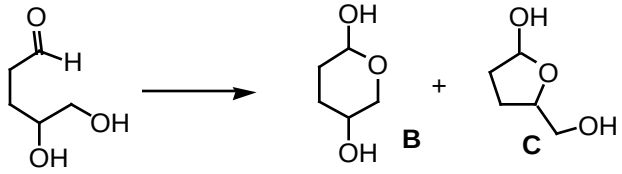
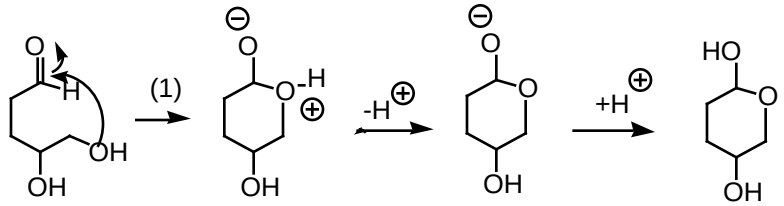
Chemistry 304B The last problem set KEY Spring, 1999

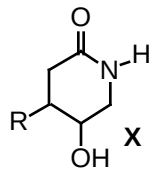
1. When two pathways are readily accessible, it is often desirable to design a catalyst which accelerates one of the pathways selectively. Consider the following reaction, which gives a mixture of **B** and **C**.



A. The formation of both **B** and **C** occurs slowly at pH 7, and without much selectivity. *Write a mechanism to show the formation of **B** at pH 7.*



B. (14 pts) In these modern times, a clever organic chemist ought to be able to analyze the reaction and create an antibody which would serve as a catalyst selective for **B**. In a crude attempt, the molecule **X** was prepared as the key structural piece of an antigen to stimulate antibody formation. From the array of antibodies produced, one was isolated which selectively accelerated the formation of **B**.



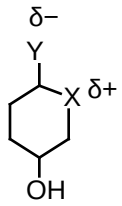
R = side chain to protein to favor antibody generation

1. *Analyze **X** as the choice for antigen. Include in your answer (a) what the goal is in designing an antigen to generate a catalyst, (b) identify and discuss the rate-determining step for formation of **B**, (c) describe the hypothetical ideal antigen, and (d) analyze **X** as the choice for the antigen; (n what aspect(s) does **X** satisfy the ideal?). It might help to consider an important resonance structure for **X**.*

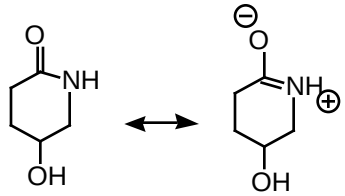
a. The Antigen sholuld mimic the transition state for the rate-determining step of the desired reactgion--this includes atom position (conformation, structure) and partial charges).

b. For **B**, rate determining step is the addition to the carbonyl (step 1)

c. The ideal antigen will have a 6-membered ring, with δ+ on a ring atom, δ- on an adjacent external atom, and an -OH substituent:

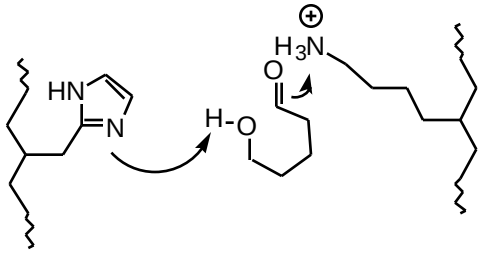


d. The compound **X** has the correct ring size, the correct -OH for binding or recognition. An important resonance structure shows there are partial charges in the right place:



2. The antibody catalyst has an "active site" which provides binding and also chemical interactions to accelerate the process. *Which of the common amino acids might be located in the active site in order to provide the chemical interactions which speed the formation of **B**? Choose the two most important candidates and explain your choice in words and pictures.*

The rate determining transition state will be stabilized by positioning a proton or Lewis Acid near the δ−, and by positioning a (-) or base near the δ+. Typical base: histidine Typical H^+: serine, tyrosine, lysine (protonated)



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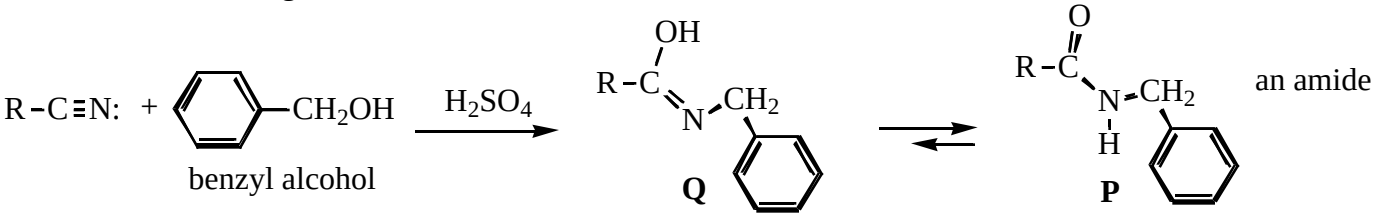
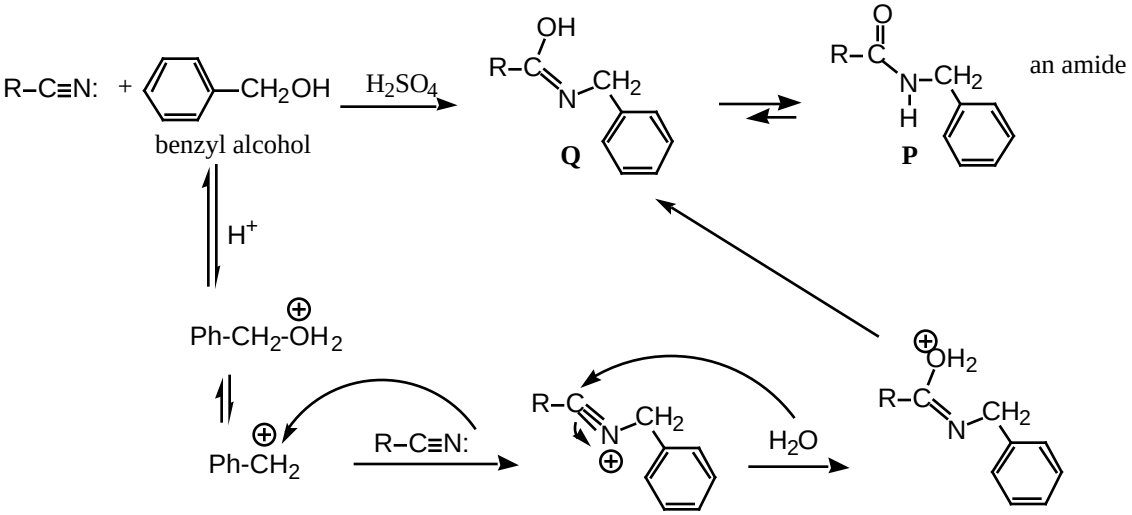
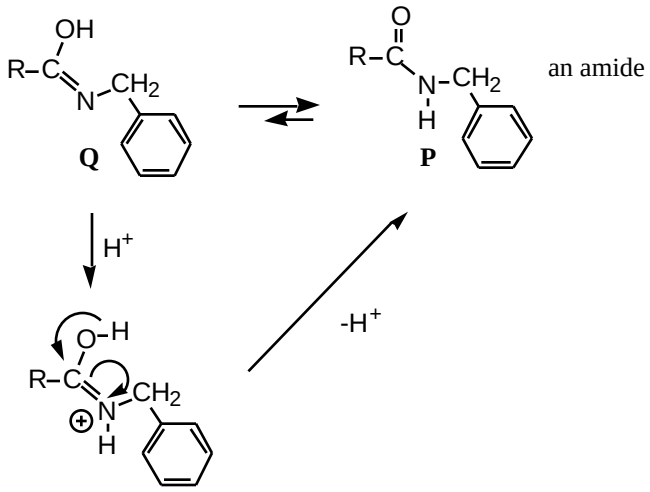
2. A special "hydrolysis" reaction can convert nitriles into amides. An example is the reaction of a nitrile (R-CN) with benzyl alcohol in the presence of strong acid. A key intermediate is **Q**, which is not stable under the reaction conditions and rearranges to **P**.



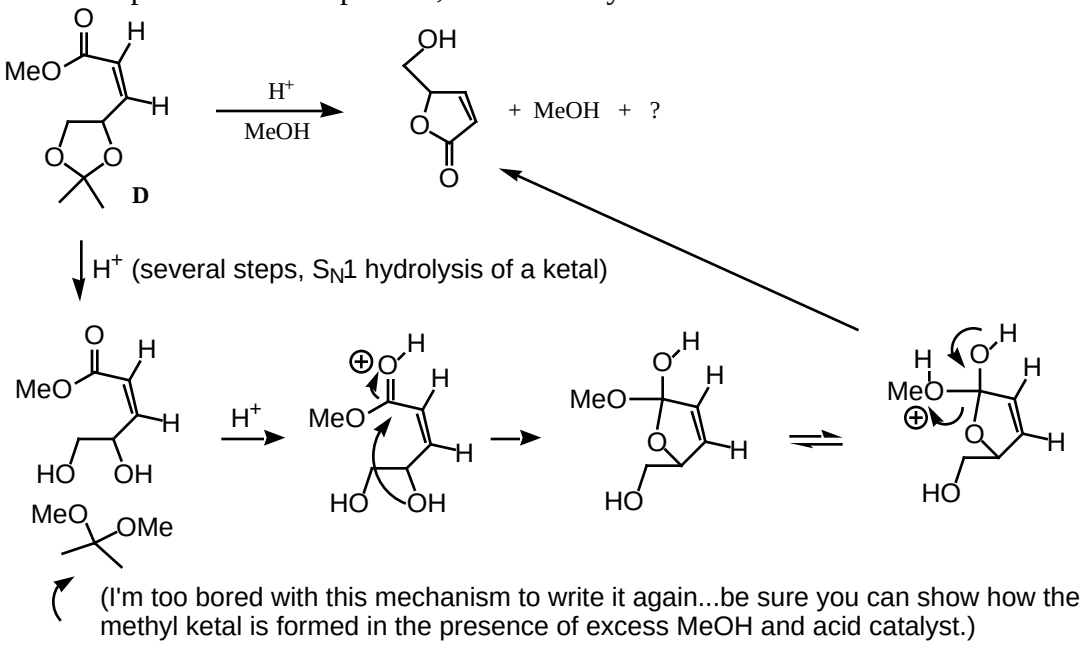
*A. Please write a careful mechanism for the conversion of the nitrile to **Q**. Your mechanism should be consistent with the fact that MeOH is not a successful replacement for benzyl alcohol. Why? Your mechanism should also be catalytic in protons (acid).* Start by noting the connectivity in **Q** relative to the reactants.



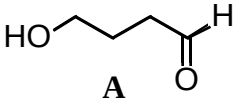
*B. Suggest how **Q** changes into **P**, especially how the acid present might accelerate this process.*



3. Note the reaction of compound **D** in the presence of methyl alcohol and acid. *Write a careful stepwise mechanism for the formation of the product, showing key intermediates and using the usual arrow formalism to show electron flow. You need not show every trivial proton transfer.* It will be helpful to note at first which atoms are preserved in the product, and how they are connected.

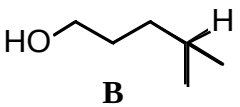


4. The molecules **A** and **B** are somewhat related structurally. Under the same conditions of <u>mild</u> treatment with acid in solution in methyl alcohol, **A** is rapidly converted to a product **C** (racemic mixture) while **B** is left unreacted. Under more vigorous conditions, with H_2SO_4 in MeOH, **B** is converted to **D.** Consider the spectral data for **C** and **D**, and the possible mechanisms.



dilute H^+, MeOH → (mild) **C**

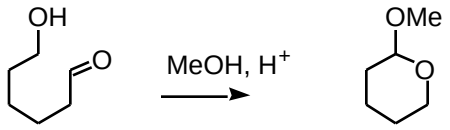
^{1}H NMR: δ 1.5 (2H, quintet); 1.7 (2H, quart), 3.5 (3H, s), 4.0 (2H, t), 5.7 (1H, t) All J = 7 Hz
IR: no significant peaks between 1500-4000 cm^{-1} except for C-H stretches
MS: parent ion at 102; P+1 is 6%



H_2SO_4, MeOH → (heat) **D**

^{1}H NMR: δ 0.9 (6H, d); 1.3-1.7 (5H, mulitplet), 3.6 (3H, s), 4.0 (2H, t). All J = 7 Hz
IR: no significant peaks between 1500-4000 cm^{-1} except for C-H stretches.
MS: parent ion at 116; P+1 is 8%

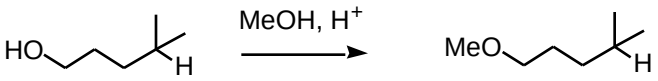
*A. (12 pts) Draw the structure of **C** and a careful mechanism for its formation.*



C

Standard hemiacetal formation followed by glycoside bond formation (acetal formation)

*B. (10 pts) Draw the structure for **D** and a careful mechanism for its formation.*



Standard acid-promoted S_N2 ether formation

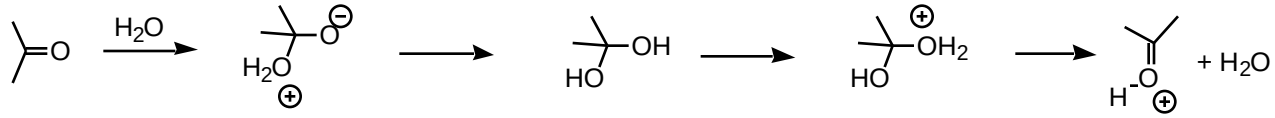
5. Consider the following observations:

A. When acetone is dissolved in H_2O, there is the expected ^1H NMR spectrum, with a singlet at δ 2.2. When the acetone is recovered from the water and studied by mass spectrometry, there is the expected pattern with the parent ion appearing at 58 mass units.

B. When acetone is dissolved in H_2O^{18} at pH 8, there is no significant change in the ^1H NMR spectrum, but the mass spectrum of the recovered acetone shows large peaks at 58 and 60. As the acetone is allowed to be in contact with the H_2O^{18}, the peak at 60 increases and the peak at 58 decreases. At higher pH (e.g., pH 10), the peak at mass 60 appears much more quickly.

C. When acetone is dissolved in D_2O, the singlet peak in the ^1H NMR spectrum for the acetone slowly becomes more complex and weaker in intensity, until, at long times, the signal for acetone disappears entirely to be replaced by a peak characteristic of HOD. Again, the changes in the ^1H NMR spectrum are faster at pH 10 compared to pH 7.

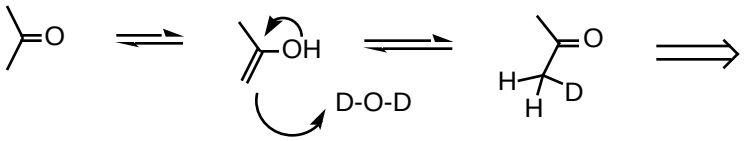
1. Use words and pictures (mechanism) to account for the change in the mass spectrum for acetone as the acetone is exposed to H_2O^{18}. Write the mechanism carefully, showing all intermediates and using the arrow formalism to show electron flow. Include in your discussion the reason why the change happens faster when the pH is raised.



Oxygen exchange by addition/elimination of water.

Accelerated by base as HO^- is generated from the water, and therefore adds faster to the carbonyl carbon in the first step.

2. What is happening in D_2O? Explain with words and a careful mechanism, including a rational for the more rapid changes at higher pH. Why does the acetone signal (singlet at δ 2.2) disappear from the NMR spectrum?



repeat in the presence of excess D_2O.

The enolization in step 1 is accelerated by abstraction of the proton next to the carbonyl carbon by base: