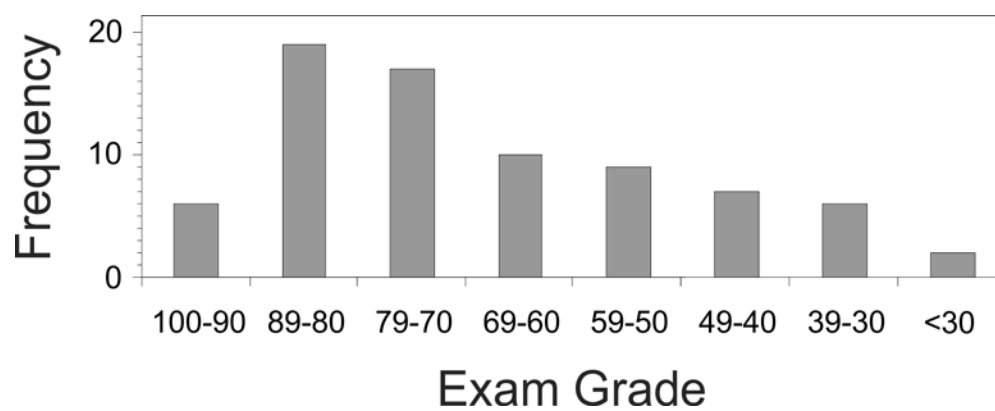
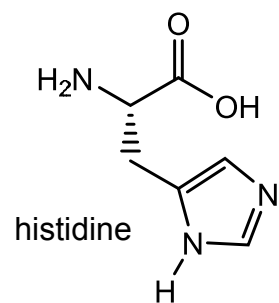


**Exam 4  
Answer Key**

Exam 4 Mean: 67  
Exam 4 Median: 71  
Exam 4 St. Dev.: 19



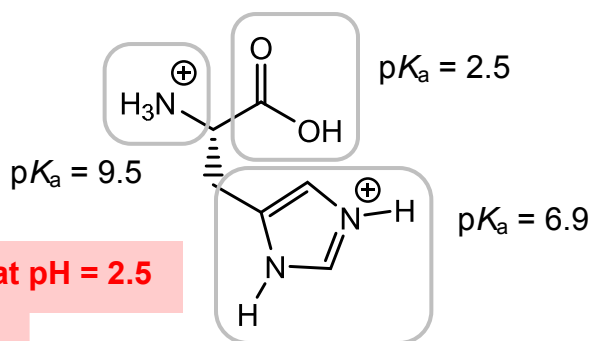
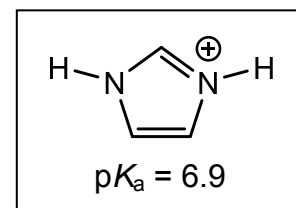
1. (24 pts) L-Histidine is one of the twenty common amino acids. The imidazole side-chain of histidine is basic, and the conjugate acid of imidazole—imidazolium ion—has a  $pK_a = 6.9$ .



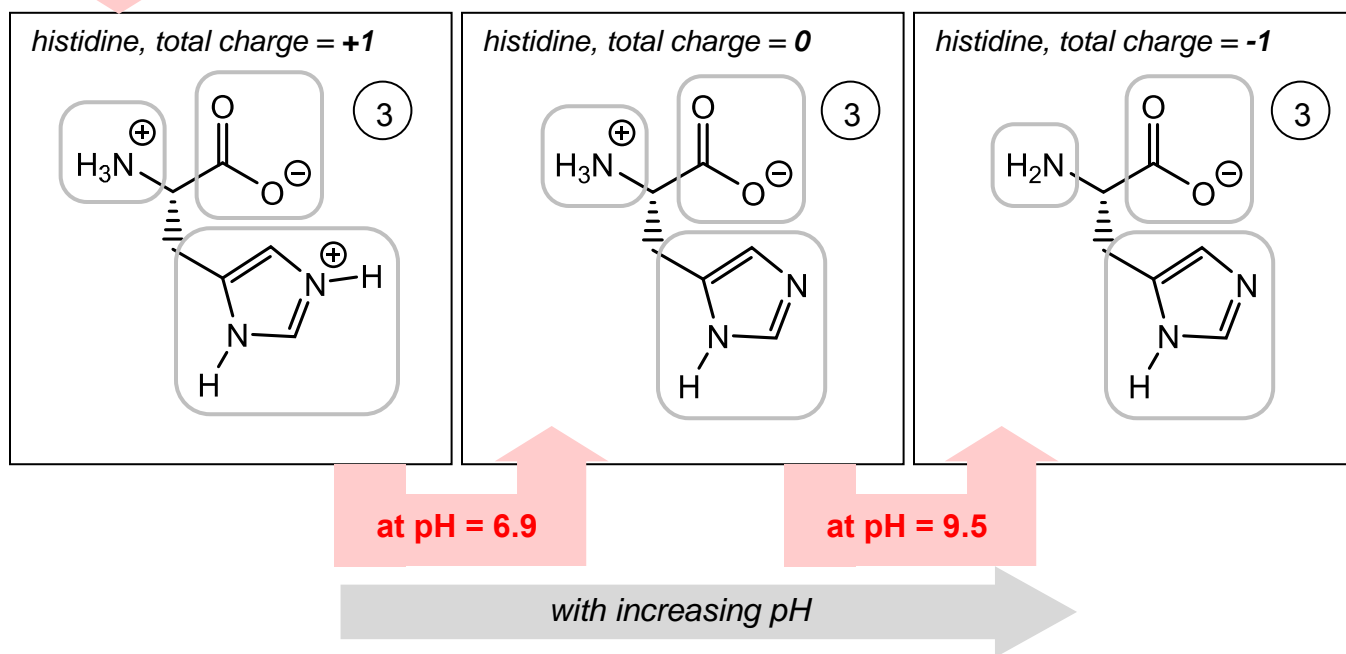
a. Histidine can exist in different charge states, depending on solution pH. In the boxes below, draw three full chemical structures of histidine that you would expect to find at different pH values. Draw structures with a total charge of +1, 0, and -1.

b. What would you predict for the isoelectric point (pI) of histidine?

pI = 8.2 3  
*for any answer between 8.1 and 8.3*



In order to determine the pI of a polyprotic acid, we can start with the fully protonated form (the form that exists at low pH), and then use the  $pK_a$ 's of each acidic proton to predict the structures that will predominate at increasing pH.



To calculate pI, we then average the  $pK_a$ 's of the two acid-base steps bordering the charge = 0 state. In this case, that is the average of 6.9 and 9.5.

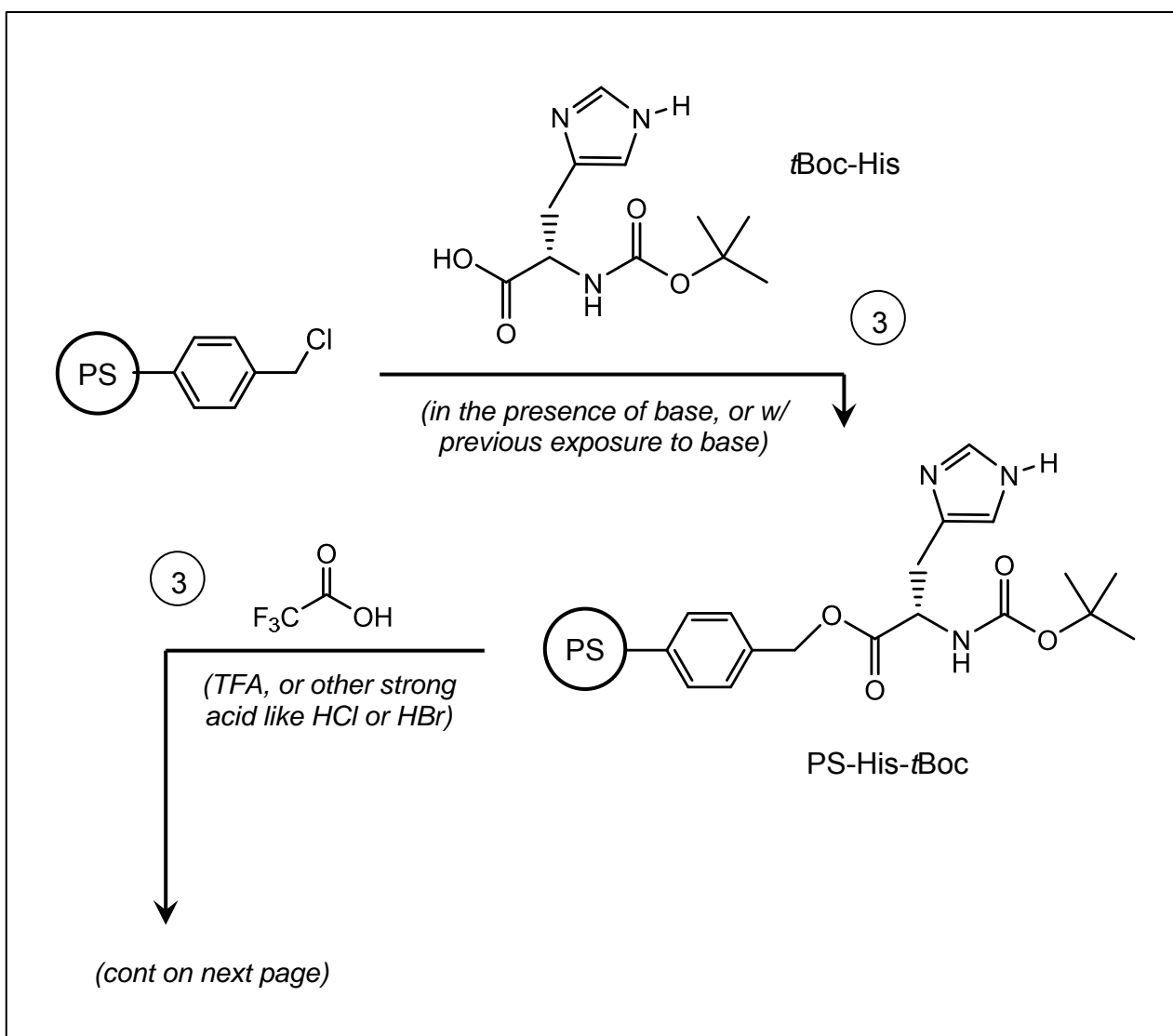
Rubric for this part:

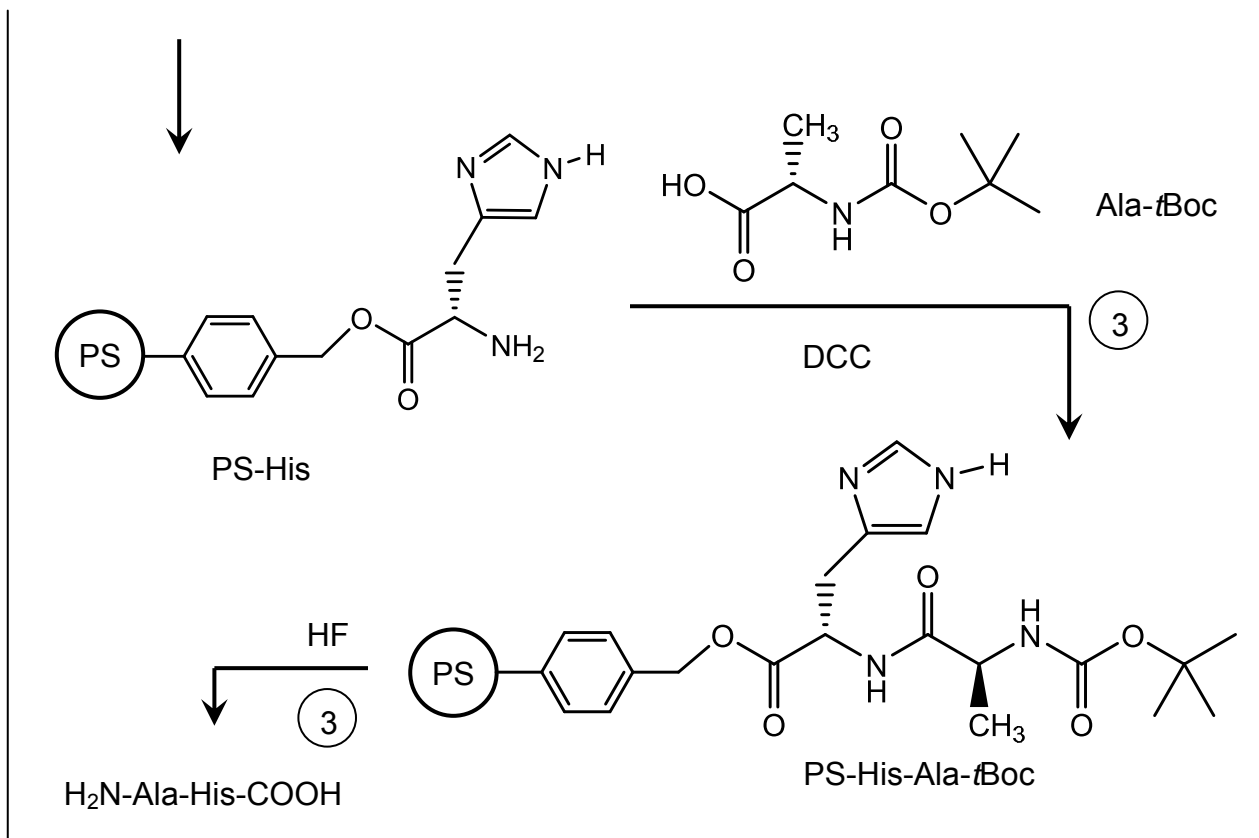
3 points for each box.

+1 point for each correctly illustrated protonation/charge site (circled in gray above, for a total of 3 points each box).

No partial credit if the total molecular charge doesn't match the box.

- c. In the box on the next page, propose a multistep, solid-phase synthesis of alanyl histidine,  $(H_2N)$ -Ala-His-(COOH), starting from chloromethylated polystyrene. You do not need to draw any chemical structures to answer this problem; you can refer to molecules by name or chemical abbreviation. In addition to the starting materials shown at right, you can use any reagents and reactions we've learned about in class.





Rubric for this part:

This synthesis requires four tasks, listed below. Each task was worth 3 points (for a total of 12 points this box). Each task is judged separately, and does not require that the synthesis makes sense, or that other tasks are correct. However, you could lose points for putting steps out of order, if having them out of order caused the synthesis to fail.

*We did not judge structures in this problem; you could abbreviate reagents, intermediates and products how you liked, as long as they were identifiable. We judged each element of your synthesis only on conceptual content.*

*-2 points if step reagents are incorrect, but reaction could otherwise be accomplished with correct reagents; or if reagents were correct, but gave the wrong outcome.*

**1. Combine PS-Cl with *t*Boc-His, or with Fmoc-His.**

For full credit, you needed to add *t*Boc-His first (and not *t*Boc-Ala).

*-1 point for adding *t*Boc-Ala first instead, or for not identifying amino acid.*

*-1 point for omitting base.*

**2. Deprotect first *t*Boc with TFA, or Fmoc with piperazine.**

*-2 points for deprotecting before adding amino acid to support (before step 1).*

**3. Add *t*Boc-Ala or Fmoc-Ala with DCC.**

-1 point for adding *tBoc/Fmoc-His* instead, or for not identifying amino acid.  
 -2 points for omitting DCC.

**4. Deprotect and cleave peptide from solid support with HF (in one step for *tBoc* synthesis), or deprotect in piperazine and cleave with HF separately for *Fmoc* synthesis.**

Fine to deprotect and cleave in separate steps.

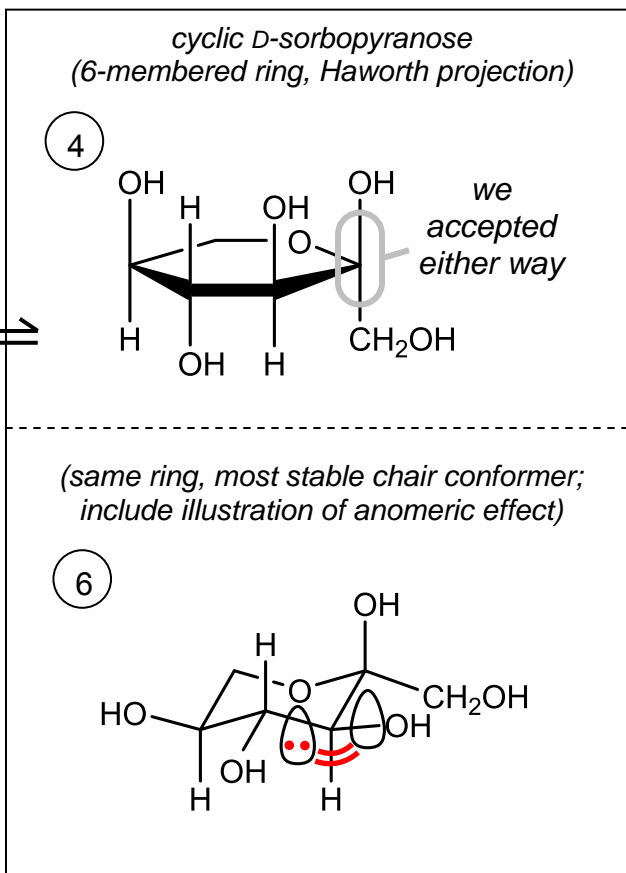
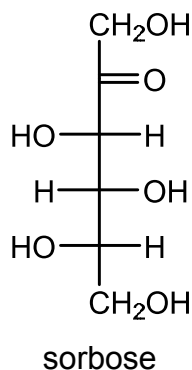
2. (26 pts) The acyclic structure of D-sorbose, an epimer of fructose, is shown below as a Fischer projection. This acyclic structure equilibrates with both 5-membered ring (furanose) and 6-membered ring (pyranose) forms.

a. In the box on the right, draw the most stable 6-membered ring structure as a Haworth projection.

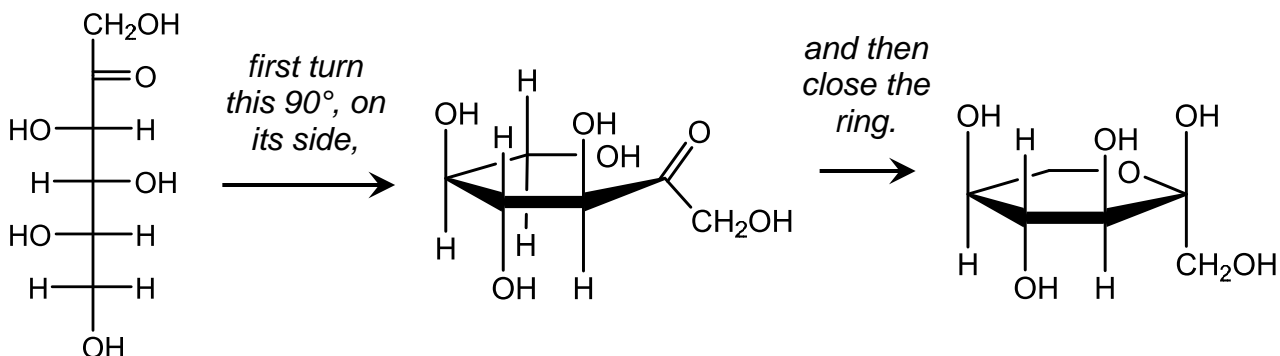
b. Then, below that Haworth projection, draw the same ring as its most stable chair conformer.

Your chair should have an axial -OH group at the anomeric carbon; this is the most stable anomer of sorbose.

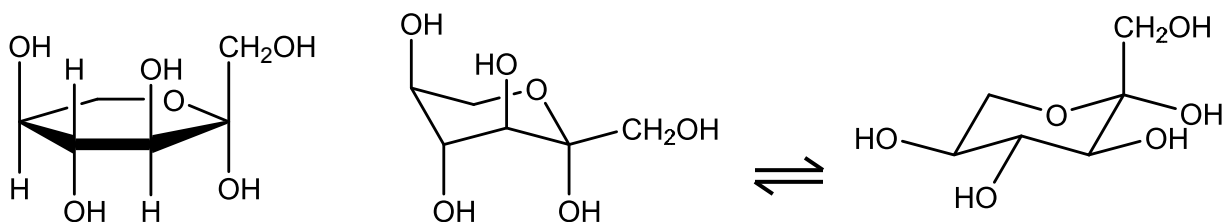
c. In your chair conformer, the axial -OH is stabilized by the “anomeric effect”, a specific molecular orbital interaction. Illustrate that molecular orbital interaction on your drawing on the previous page, drawing lobes for orbitals.



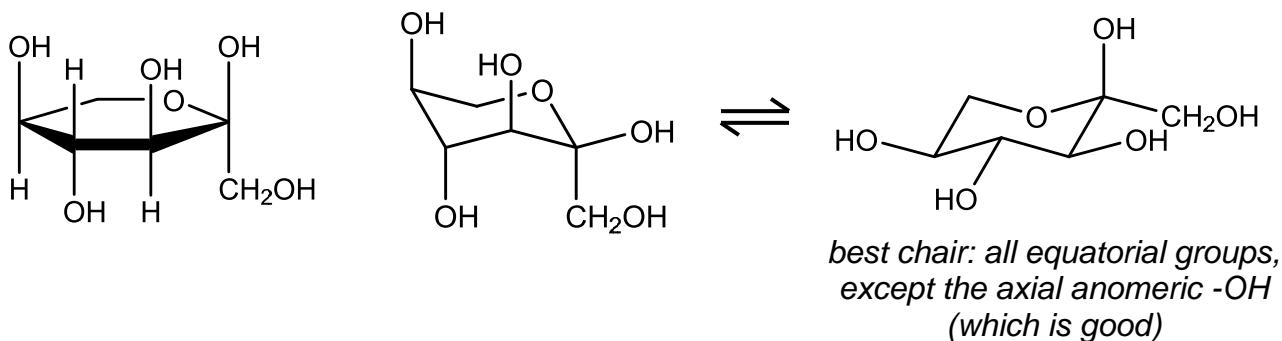
This problem asked you to draw a six-membered ring from the acyclic sorbose structure, and the starting acyclic structure is mostly ready for you to do this--no bonds need to be twisted in order to lie up all six atoms that will be in the ring.



In principle, the -OH and -CH<sub>2</sub>OH groups on the anomeric carbon could go either way, up or down. But I think one of these ways is more stable than the other; the most stable arrangement of groups we can draw is a chair in which the anomeric -OH is axial, the -CH<sub>2</sub>OH is equatorial, and as many of the other groups are equatorial as we can manage. If we imagine the anomeric -OH down, neither of the resulting equilibrating chairs was that great:



But if you drew the anomeric -OH up, you could draw the most stable chair of them all:



So when the problem asked for the most stable 6-membered ring, this was the correct answer. We accepted the other ring (-OH down, -CH<sub>2</sub>OH up) as an answer to the first part, even though technically it is incorrect, and took off points from the second part if you drew this arrangement.

Rubric for this part:

4 points for Haworth 6-membered ring.

*C2 (anomeric) carbon can go either way for this problem only. (In reality, it will go up, but we didn't grade that here.*

*-1 point for each incorrect functionality or stereochemistry at each carbon.*

4 points for chair.

*For sorbose, most stable chair puts as many large groups equatorial as possible. That's all of them!*

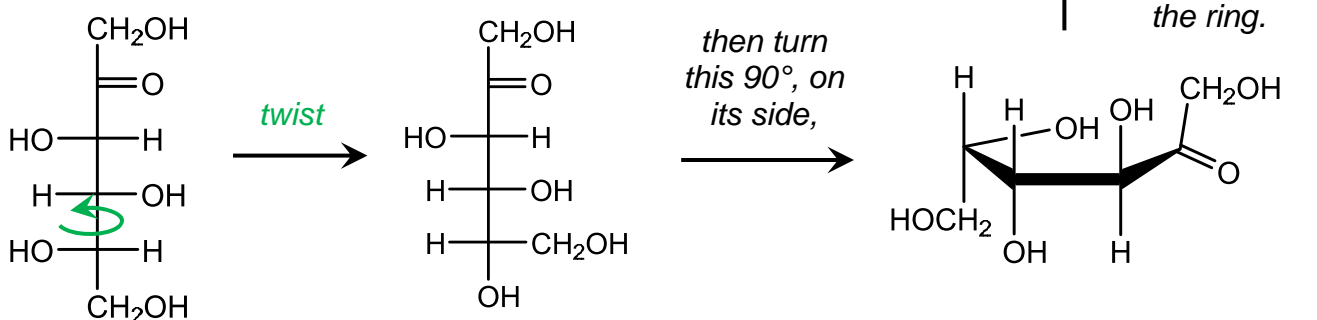
*-1 point for each non-equatorial -OH other than C2 (anomeric).*

2 points for drawing orbitals.

*No partial credit. You did not have to draw electrons, just orbital lobes.*

- d. In the box on this page at right, draw the 5-membered ring (furanose) structure as a Haworth projection.

Once again, we can take a vertical Fisher projection, turn it on its side, and curl it to create the Haworth projection cycle. This time, we have to rotate a bond to place the right -OH group in the cyclized set of atoms:



This problem specifically asked for the  $\alpha$ -anomer in the box, but we accepted either the  $\alpha$  or  $\beta$ -orientation of groups in your answer.

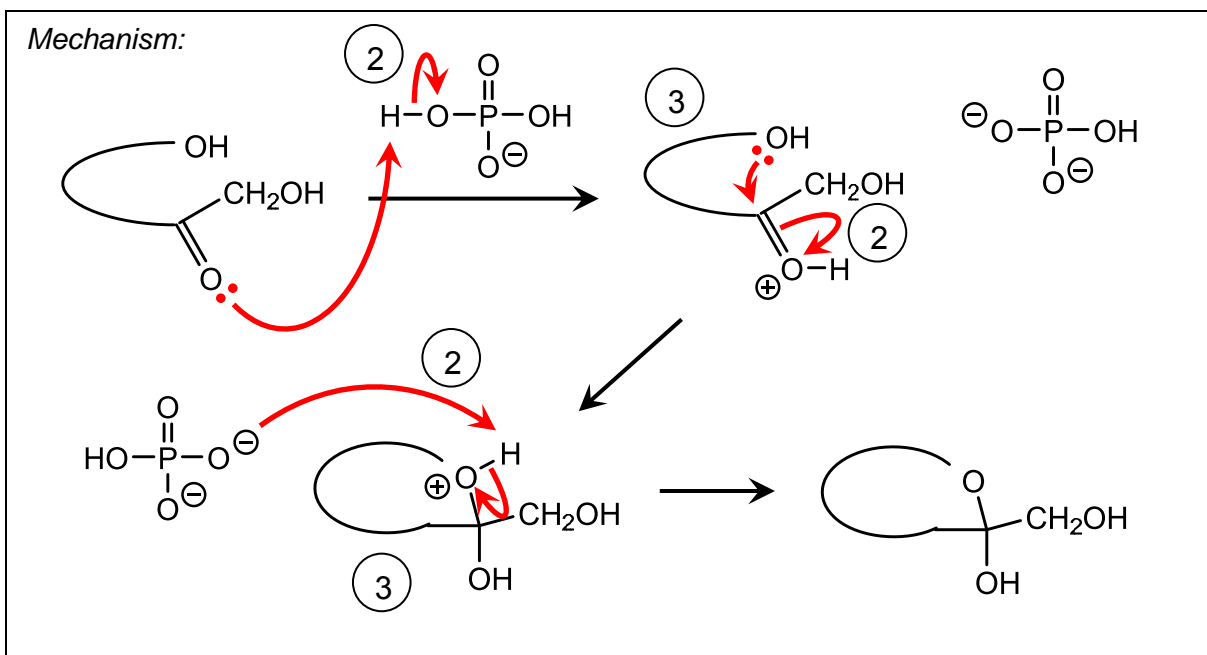
Rubric for this part:

4 points for Haworth 5-membered ring.

*C2 (anomeric) carbon can go either way for this problem only.*

*-1 point for each incorrect functionality or stereochemistry at each carbon.*

- e. Acyclic and cyclic sorbose equilibrate spontaneously in acidic phosphate buffer. In the box below, draw a mechanism (using “electron pushing”) that illustrates how acyclic sorbose becomes cyclic sorbose under acid catalysis. Feel free to abbreviate the sugar backbone and any unchanged -OH functional groups as a cartoon loop or squiggle, as shown; you do not need to draw the entire sugar structure.



Rubric: (12 points total.)

2 points for each electron-pushing step.

3 points for each intermediate.

Overall notes:

Overall, the minimum score for each step is zero; errors in a step cannot earn you negative points that count against another, correct step.

Spectators may be omitted.

Resonance is NOT a mechanistic step; it is just multiple ways of drawing the same intermediate. As a result, we did not evaluate electron-pushing that showed resonance—you can push electrons for resonance, or not, your choice. In addition, resonance does not have to be shown as an explicit “step”—it can be combined with adjacent steps, for full credit.

-1 point, for each arrow in each step, for errors in drawing arrows. Arrow must start at an electron pair, and end at nucleus where electrons will newly interact. Can only lose points if you get them.

-1 point for each minor error in charge, valency, structure, etc.; if error propagates, points are taken off only for initial error.

-1 point for each use of a generic or incorrect acid/nucleophile/base. You can pretty much only use  $\text{H}_2\text{PO}_4^-$  and  $\text{HPO}_4^{2-}$  as acid and base in this problem.

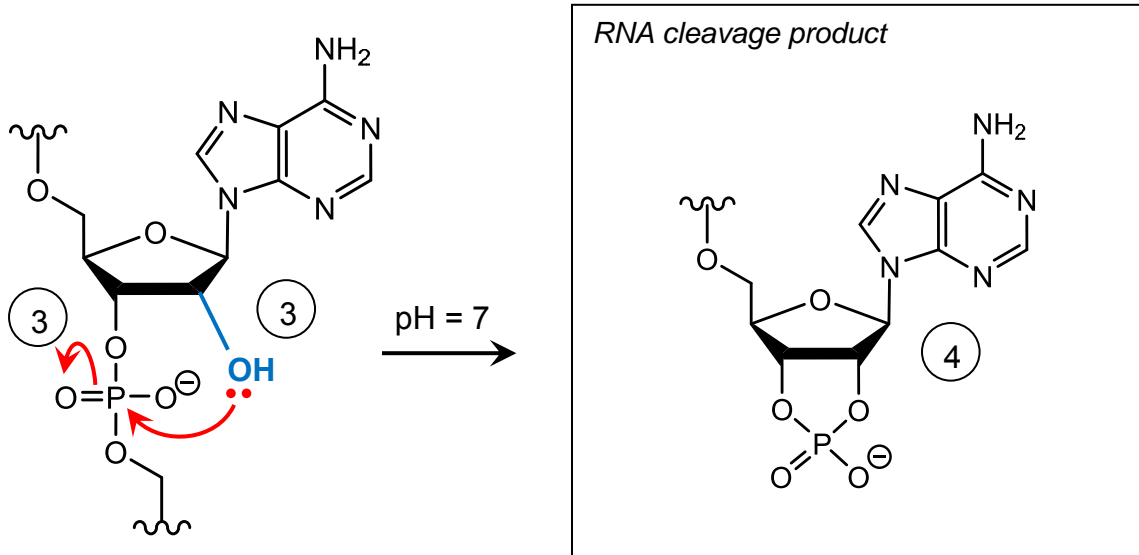
If you combine steps that can't be combined, you can get points for arrows that are in the rubric, but not for the intermediate you skipped.



3. (13 pts)

a. A generic structure of an adenine nucleotide in DNA is shown on the next page. **Draw one change to that structure** so that it shows RNA instead. Draw directly onto my structure—there is no need to draw a whole new molecule.

b. This change makes RNA undergo intramolecular cleavage more rapidly than DNA. In the box on the right, draw the cyclic phosphate generated by RNA strand cleavage at pH = 7.



c. On the starting material above, add curved arrows to illustrate the first step in the mechanism of this cleavage reaction.

Rubric for parts (a) - (c):

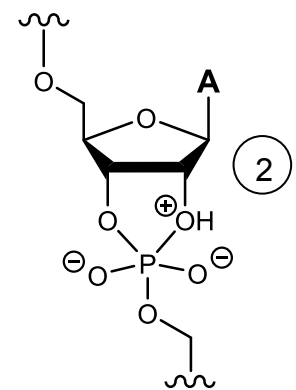
3 points for adding an -OH group to the 2' carbon.

3 points for electron pushing of -OH onto phosphate P=O bond.

*1 point partial for just one of two arrows correct.*

4 points for cyclic phosphate structure.

*2 points partial for drawing pentavalent phosphorus that is formed prior to cleavage.*



d. At pH = 7, which of the following statements about DNA and RNA is true?

RNA is more stable than DNA.

RNA is less stable than DNA.

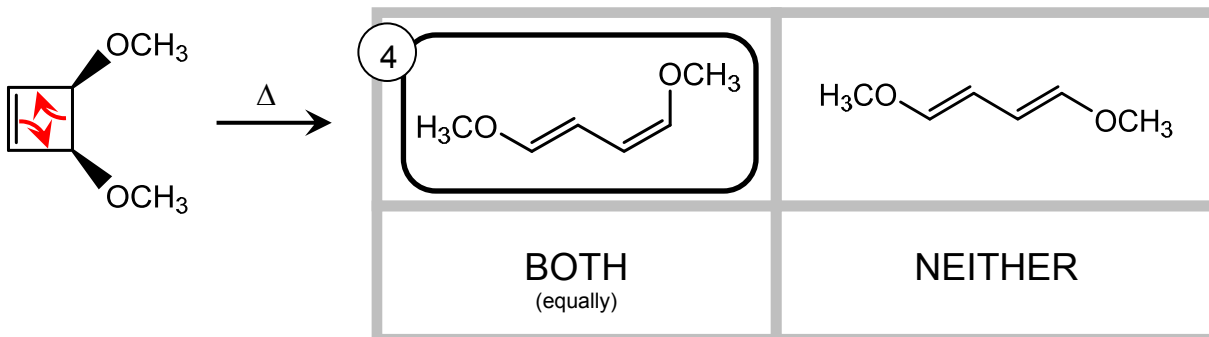
or

RNA and DNA are equally stable.

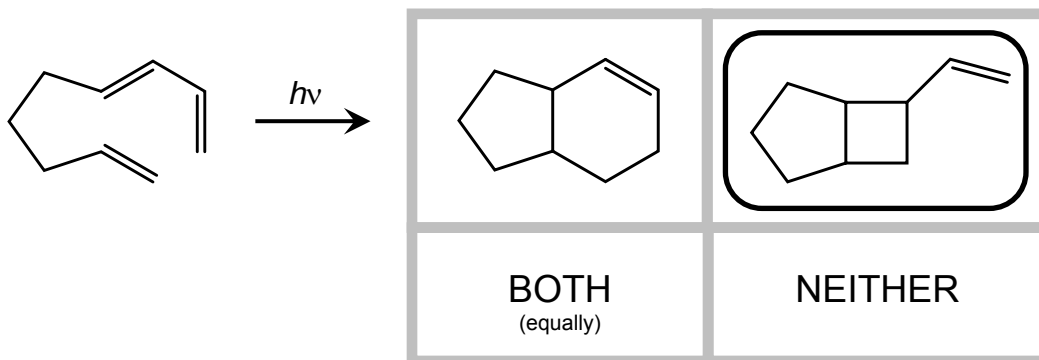
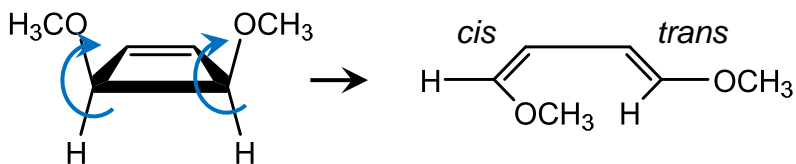
(Circle one.)

3

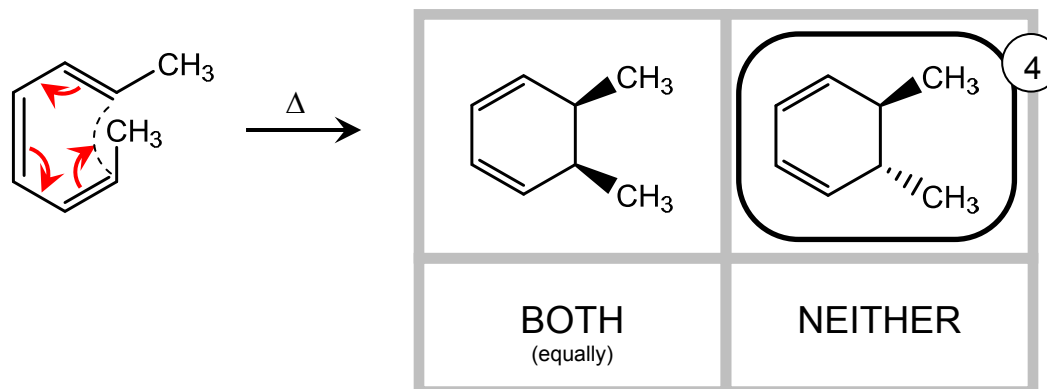
4. (12 pts) Each of the reactions below is drawn with two possible products. Circle the preferred product. If the two products are produced equally, circle "BOTH". If neither product would result from the reaction, circle "NEITHER". **Circle one answer only.**



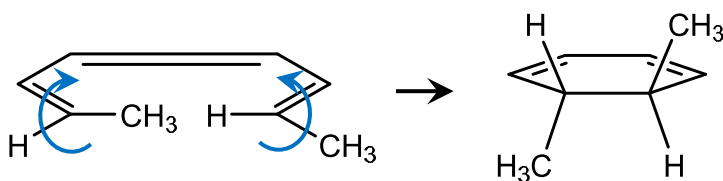
This is an electrocyclic ring opening reaction. The Woodward-Hoffman rules for electrocyclic ring opening reactions say that, if the reaction involves an even number of pairs of electrons (i.e., an even number of drawn curly arrows), it is conrotatory.



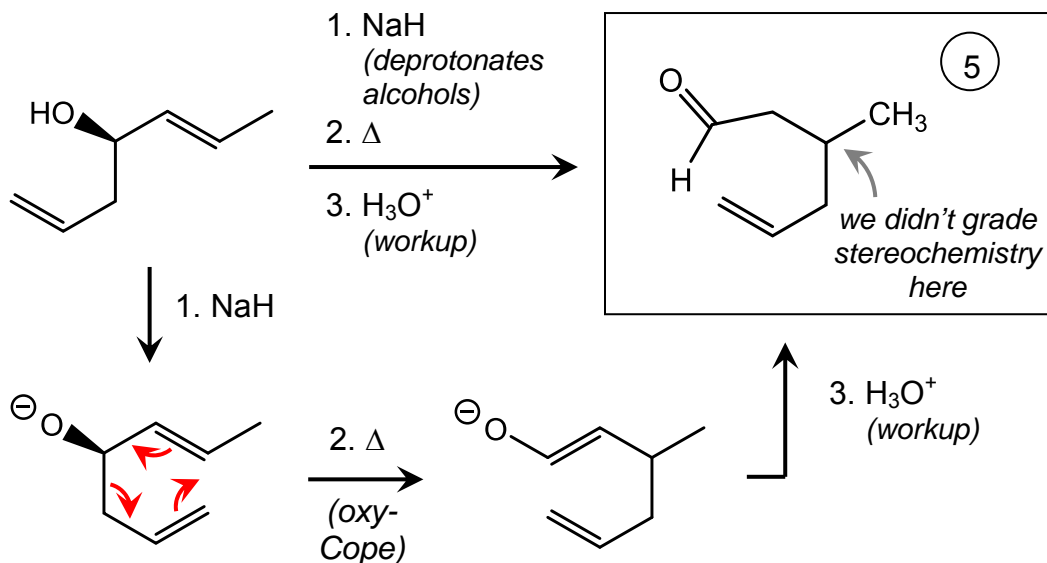
This question asks, what type of cycloaddition reaction is photochemically allowed by the Woodward-Hoffman rules: a Diels-Alder ([4+2]) reaction, or a [2+2] reaction? The Diels-Alder reaction works with heat, not light, and the [2+2] cycloaddition (shown by the product on the right) works with light, not heat.



Electrocyclic ring closure. This one is drawn with three curved arrows, so Woodward-Hoffman rules say disrotatory:



5. (25 pts) For each of the reactions below and on the next page, fill in the empty box corresponding to reactants or product. Give only one answer in each box. For reactions that you expect to yield multiple products, draw one major product. For reactions that yield multiple enantiomers, draw only one enantiomer in the box, and include the note “+ enantiomer”.

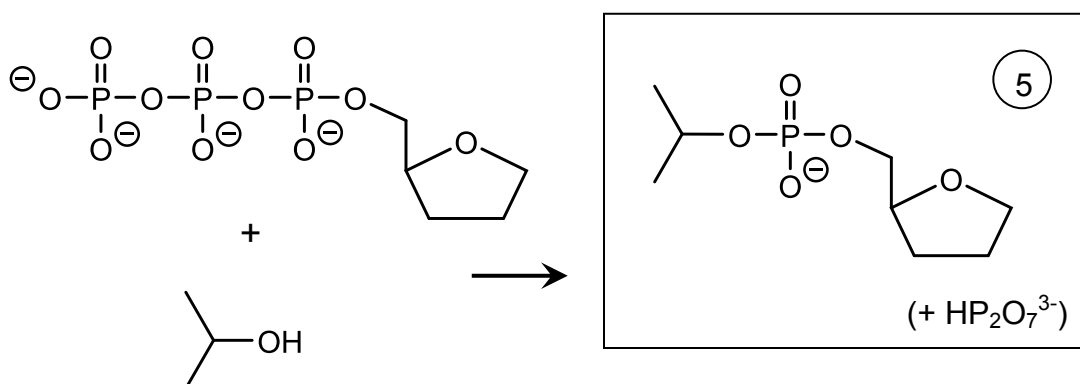


Rubric for this question:

Full credit (5 points) for correct product structure.

We did not grade stereochemistry, or whether you included "+ enantiomer" or not, in this problem.

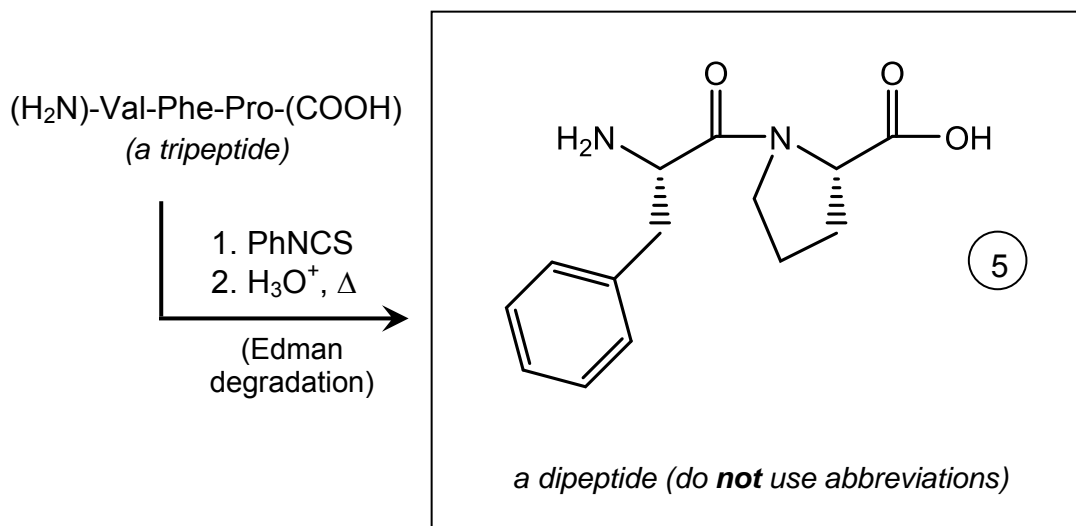
-2 points for each for each clearly trivial structure mistake. This included having an extra carbon in the chain, or omitting the methyl group.



Rubric for this question:

Full credit (5 points) for correct product structure.

-2 points for each for each clearly trivial structure mistake.

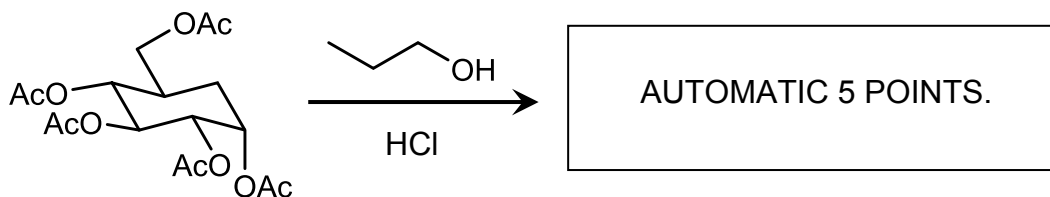


Rubric for this part:

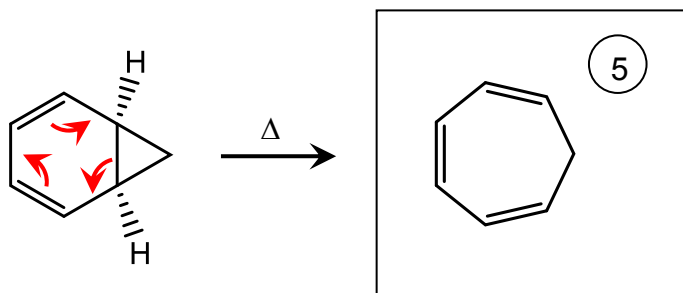
5 points for correct structure.

-1 point for each stereochemistry error.

-2 points for each clearly trivial structure mistake.



The starting material was supposed to be a sugar, but it's missing an oxygen in the ring. As a result, the starting material doesn't have a glycosidic carbon (where the reaction is supposed to happen), and nothing would happen.



Rubric for this part:

5 points for correct structure.

*-2 points for each clearly trivial structure mistake; number of carbons in the ring, and number of double bonds, were **\*not\*** trivial errors.*