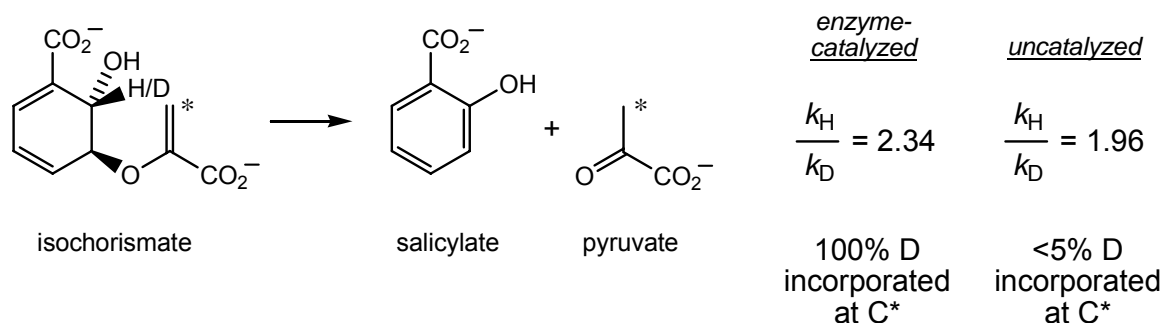## Problem Set 8
Due: *In class, Friday, December 1*

1. Hilvert and coworkers recently reported kinetic data for isochorismate pyruvate lyase (IPL), an enzyme that catalyzes the conversion of isochorismate to salicylate and pyruvate.[1] Kinetic isotope data for both the enzyme-catalyzed reaction, as well as for the uncatalyzed reaction (conducted in aqueous buffer at pH 7), are given below.

		enzyme-catalyzed	*uncatalyzed*
		$\dfrac{k_H}{k_D} = 2.34$	$\dfrac{k_H}{k_D} = 1.96$
isochorismate	salicylate pyruvate	100% D incorporated at C*	<5% D incorporated at C*

   a) In principle, this elimination reaction might occur by three different mechanisms: (i) E2, where either an external base or enzyme amino acid attacks the (H/D); (ii) E1, where pyruvate leaves first to generate an intermediate cation; and (iii) Claisen rearrangement, where the reaction occurs in one, concerted step. Draw the rate-determining transition state for each of these mechanisms.

   b) The enzyme-catalyzed and uncatalyzed reactions could proceed by the same mechanism or by different mechanisms. Which of the three possible mechanisms is consistent with the observed kinetic isotope effects for each reaction condition?

   c) The authors were also able to track the isotope in the product. Which of the three possible mechanisms is consistent with the isotope incorporation observed for each reaction condition?

   d) How might the IPL enzyme catalyze each of the three possible mechanisms?

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[1] DeClue, M. S.; Baldridge, K. K.; Künzler, D. E.; Kast, P.; Hilvert, D. *J. Am. Chem. Soc.* **2005**, *127*, 15002-15003.

2. Consider the nucleophilic substitution reaction shown in the net reaction below. Three possible mechanisms are also given, where single arrows indicate irreversible steps.
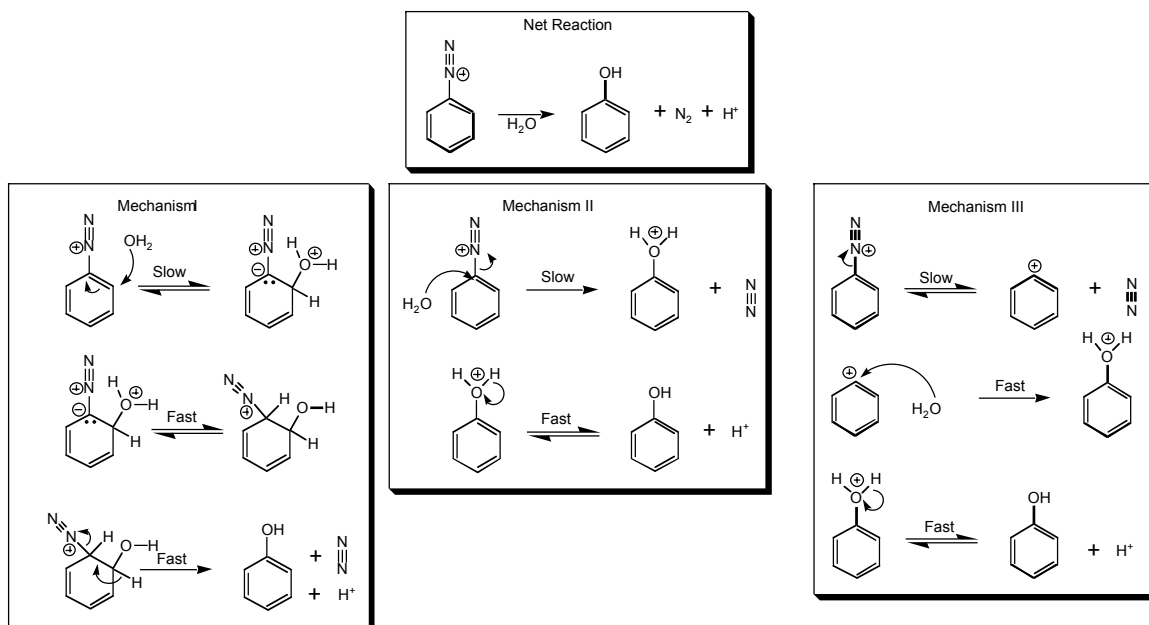
a) For the following observations, indicate whether they are consistent or not with each of the above three mechanisms.

   (i) Labeled $[\text{Ar-}^{15}\text{N}\equiv\text{N}]^+$ shows a significant heavy atom isotope effect, $k_{14N}/k_{15N} = 1.04$.

   (ii) When the reaction is interrupted before completion, a small amount of $[\text{Ar-N}\equiv^{15}\text{N}]^+$ can be detected, which has been formed from the $[\text{Ar-}^{15}\text{N}\equiv\text{N}]^+$ reactant.

   (iii) Labeling both of the *ortho*-hydrogens resulted in a kinetic isotope effect of $k_H/k_D = 1.22$.

   (iv) $\Delta S^{\ddagger} = +44$ J mol^{-1} K^{-1}.

b) Consider a series of aryl diazonium ions substituted at the para position. What will be the slope of a log(k) vs. σ plot (i.e. positive, negative or close to zero) for the mechanism that is most consistent with the combined data above? Briefly explain your answer.

Problem to try on your own:

MPOC, Chapter 8: Problem 28.