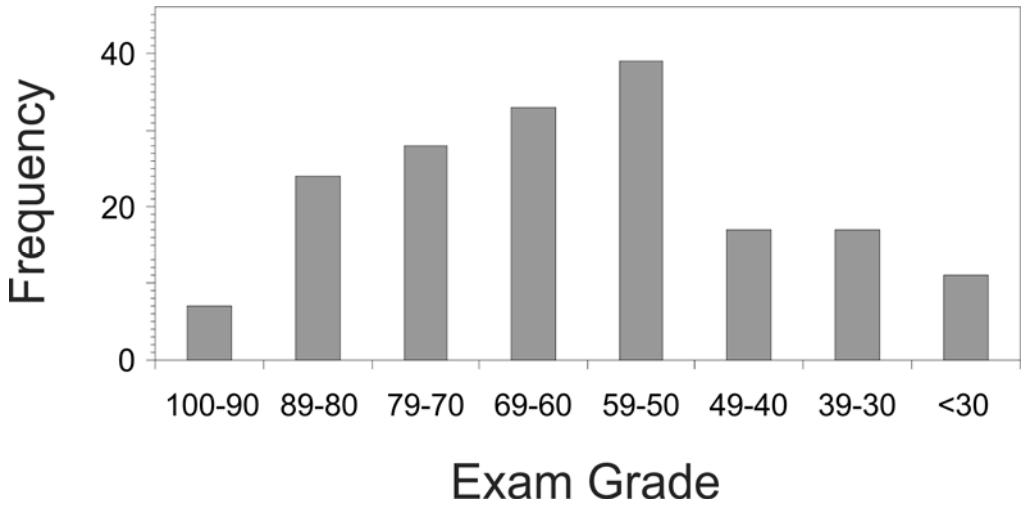
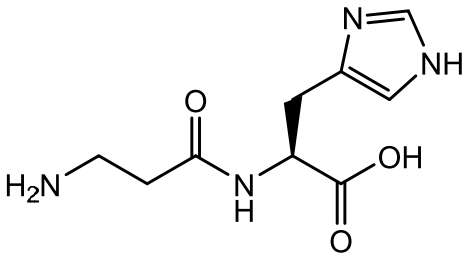
Exam 4
Answer Key

Exam 4 Mean:	61
Exam 4 Median:	61
Exam 4 St. Dev.:	19

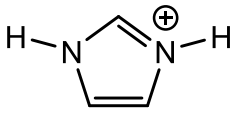


1. (25 pts) Carnosine (shown at right) is an antioxidant dipeptide found in muscle. Carnosine is unusual in that it contains β-glycine—a variant of glycine that contains two carbons in between the amine and the carboxylic acid, rather than just one.



carnosine

Helpful information for this problem:

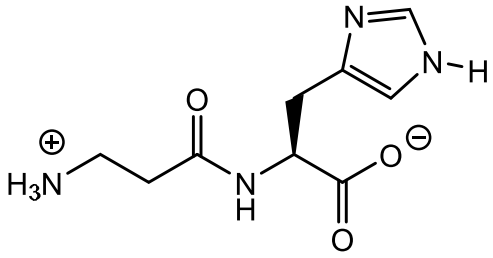


imidazolium (pK_a = 6.9)

a. In the box at right, draw the structure of carnosine that you would expect to find most commonly at its isoelectric point (pI).

carnosine structure at pH = pI:

4



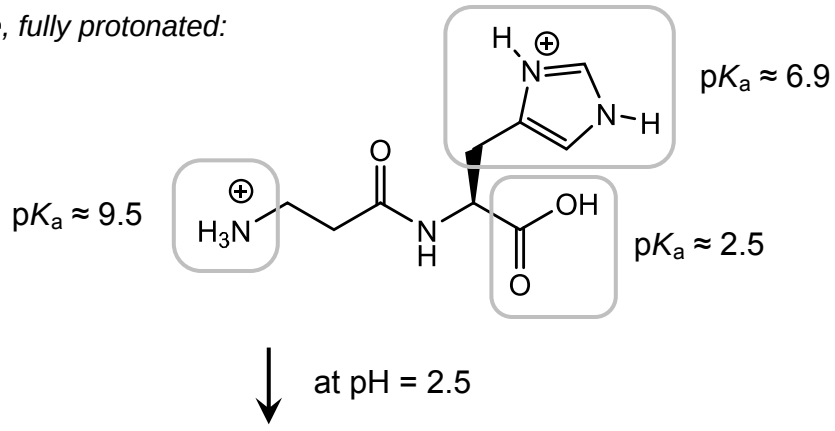
Rubric for this part:
4 points.

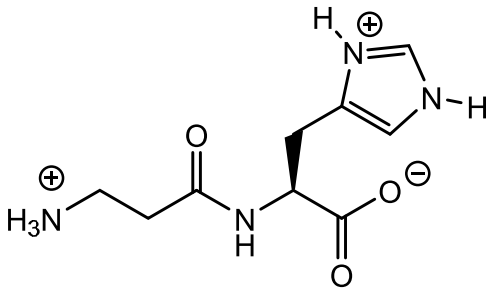
1 point partial for each correct protonation/charge site (out of 3, shown circled below, for a total of 3 points).

1 point partial for drawing any charge = 0 species.

Carnosine has three acidic groups, each of which has a different pK_a. At extremely low pH, all of these acidic groups are protonated, and the molecule is as positively charged as it can be. As the pH is increased, the molecule loses protons in succession:

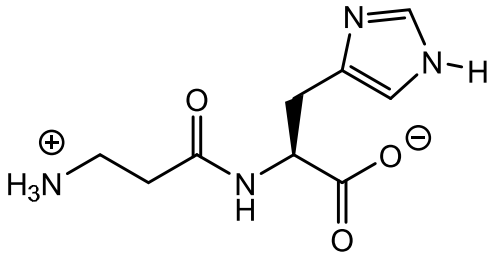
carnosine, fully protonated:





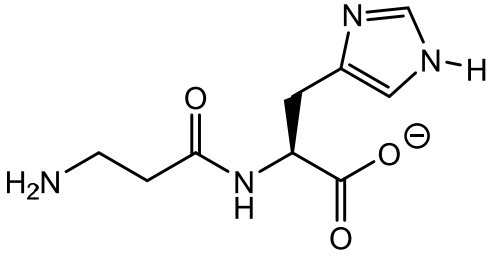
*total charge = **+1***

at pH = 6.9



*total charge = **0***

at pH = 9.5



*total charge = **-1***

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

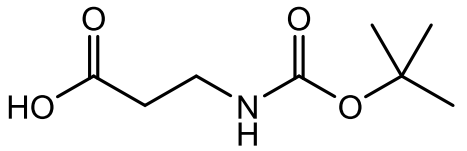
pI = 8.2 (4)

We accepted answers between 8.1 and 8.3, inclusive.

We can calculate pI by averaging the pK_a's of the acidic groups that are deprotonated to create and then deprotonate the charge = 0 state. Here, those two acidc groups are the imidazolium (pK_a ≈ 6.9) and ammonium (pK_a ≈ 9.5) group.

c. Carnosine could be synthesized via solid-phase peptide synthesis, using *t*Boc-protected β-glycine ("*t*Boc-β-Gly") as a reagent. Draw the complete chemical structure of *t*Boc-β-Gly in the box at right.

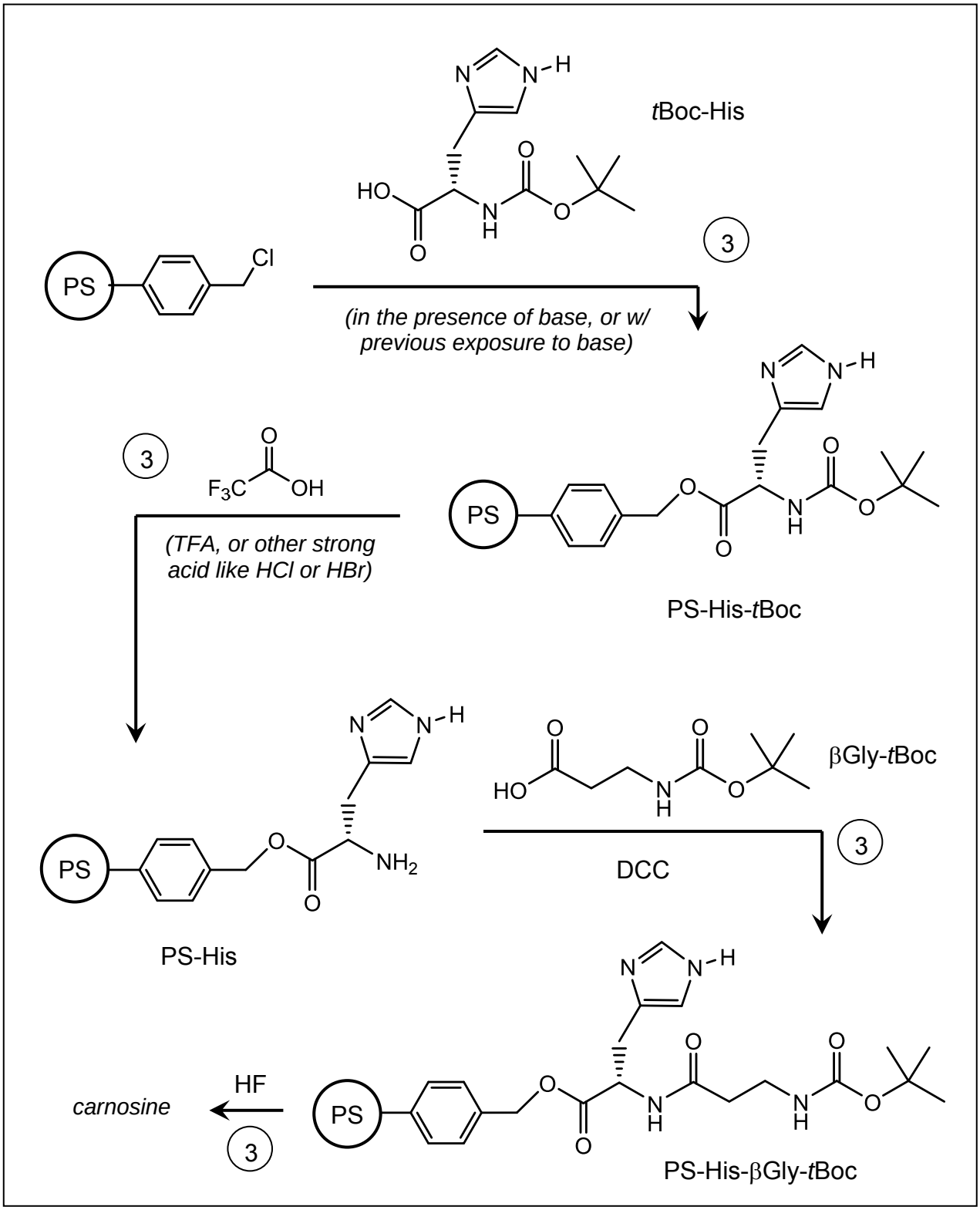
structure of tBoc-β-Gly: (4)



Rubric for this part:
4 points.
2 points partial for any protecting group structure attached to the nitrogen atom of β-glycine.

d. In the box below, propose a multistep solid-phase synthesis of carnosine, using chloromethylated polystyrene ("PS—Cl") and the *t*Boc-protected amino acids *t*Boc-β-Gly and *t*Boc-His. In addition to these starting materials, you can use any reagents and reactions we've learned about in class. You do not need to draw any chemical structures to answer this problem; you can refer to molecules by name or chemical abbreviation.

Answer on the next page. I have drawn everything out, but you were free to use names or abbreviations in place of any structures.


tBoc-His
PS
Cl
3
(in the presence of base, or w/ previous exposure to base)
PS-His-tBoc
(TFA, or other strong acid like HCl or HBr)
PS-His
βGly-tBoc
DCC
PS-His-βGly-tBoc
HF
carnosine

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.**
   For full credit, you needed to add *t*Boc-His first (and not *t*Boc-βGly).
   -1 point for adding tBoc-βGly first instead, or for not identifying amino acid.
   -1 point for omitting base.

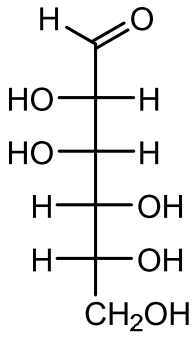
2. **Deprotect first *t*Boc with TFA.**
   -2 points for deprotecting before adding amino acid to support (before step 1).

3. **Add *t*Boc-βGly with DCC.**
   -1 point for adding tBoc-His instead, or for not identifying amino acid.
   -2 points for omitting DCC.

4. **Deprotect and cleave carnosine from solid support with HF.**
   Fine to deprotect and cleave in separate steps.

+1 POINT AUTOMATIC, BECAUSE I DID THE PROBLEM MATH WRONG.

2. (14 pts) D-Mannose, like D-glucose, is an aldohexose. The acyclic structure of mannose is shown at right, as a Fischer projection.



D-mannose

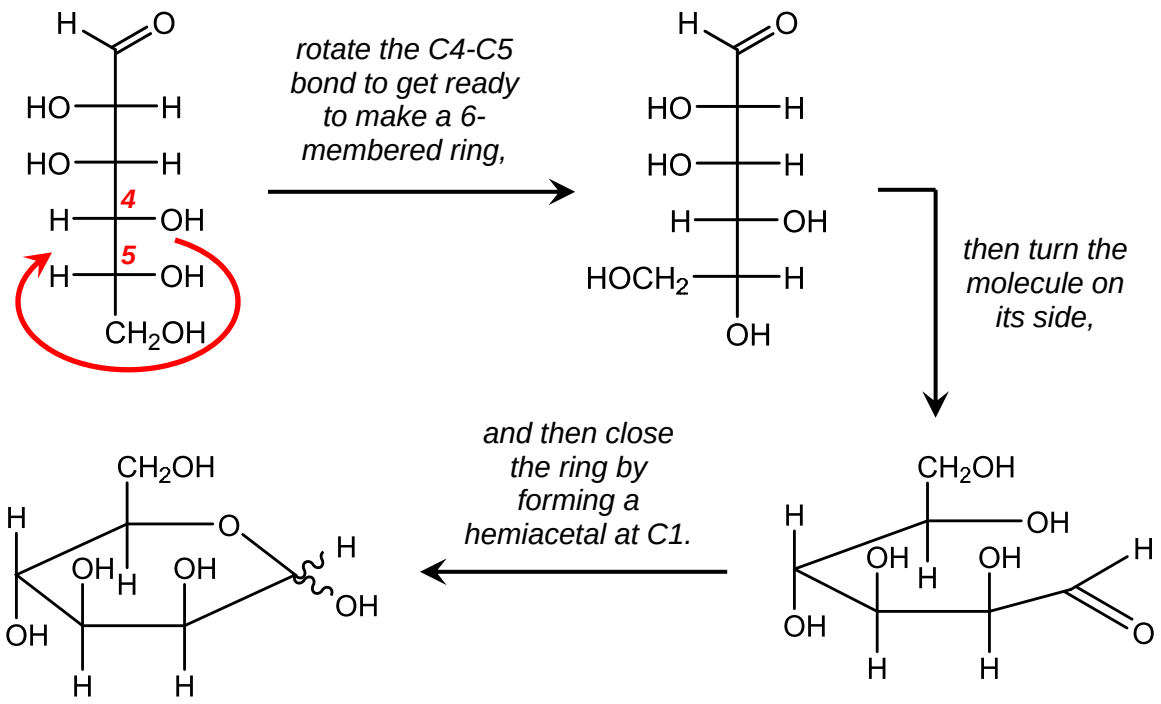
   a. Acyclic D-mannose equilibrates with a cyclic, 6-membered-ring, α-anomer mannopyranose form. Draw the most stable chair conformer of that cyclic α-anomer in the box on the next page on the left.

   b. The α-anomer is influenced by the "anomeric effect", a specific molecular orbital interaction. Illustrate that molecular orbital interaction on your drawing on the next page, drawing lobes for orbitals.

   c. Does the anomeric effect stabilize

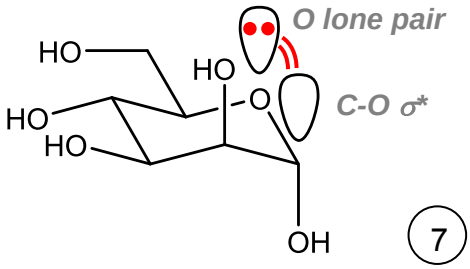
the α-anomer more? (3) **the β-anomer more?** *or* **both anomers equally?**

(Circle one answer.)



I've drawn the molecule above as a flat Haworth projection, with squiggles at C1 to show that we don't know stereochemistry at that position yet. The problem asks for the most stable chair conformer. That's going to be the one with the most equatorial groups at each carbon other than C1 (the anomeric carbon). Then, at C1, the problem instructs us to position the C1 alcohol in the <u>axial</u> position when it tells us to draw the α-anomer.

cyclic α-D-mannopyranose
(chair conformer)
with anomeric effect shown w/ orbitals



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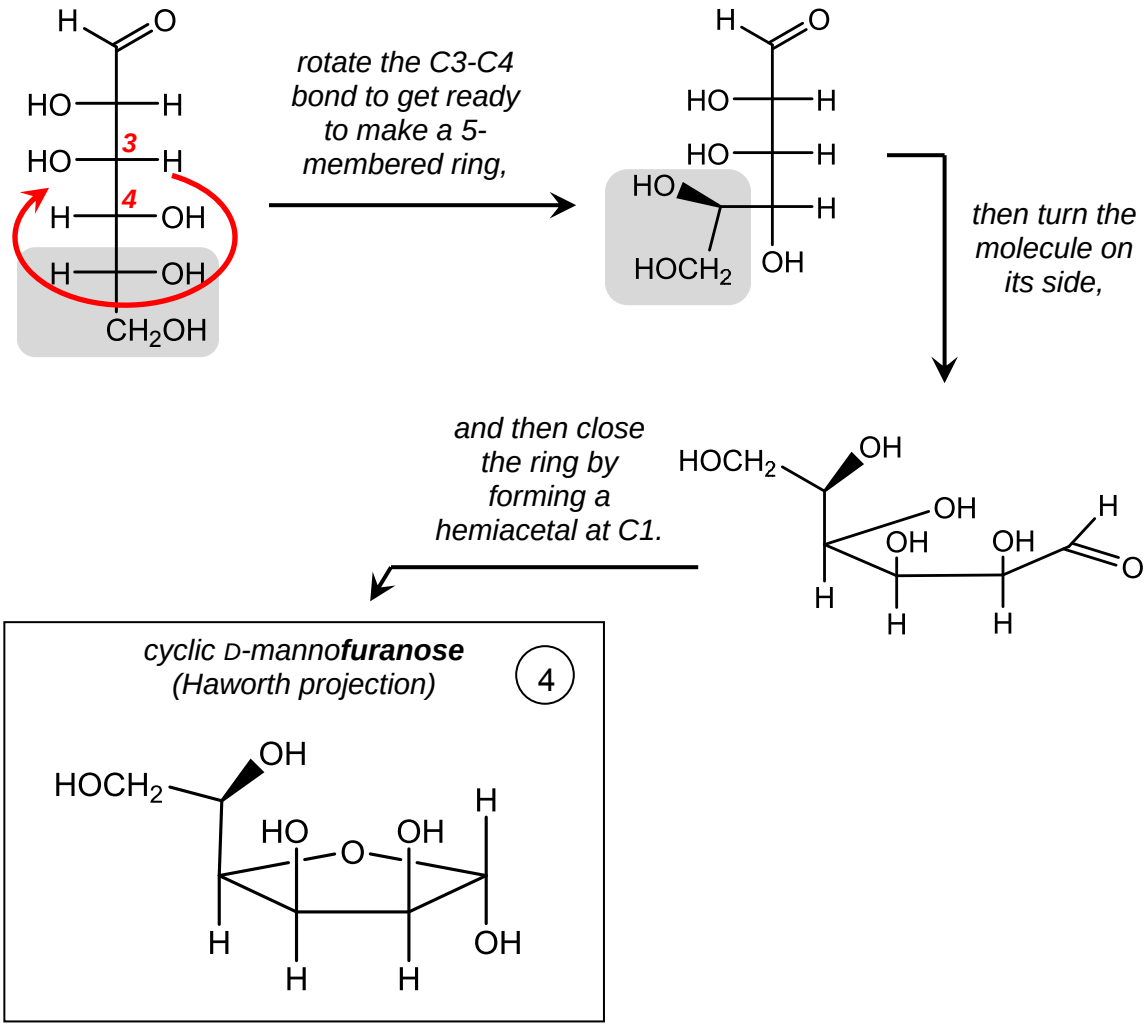
Question (b) asks us to draw the anomeric effect. This is an interaction between an axial lone pair on oxygen and the empty C-O σ* orbital at C1.

<u>Rubric for this part:</u>
4 points for sugar structure.
-1 point for each incorrect functionality or stereochemistry at each carbon.
3 points for drawing orbitals.
No partial credit. You did not have to draw electrons, just orbital lobes.

d. The two D-mannose structures above also equilibrate with a five-membered-ring, furanose form. Illustrate one furanose ring that can be made by D-mannose in the box at right below.



Rubric for this part:

4 points for sugar structure.

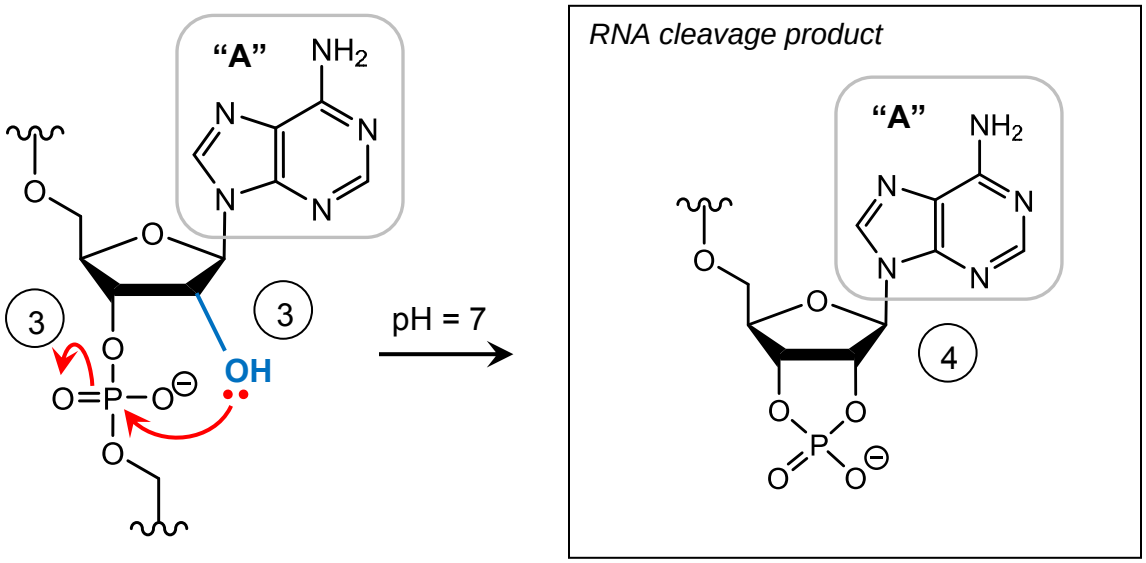
I've illustrated stereochemistry at the exocyclic carbon, but we didn't grade on this.

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

3. (13 pts)

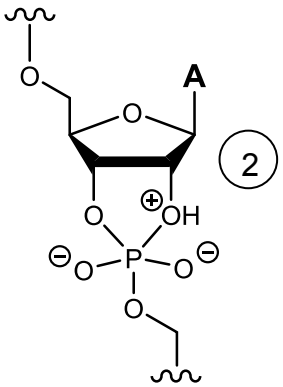
a. A generic structure of an adenine nucleotide in DNA is shown below. **Draw one change to that structure** so that it shows RNA instead. Draw directly onto my structure—there is no need to draw a whole new molecule.

b. This change helps RNA undergo intramolecular cleavage. In the box below, draw the **cyclic phosphate** that is formed from RNA strand cleavage at pH = 7. Feel free to abbreviate the adenine base as "**A**".



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

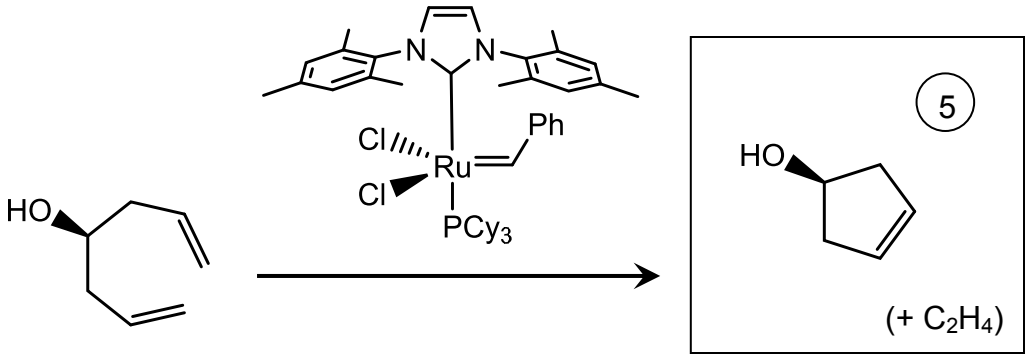
Rubric for parts (a) - (c):
3 points for adding an -OH group to the 2' carbon.
3 points for electron pushing of -OH onto phosphate P=O bond.
1 point partial for just one of two arrows correct.
4 points for cyclic phosphate structure.
2 points partial for drawing pentavalent phosphorus that is formed prior to cleavage.



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

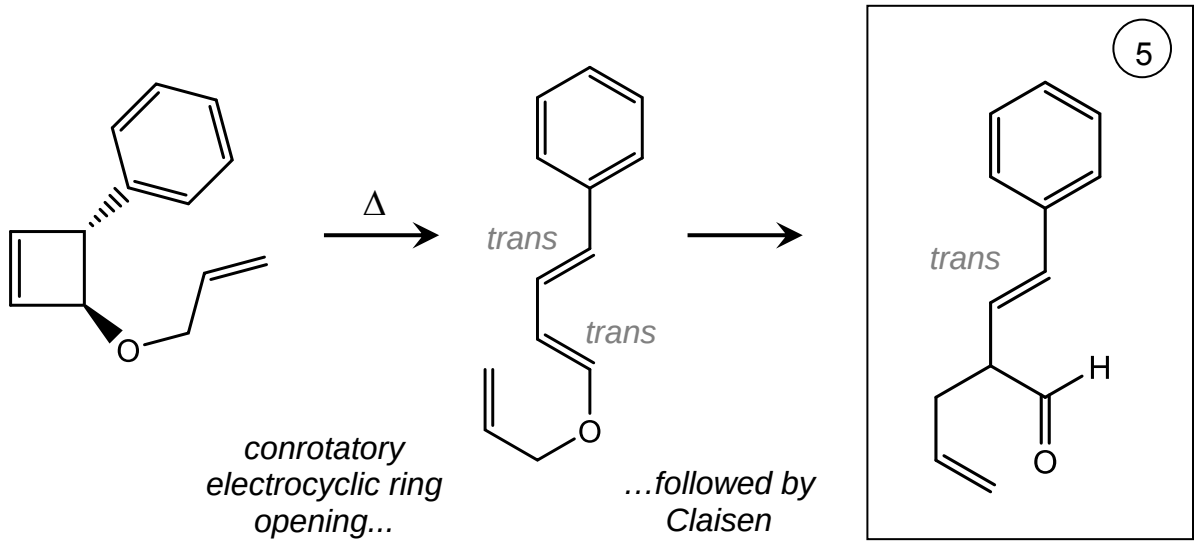
RNA is more stable than DNA. **RNA is less stable than DNA.** (3) *or* **RNA and DNA are equally stable.** *(Circle one.)*

4. (20 pts) For each of the reactions below, fill in the empty box corresponding to products. 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".



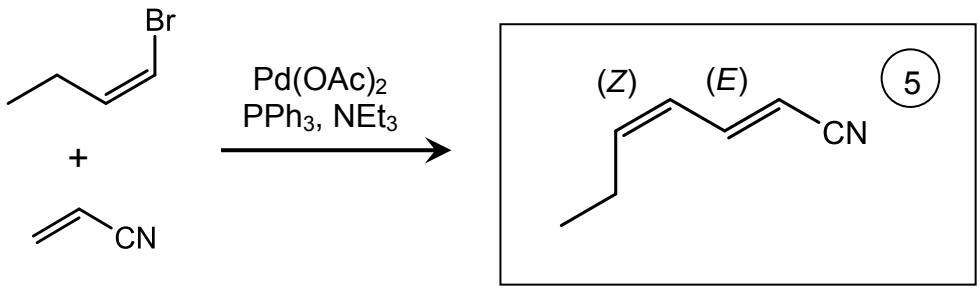
Ring-closing olefin metathesis.

Rubric for this part:
5 points for correct structure.
*-2 points for each clearly trivial structure mistake. This includes incorrect number of carbons in the ring. Omitting double bond is *not* a trivial mistake.*
No need to illustrate stereochemistry--molecule is achiral.



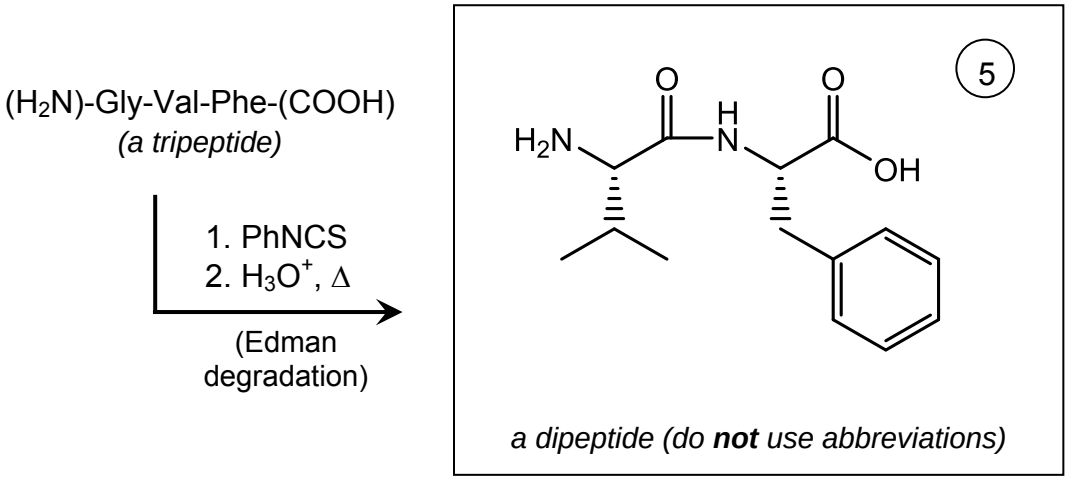
Rubric for this part:
5 points for correct structure.
4 points partial for cis-double bond in prduct instead of trans.
3 points partial for stopping at electrocyclic ring opening product, as long as product is trans-tran.

2 points partial for any other alkene stsreochemistry combination (cis/cis, or cis/trans) in electrocyclic ring opening product.
*-2 points for each clearly trivial structure mistake. This includes incorrect number of carbons in the ring. Omitting double bond is *not* a trivial mistake.*



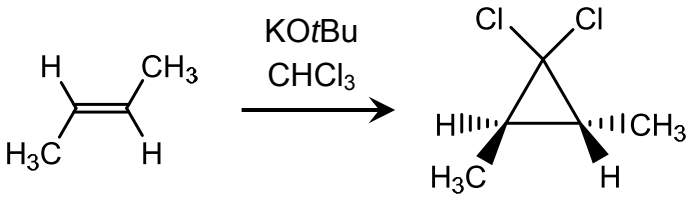
Heck reaction.

Rubric for this part:
5 points for correct structure.
3 points partial for correct structure, but incorrect alkene stereochemistry on either alkene.
-2 points for each clearly trivial structure mistake.

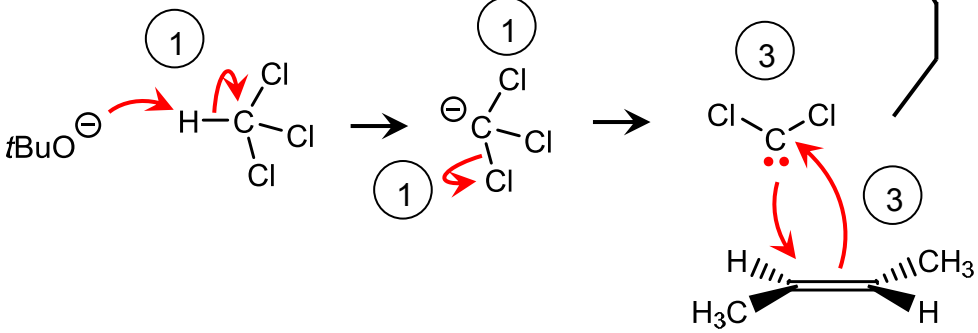


Rubric for this part:
5 points for correct structure.
-1 point for each stereochemistry error.
-2 points for each clearly trivial structure mistake.

5. (12 pts) **Draw a mechanism** (using "electron pushing") for the reaction shown below. Draw each mechanistic step explicitly; don't cheat by combining multiple processes in a single step, or by taking shortcuts. Use only the molecules shown in the problem.



Mechanism:



What unique type of reactive intermediate is generated in this reaction? (Answer in one word, in the box on the right.)

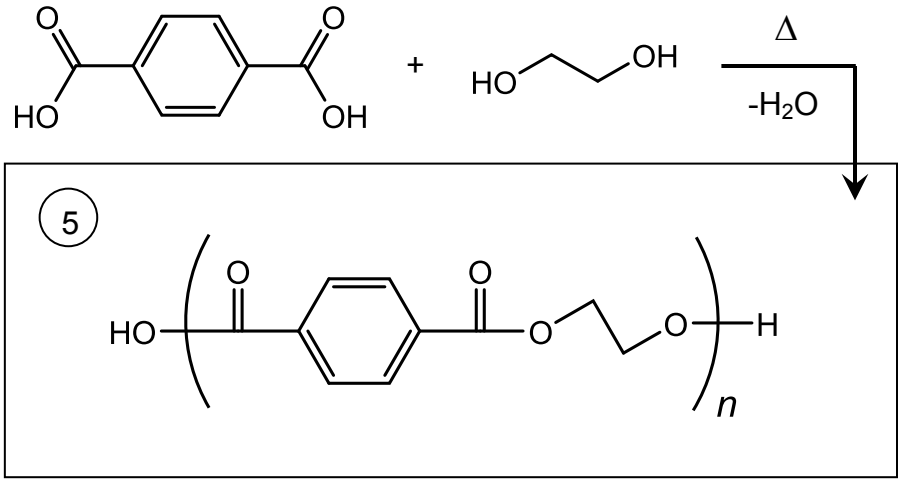
CARBENE (3)

Rubric for mechanism:

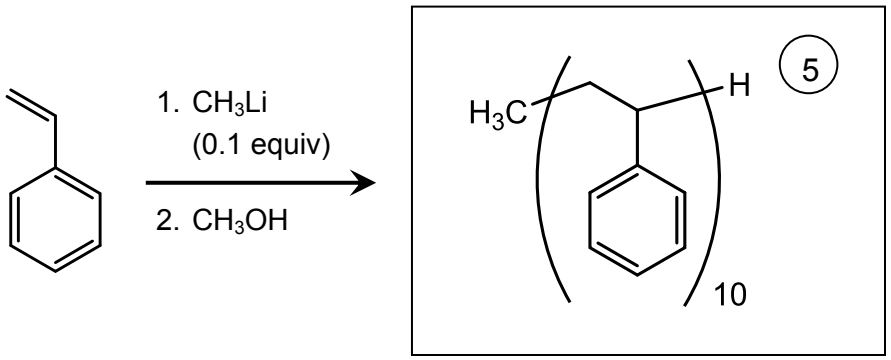
3 points for electron-pushing to carbene.
3 points for illustrating carbene.
3 points for electron-pushing carbine addition to alkene.
Overall notes:

Overall, the minimum score for each step is zero; errors in a step cannot earn you negative points that count against another, correct step.
Things that have left for good (Cl^-) and spectators (K^+) may be omitted.
-2 points, 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. (So, you could only lose 1 point on the 1 point steps.)
-1 point for each minor error in charge, valency, structure, etc.; if error propagates, points are taken off only for initial error.
-2 points for each use of a generic or incorrect acid/nucleophile/base.

6. (16 pts)
   a. For each of the polymer syntheses proposed on the next page, draw the polymer product using bracket notation ("[-M-]$_n$"). If *n* is known, define it. If there is a part of the polymer structure that isn't known (*e.g.*, the initiating or terminating group), draw this as a squiggle in your structure.



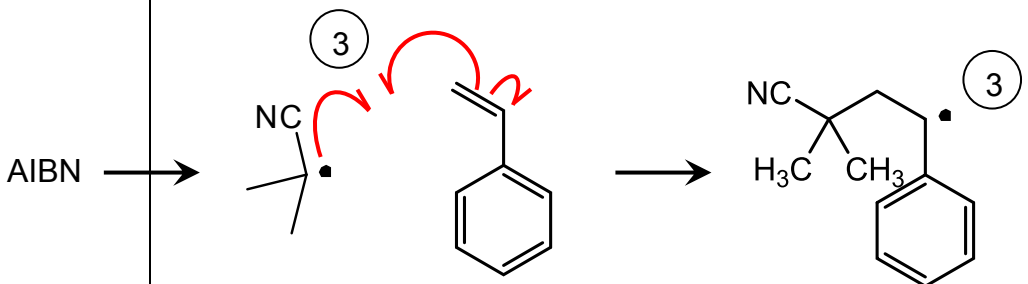
Rubric for this question:
5 points for correct structure.
3 points partial incorrect termini, but otherwise correct.
-2 points for trivial structural mistake (including omitting or extra carbons).



Rubric for this question:
5 points for correct structure.
-1 point for "n" instead of "10".
-2 points for each incorrect terminus.
-2 points for trivial structural mistake (including omitting or extra carbons).

b. If the second polymerization above were initiated with AIBN instead of with an anion, the mechanism of polymerization would be different. In the box below, **add curved arrows** (using "electron pushing") that show how the 2-cyanopropyl radical from AIBN would initiate polymerization. Then draw the product of this step.

AIBN initiation step: add curved arrows & step product



Rubric for this question *(7 points total this box):*
Overall notes:
3 points for arrow pushing.
-2 points, for each arrow in each step, for errors (including omission) in drawing arrows. This problem requires single-barbed, unpaired electron arrows.
3 points for intermediate structure.
-2 points for trivial structure mistakes (such as omitting methyl groups from AIBN side).