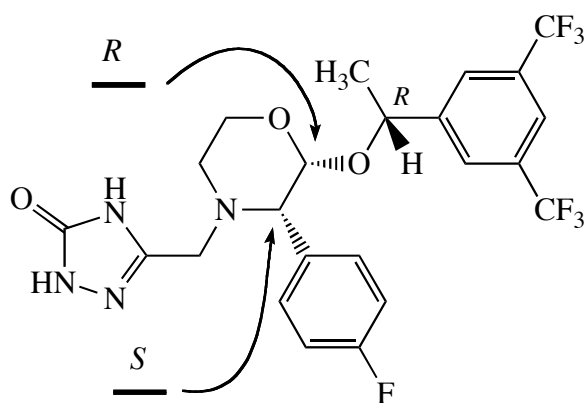


1. (8 pts.) The structure of aprepitant, the active ingredient in Emend, a drug used to treat nausea and vomiting resulting from cancer chemotherapy, is shown. Aprepitant has three stereocenters.



(a) (4 pts.) In the drawing above, arrows point to two of Aprepitant's stereocenters. On the heavy lines next to the arrows, indicate the configurations of these stereocenters.

(b) (4 pts.) The third stereocenter in Aprepitant has the R configuration. Draw in the H atom attached to this stereocenter, and use a bold or hashed wedge to indicate an R configuration.

2. (5 pts. each, 30 pts. total.) Describe the relationship of each pair of structures as specifically as possible and in no more than two words.

(a)



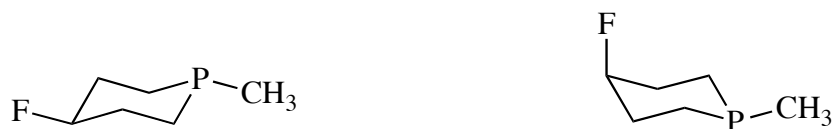
homomers

(b)



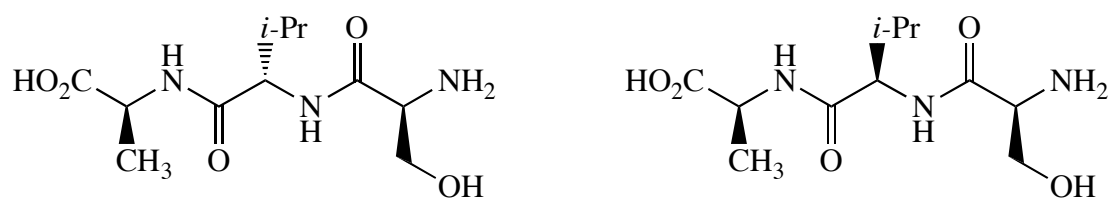
conformational diastereomers

(c)



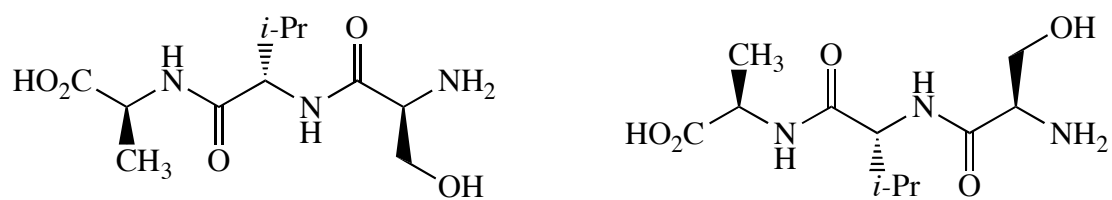
configurational diastereomers
(P's lone pair does not invert)

(d)



configurational diastereomers

(e)



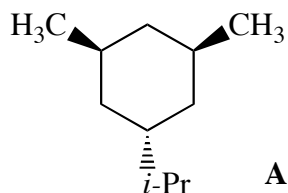
configurational enantiomers

(f)

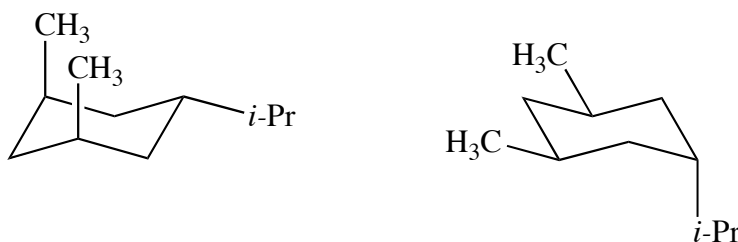


configurational diastereomers

3. (24 pts. total.) Consider compound **A** below.



(a) (8 pts.) Draw **A** in *both* of its chair forms.



(b) (4 pts.) Using the table below, compute the approximate difference in energy between the structures you drew in (a).

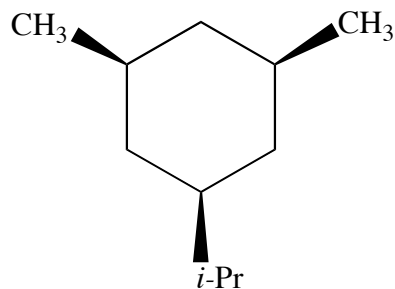
Interacting axial groups	Cost of <i>single</i> 1,3-diaxial interaction
CH ₃ and H	0.85 kcal/mol
1° alkyl (e.g., Et) and H	0.90 kcal/mol
2° alkyl (e.g., <i>i</i> -Pr) and H	1.1 kcal/mol
3° alkyl (e.g., <i>t</i> -Bu) and H	2.7 kcal/mol
CH ₃ and CH ₃	3.7 kcal/mol

Approximate difference in energy: $[3.7 + (2 \times 0.85)] - (2 \times 1.1) = 3.2 \text{ kcal/mol}$

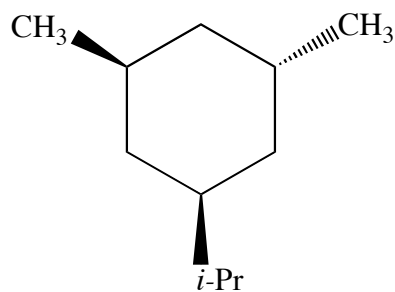
(c) (4 pts.) Circle the structure you drew in (a) that is lower in energy, and explain below what led you to choose that structure.

The structure on the right is lower in energy because its two 1,3-diaxial interactions between *i*-Pr and H cost less than the Me–Me interaction and the two Me–H interactions in the structure on the left.

(d) (4 pts.) By adding wedged bonds (bold or hashed) to the drawing below, draw the compound that is lowest in energy among **A** and its diastereomers.



(e) (4 pts.) By adding wedged bonds (bold or hashed) to the drawing below, draw a chiral diastereomer of **A**. (If **A** is chiral, you may draw **A**.)



4. (4 pts. each, 20 pts. total.) Undergraduate researcher Sally Humdinger prepares a sample of (1*R*,2*R*)-ephedrine. She measures its enantiomeric ratio (er) to be 7:1. For enantiopure (1*S*,2*S*)-ephedrine, $[\alpha]_{\text{D}}^{25} = +52^{\circ}$.

(a) What is the ee of Sally's sample of ephedrine?

$$ee = (7 - 1) / (7 + 1) = 75\%$$

(b) What $[\alpha]_{\text{D}}^{25}$ would Sally expect to observe for her sample of ephedrine? Give the *sign* and the *magnitude*.

Magnitude: $[\alpha]_{\text{obs}}^{25} = [\alpha]_{\text{D}}^{25} \times ee = 52 \times 0.75 = 39^{\circ}$

Sign: Sally's sample is mostly the opposite enantiomer of the reference, so hers is levorotatory.

Answer: -39° .

(c) Sally's lab partner gives her a sample of (1*R*,2*S*)-ephedrine. Should Sally expect this sample to be dextrorotatory or levorotatory, or is there no way to tell? Explain your answer.

There is no way to tell whether a diastereomer would be dextrorotatory or levorotatory.

(d) Sally used chiral chromatography to measure her sample's er. Explain how this method works.

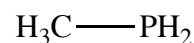
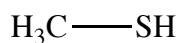
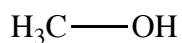
The sample is allowed to pass through a chiral substance. One enantiomer interacts more strongly with the substance, so its passage is slowed. The two enantiomers emerge at different times.

(e) (Extra credit) Sally tells her labmate Will Wurklanghauers that her starting materials for making (1*R*,2*R*)-ephedrine have no stereocenters. Will tells her that's impossible. Who is right, and why?

Optically inactive starting materials always give optically inactive products. At least one of Sally's starting materials must have been optically active, hence chiral. Most compounds with no stereocenters are achiral, but some are not. So Sally may very well be right.

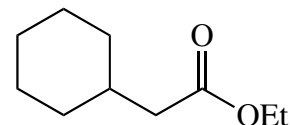
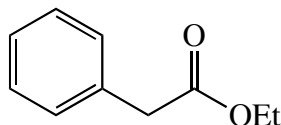
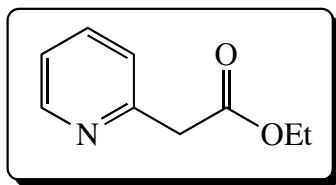
5. (4 pts. each, 12 pts. total.) Circle the *most acidic* compound in each set, and explain *briefly* (no more than a grammatically correct sentence or two) why you circled that compound. *No credit will be given without a valid explanation.*

(a)



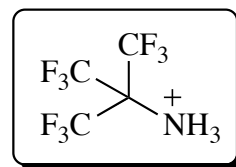
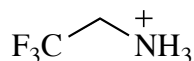
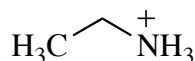
S is below O and to the left of P, so S is most acidic.

(b)



In each case, the C next to the carbonyl is the most acidic C in the compound. The first and second compounds have greater resonance stabilization of the conjugate base, and the first compound has greater resonance stabilization than the second because N is more electronegative than C, so it can better bear a $-$ charge.

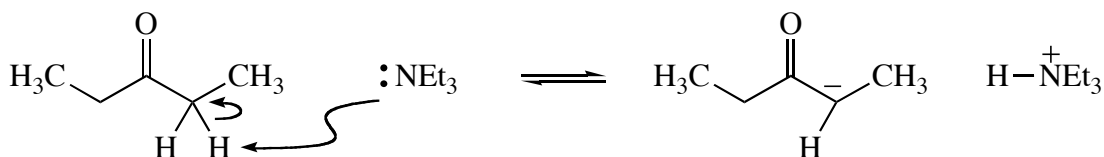
(c)



More inductively electron-withdrawing groups nearby make N a better acid.

6. More acid–base chemistry.

(a) (6 pts.) Complete the following acid–base reaction, using curved arrows to show the movement of electrons. You may find it advisable to obey Grossman’s rule before you begin.



(b) (4 pts.) The pK_a of the acid on the left is 20, and the pK_a of the acid on the right (if you answered (a) correctly) is 10. Does the equilibrium for this reaction lie to the right or to the left, and what is the equilibrium constant?

It lies on the left (weaker acid), and the equilibrium constant is 10^{-10} .