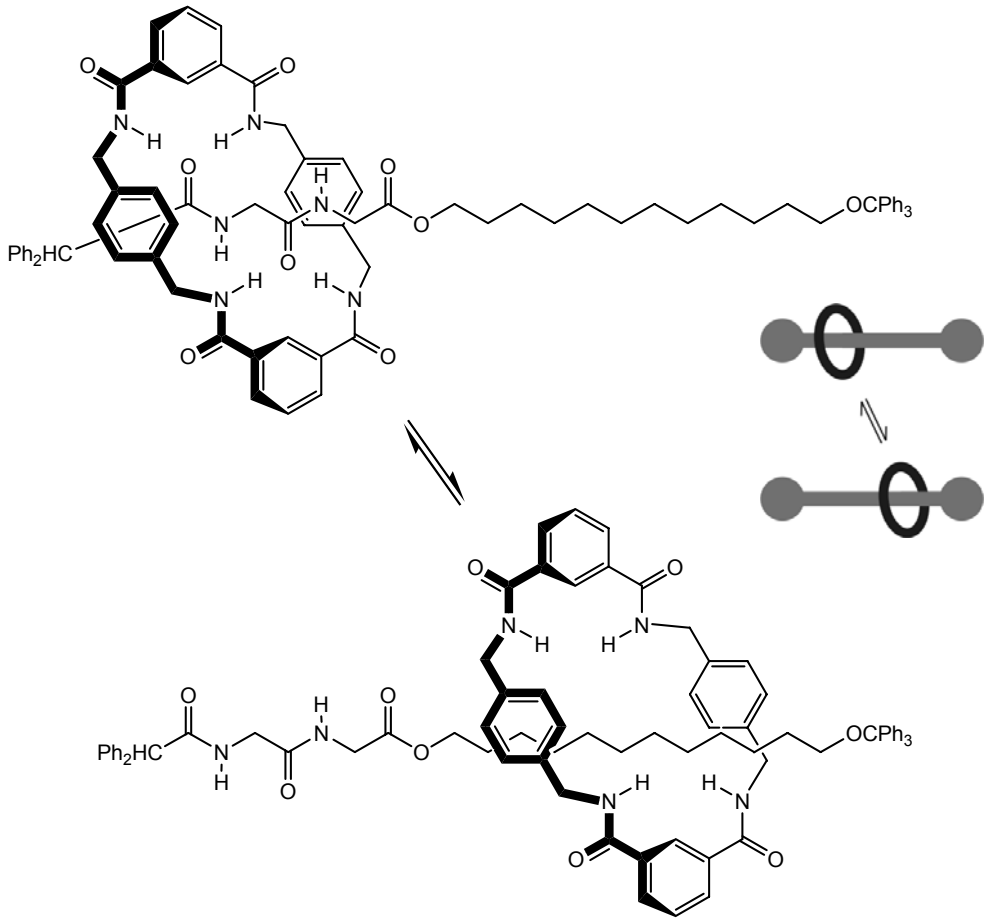
Chemistry 4011/8011 Friday, September 15

Problem Set 2
Due: *In class, Friday, September 22*

1. David Leigh (University of Edinburgh) and coworkers have synthesized pairs of interlocking molecules whose configuration responds to their solvent environment.[1,2] For example, the linear component of the rotaxane shown below has, in effect, two "stations" at which the ringed component can spend most of its time.



In this molecule, the large di-/tri-phenylmethyl groups on the ends of the straight chain prevent the macrocyclic ring from unthreading. (These groups are too large to fit through the macrocyclic ring.) Leigh found that the predominant "station" of the macrocycle depended on the solvent environment.

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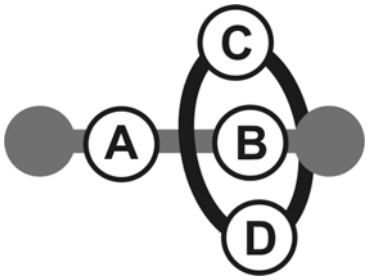
[1] Leigh, D. A.; Troisi, A.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 350-353.
[2] Leigh, D. A.; Moody, K.; Smart, J. P.; Watson, K. J.; Slawin, A. M. Z. *Angew. Chem., Int. Ed.* **1996**, *35*, 306-310.

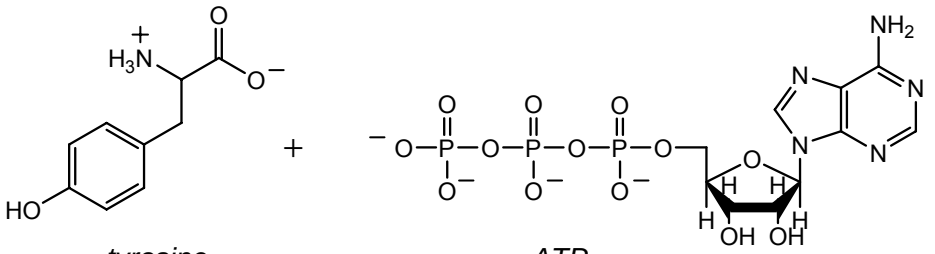
a) Where would you expect the macrocycle to spend most of its time in:

   i. A nonpolar solvent such as $CHCl_3$? Why?
   ii. An electron donor solvent such as dimethylsulfoxide, $(CH_3)_2S{=}O$? Why?
   iii. An electron acceptor (hydrogen donor) solvent such as methanol? Why?

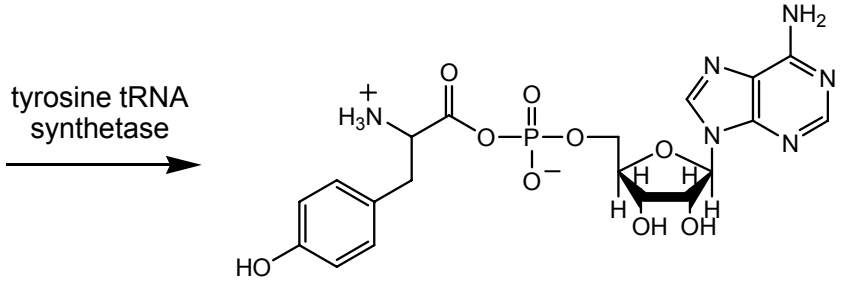
b) Propose your own rotaxane, with interaction groups A, B, C and D, that uses different sorts of interactions to control the response of the ring to its solvent environment. (In other words, don't use the same interactions that Leigh did. You may want to use *MPOC* Chapter 3 as inspiration for types of interactions.) Under what solvent conditions would your macrocycle shuttle from one station to the other?



2. Proteins typically bind other proteins and small molecules through multiple, low-energy interactions. One method that biochemists use to determine which amino acids participate in such interactions is site-directed mutagenesis—a technique in which, using molecular biology, one residue in the protein is substituted for a different one. Alan Fersht and coworkers have used this method to analyze the catalytic pocket of tyrosyl tRNA synthetase, an enzyme that catalyzes the formation of tyrosyl adenylate from tyrosine and ATP:[3]



tyrosine + *ATP*



tyrosine adenylate

In order to perform this catalysis, the enzyme has to bind one molecule of ATP and one molecule of tyrosine, each with a characteristic binding constant K_d:

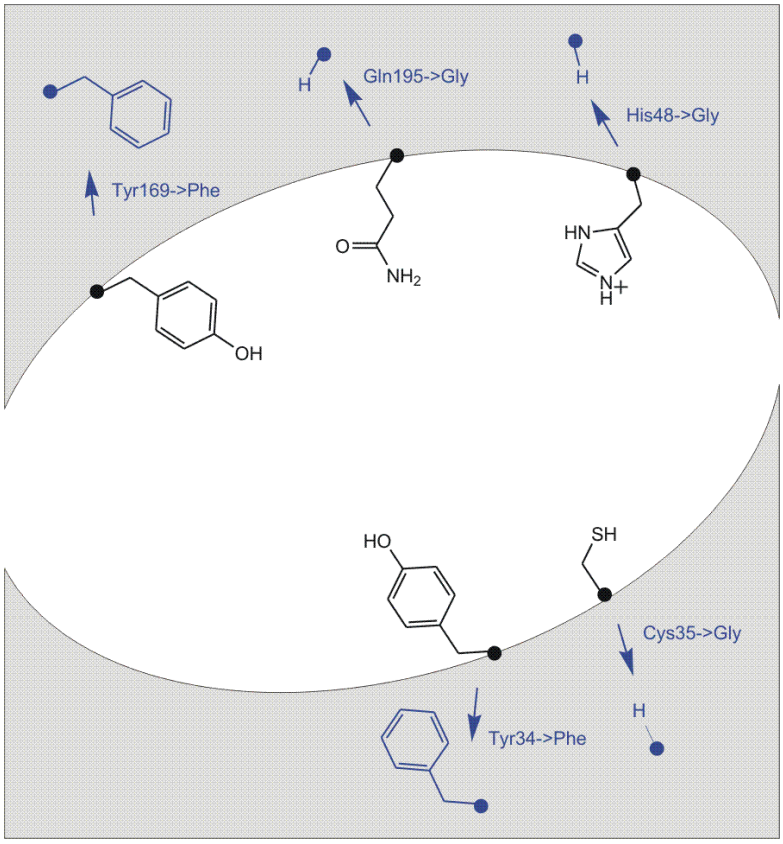
$$K_{d,\,ATP} = \frac{[enzyme][ATP]}{[enzyme \bullet ATP]};\quad K_{d,\,tyr} = \frac{[enzyme][tyrosine]}{[enzyme \bullet tyrosine]}.$$

On the next page are the results of experiments in which the Fersht group successively replaced one amino acid in the binding pocket of tyrosyl tRNA synthetase with another, and studied how this change affected the affinity of the enzyme for ATP and tyrosine. For each substitution, a value is listed for

$$K_{rel,ligand} = K_{d,ligand(substituted)}/K_{d,ligand(unsubstituted)}.$$

[3] Fersht, A. R.; Shi, J.-P.; Knill-Jones, J.; Lowe, D. M.; Wilkinson, A. J.; Blow, D. M.; Brick, P.; Carter, P.; Waye, M. M. Y.; Winter, G. *Nature* **1985**, *314*, 235-238.

	$K_{rel,ATP}$	$K_{rel,tyr}$
Tyr34 →Phe	1.0	2.3
Cys35 →Gly	2.7	1.1
His48 →Gly	1.2	1.3
Tyr169 →Phe	1.0	460
Gln195 →Gly	1.3	44



a) Which amino acid substitutions in the binding pocket had an effect on binding which substrate, and which didn't? For each substitution, are the substrates bound more or less tightly? In kcal/mol, how much more or less tightly?

b) What interactions may have been changed by each substitution? Draw the substrates in the binding pocket in a way that shows these interactions.

c) The strengths of the hydrogen bonds shown in *MPOC* Table 3.7 are between 3 and 9 kcal/mol. How do the interactions you described compare with this? If there are differences, why would there be?