class, Friday, December 8*

1. One theory of how self-sustaining, self-replicating life began on this planet begins with molecules—and the idea that somehow, complex molecules developed the ability to build copies of themselves from simple precursors. Ghadiri and coworkers have investigated peptides that either catalyze their own synthesis, or that catalyze the construction of a similar peptide structures, from two smaller fragments.[1-3]



In reference 3 (footnote below), the blue and red product peptides are the same, and the system is self-replicating (autocatalytic). However, in references 1 and 2, the peptide sequences are different, and the blue peptide is just a catalyst. The following questions require information from these three papers, and you will need to read at least references 1 and 3.

a) Reference 3 shows that the product peptide stabilizes the rate-determining transition state on the way to its own synthesis from starting materials. By how much (in kcal/mol) is the transition state stabilized?

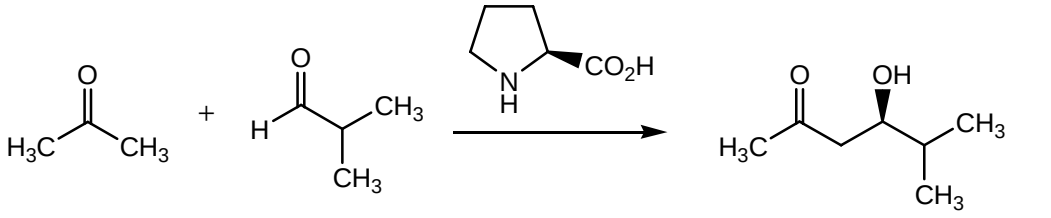
b) To explore the catalytic mechanism for this system, the authors tested the effect of "crippled" catalysts that recognized only one of the two reacting fragments. What did these experiments say about the structure of the transition state, and about the relative influence of the catalyst on $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the overall process?

c) In References 1 and 2, the authors describe a system that exhibits better turnover—in other words, a catalyst that is not inhibited by product. Though

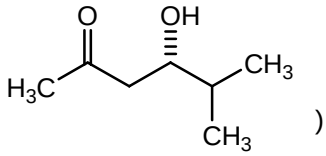
[1] Severin, K.; Lee, D. H.; Kennan, A. J.; Ghadiri, M. R. *Nature* **1997**, *389*, 706-709.
[2] Kennan, A. J.; Haridas, V.; Severin, K.; Lee, D. H.; Ghadiri, M. R. *J. Am. Chem. Soc.* **2001**, *123*, 1797-1803.
[3] Lee, D. H.; Granja, J. R.; Martinez, J. A.; Severin, K.; Ghadiri, M. R. *Nature* **1996**, *382*, 525-528.

they don't explain why this is true, one reason may lie in the different affinities of the catalyst for the product states P* and P. Why might the catalyst bind these differently, and why might this difference provide the basis for turnover? In your answer, include a potential energy diagram that describes the uncatalyzed reaction as well as intermolecular interactions between the catalyst and the starting material, rate-determining transition state, and product states.

2. Movassaghi and Jacobsen have described L-proline as "the simplest 'enzyme'",[4] in that it functions as a remarkably simple yet enantiospecific catalyst for the aldol reaction. For example, they note that L-proline was used to catalyze the enantioselective aldol addition of acetone to isobutylaldehyde:[5]



(and not



).

a) Although the aldol reaction can normally be catalyzed by a base, and proline has a basic amine, in this case proline acts instead to change the mechanism of the reaction. Draw rate-determining transition states for the proline-catalyzed generation of each of the two products above. How do the energies of these transition states compare—which is higher?

b) Proline could also act as a simple, specific base catalyst (even though I just told you it doesn't). What would be the structures of the two rate-determining transition states (on the way to the two products above) in this case? How would the energies of these transition states compare to those in part (a)?

[4] Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904-1905.
[5] List, B.; Lerner, R. A.; Barbas, C. F. III *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

3. Penicillin is hydrolyzed and rendered inactive by penillicinase (also known as β-lactamase), an enzyme present in some resistant strains of bacteria. The molar mass of this enzyme is 29,000 g/mole. The amount of penillicin hydrolyzed in 1 minute in a 10 mL solution containing 10^{-9} g of purified enzyme was measured as function of the concentration of penicillin (in μmol/L). (Assume the concentration of penicillin does not change appreciably during the assay, such that the experiment measures an initial rate.)

penicillin (μM)	amt hydrolyzed (nmol)
1	0.11
3	0.25
5	0.34
10	0.45
30	0.58
50	0.61

What are K_M, V_{max}, and the turnover number for penicillinase? Show the data plot that you used to obtain these values.