

## 5.11: PROCHIRALITY

### OBJECTIVES

After completing this section, you should be able to

1. identify a compound as being prochiral.
2. identify the *Re* and *Si* faces of prochiral  $sp^2$  centre.
3. identify atoms (or groups of atoms) as *pro-R* or *pro-S* on a prochiral  $sp^3$  centre.

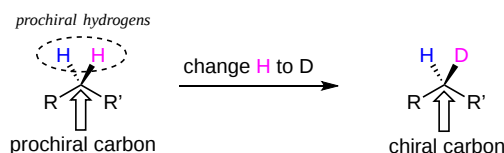
### KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- prochiral
- *pro-R*
- *pro-S*
- *Re*
- *Si*

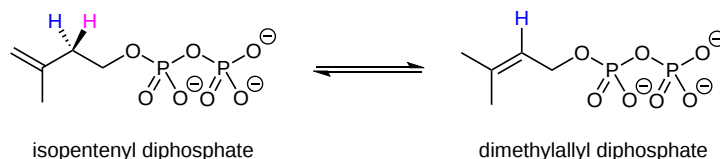
### PROCHIRAL CARBONS

When a tetrahedral carbon can be converted to a chiral center by changing only one of the attached groups, it is referred to as a '**prochiral**' carbon. The two hydrogens on the prochiral carbon can be described as 'prochiral hydrogens'.

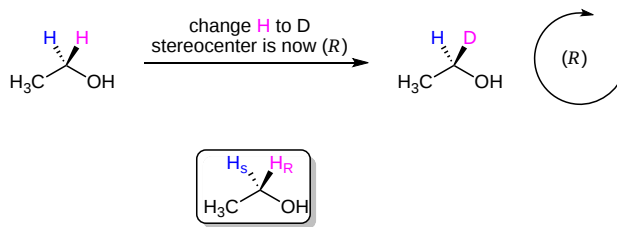


Note that if, in a 'thought experiment', we were to change either one of the prochiral hydrogens on a prochiral carbon center to a deuterium (the  $^2\text{H}$  isotope of hydrogen), the carbon would now have four different substituents and thus would be a chiral center.

Prochirality is an important concept in biological chemistry, because enzymes can distinguish between the two 'identical' groups bound to a prochiral carbon center due to the fact that *they occupy different regions in three-dimensional space*. Consider the isomerization reaction below, which is part of the biosynthesis of isoprenoid compounds. We do not need to understand the reaction itself (it will be covered in chapter 14); all we need to recognize at this point is that the isomerase enzyme is able to distinguish between the prochiral 'red' and the 'blue' hydrogens on the isopentenyl diphosphate (IPP) substrate. In the course of the left to right reaction, IPP specifically loses the 'red' hydrogen and keeps the 'blue' one.



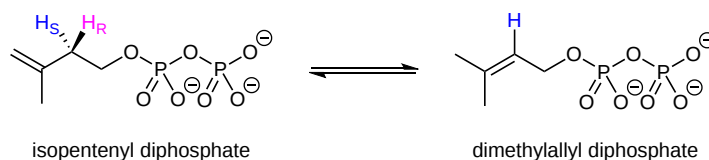
Prochiral hydrogens can be unambiguously designated using a variation on the *R/S* system for labeling chiral centers. For the sake of clarity, we'll look at a very simple molecule, ethanol, to explain this system. To name the 'red' and 'blue' prochiral hydrogens on ethanol, we need to engage in a thought experiment. If we, in our imagination, were to arbitrarily change red H to a deuterium, the molecule would now be chiral and the chiral carbon would have the *R* configuration (D has a higher priority than H).



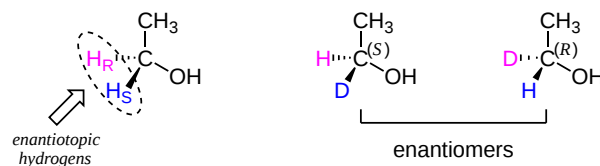
For this reason, we can refer to the red H as the *pro-R* hydrogen of ethanol, and label it  $H_R$ . Conversely, if we change the blue H to D and leave red H as a hydrogen, the configuration of the molecule would be *S*, so we can refer to blue H as the *pro-S* hydrogen of ethanol, and

label it  $H_S$ .

Looking back at our isoprenoid biosynthesis example, we see that it is specifically the *pro-R* hydrogen that the isopentenyl diphosphate substrate loses in the reaction.

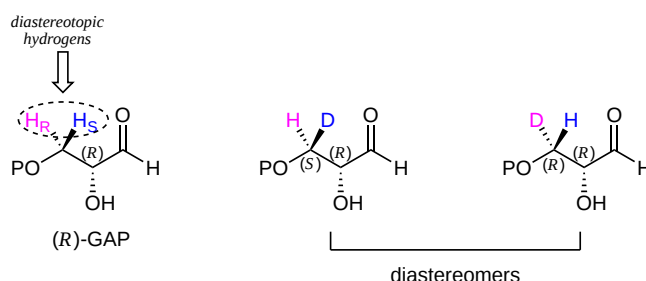


Prochiral hydrogens can be designated either enantiotopic or diastereotopic. If either  $H_R$  or  $H_S$  on ethanol were replaced by a deuterium, the two resulting isomers would be enantiomers (because there are no other stereocenters anywhere on the molecule).



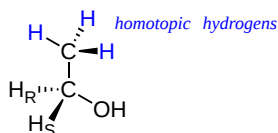
Thus, these two hydrogens are referred to as **enantiotopic**.

In (*R*)-glyceraldehyde-3-phosphate ((*R*)-GAP), however, we see something different:



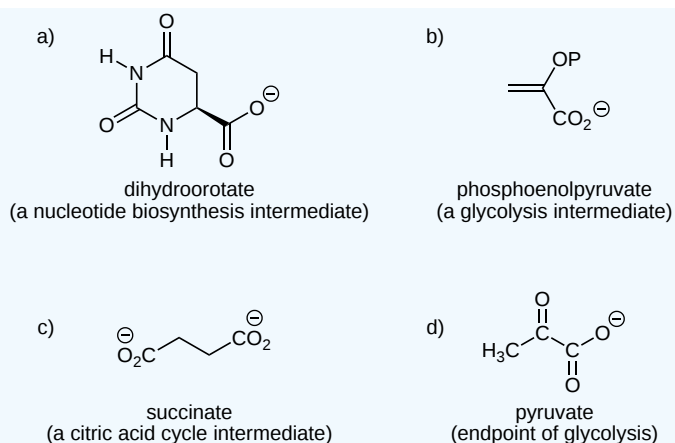
*R*)-GAP already has one chiral center. If either of the prochiral hydrogens  $H_R$  or  $H_S$  is replaced by a deuterium, a second chiral center is created, and the two resulting molecules will be diastereomers (one is *S,R*, one is *R,R*). Thus, in this molecule,  $H_R$  and  $H_S$  are referred to as **diastereotopic** hydrogens.

Finally, hydrogens that can be designated neither enantiotopic nor diastereotopic are called **homotopic**. If a homotopic hydrogen is replaced by deuterium, a chiral center is *not* created. The three hydrogen atoms on the methyl ( $CH_3$ ) group of ethanol (and on *any* methyl group) are homotopic. An enzyme cannot distinguish among homotopic hydrogens.

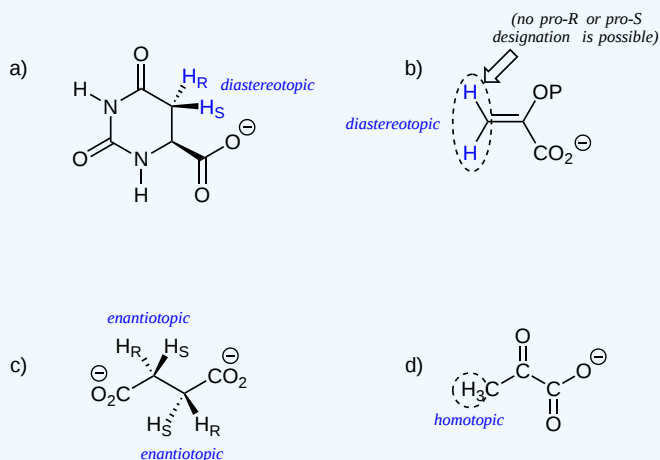


### ? EXAMPLE 5.11.1

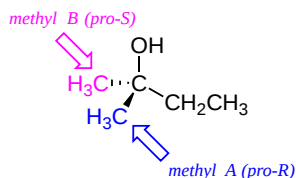
Identify in the molecules below all pairs/groups of hydrogens that are homotopic, enantiotopic, or diastereotopic. When appropriate, label prochiral hydrogens as  $H_R$  or  $H_S$ .



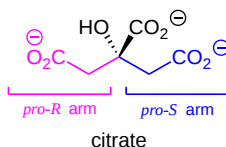
## Answer



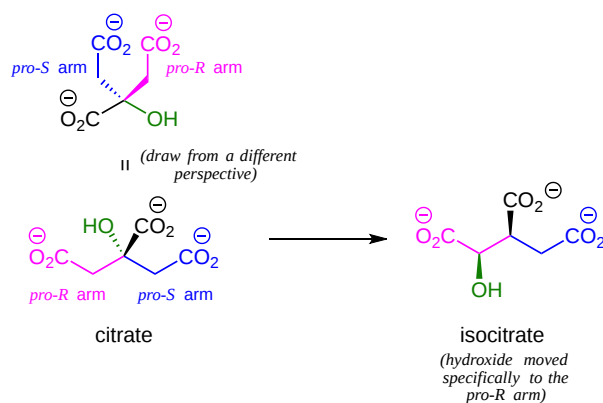
Groups other than hydrogens can be considered prochiral. The alcohol below has two prochiral methyl groups - the red one is *pro-R*, the blue is *pro-S*. How do we make these designations? Simple - just arbitrarily assign the red methyl a higher priority than the blue, and the compound now has the *R* configuration - therefore red methyl is *pro-R*.



Citrate is another example. The central carbon is a prochiral center with two 'arms' that are identical except that one can be designated *pro-R* and the other *pro-S*.

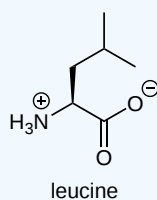


In an isomerization reaction of the citric acid (Krebs) cycle, a hydroxide is shifted specifically to the *pro-R* arm of citrate to form isocitrate: again, the enzyme catalyzing the reaction distinguishes between the two prochiral arms of the substrate (we will study this reaction in chapter 13).

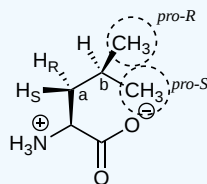


### ? EXERCISE 5.11.1

Assign *pro-R* and *pro-S* designations to all prochiral groups in the amino acid leucine. (Hint: there are two pairs of prochiral groups!). Are these prochiral groups diastereotopic or enantiotopic?

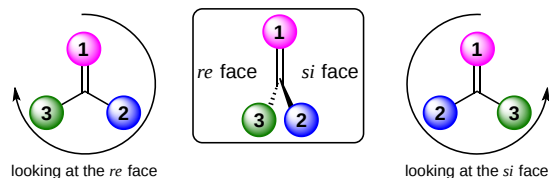


Answer

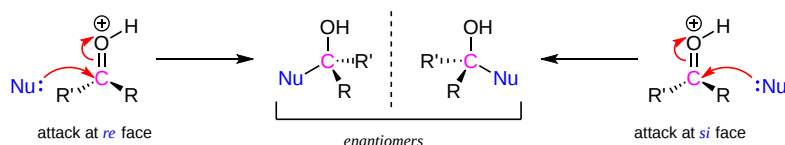


## PROCHIRAL CARBONYL AND IMINE GROUPS

Trigonal planar,  $sp^2$ -hybridized carbons are not, as we well know, chiral centers— but they can be prochiral centers if they are bonded to three different substituents. We (and the enzymes that catalyze reactions for which they are substrates) can distinguish between the two planar ‘faces’ of a prochiral  $sp^2$  - hybridized group. These faces are designated by the terms *re* and *si*. To determine which is the *re* and which is the *si* face of a planar organic group, we simply use the same priority rankings that we are familiar with from the R/S system, and trace a circle: *re* is clockwise and *si* is counterclockwise.

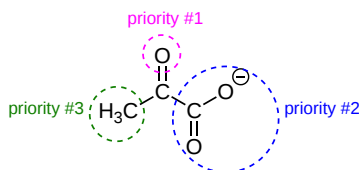


When the two groups adjacent to a carbonyl ( $C=O$ ) are not the same, we can distinguish between the *re* and *si* ‘faces’ of the planar structure. The concept of a trigonal planar group having two distinct faces comes into play when we consider the stereochemical outcome of a nucleophilic addition reaction. Nucleophilic additions to carbonyls will be covered in greater detail in **Chapter 19**. Notice that in the course of a carbonyl addition reaction, the hybridization of the carbonyl carbon changes from  $sp^2$  to  $sp^3$ , meaning that the bond geometry changes from trigonal planar to tetrahedral. If the two R groups are not equivalent, then a chiral center is created upon addition of the nucleophile. The configuration of the new chiral center depends upon which side of the carbonyl plane the nucleophile attacks from. Reactions of this type often result in a 50:50 racemic mixture of stereoisomers, but it is also possible that one stereoisomer may be more abundant, depending on the structure of the reactants and the conditions under which the reaction takes place.

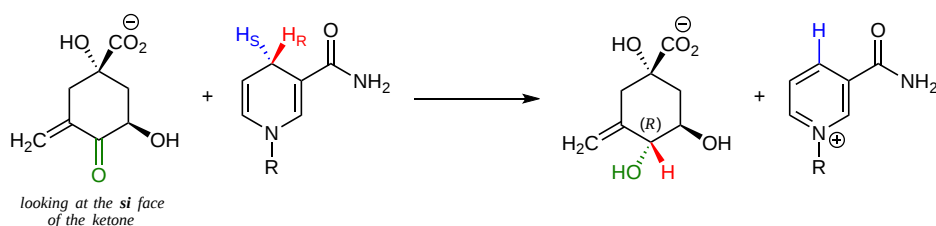


Note: *R* is higher priority than *R'*

Below, for example, we are looking down on the *re* face of the ketone group in pyruvate. If we flipped the molecule over, we would be looking at the *si* face of the ketone group. Note that the carboxylate group does not have *re* and *si* faces, because two of the three substituents on that carbon are identical (when the two resonance forms of carboxylate are taken into account).



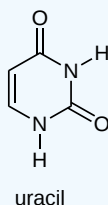
As we will see in chapter 10, enzymes which catalyze reactions at carbonyl carbons act specifically from one side or the other.



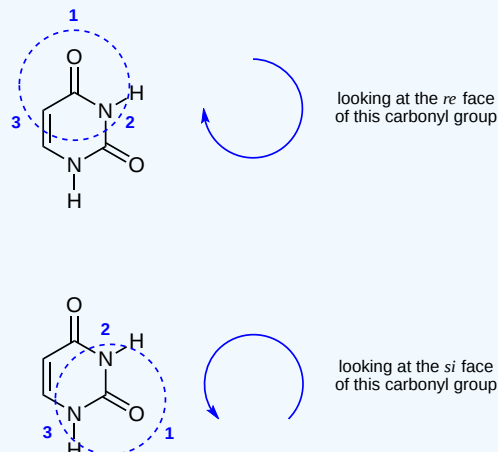
We need not worry about understanding the details of the reaction pictured above at this point, other than to notice the stereochemistry involved. The *pro-R* hydrogen (along with the two electrons in the C-H bond) is transferred to the *si* face of the ketone (in green), forming, in this particular example, an alcohol with the *R* configuration. If the transfer had taken place at the *re* face of the ketone, the result would have been an alcohol with the *S* configuration.

### ? EXERCISE 5.11.2

For each of the carbonyl groups in uracil, state whether we are looking at the *re* or the *si* face in the structural drawing below.



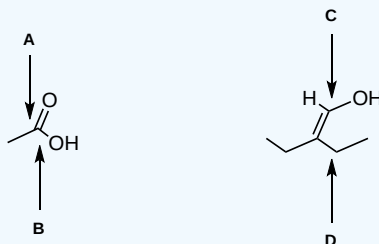
Answer



### ? EXERCISE 5.11.3

a) State which of the following hydrogen atoms are *pro-R* or *pro-S*.

b) Identify which side is Re or Si.

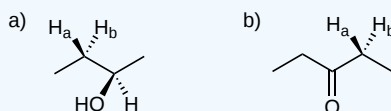


#### Answer

- a) Left compound:  $H_a = \text{pro-S}$  and  $H_b = \text{pro-R}$ ; Right compound:  $H_a = \text{pro-R}$  and  $H_b = \text{pro-S}$   
 b) A – Re; B – Si; C – Re; D – Si

### ? EXERCISE 5.11.4

State whether the H's indicated below are *pro-R* or *pro-S* for the following structures.

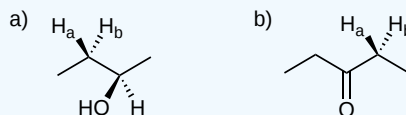


#### Answer

- a)  $H_a$  is *pro-R*;  $H_b$  is *pro-S*  
 $H_a$  is *pro-R*;  $H_b$  is *pro-S*

### ? EXERCISE 5.11.5

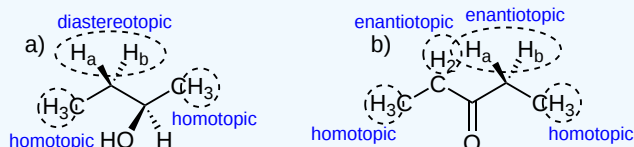
In the structures below, determine if the H's are homotopic, enantiotopic, or diastereotopic.



#### Answer

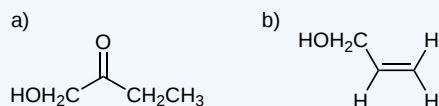
In a), the  $CH_2$  is diastereotopic since there is another chiral center on the molecule. Both  $CH_3$ 's are homotopic since replacing one of them doesn't create a chiral center.

In b), the  $CH_2$ 's are enantiotopic since it would create the only chiral center on the molecule. Both  $CH_3$ 's are homotopic since replacing one of them doesn't create a chiral center.



## ? EXERCISE 5.11.6

State whether you are looking down at the molecule from the re face or si face.



### Answer

- You are looking at the **si face**. The re face would be if you were facing the molecule from the back.
- You are looking at the **re face**. The si face would be if you were facing the molecule from the back.

This page titled [5.11: Prochirality](#) is shared under a [CC BY-SA 4.0](#) license and was authored, remixed, and/or curated by [Steven Farmer](#), [Dietmar Kennepohl](#), [Zachary Sharrett](#), & [Zachary Sharrett](#).

- [5.11: Prochirality](#) by Dietmar Kennepohl, Steven Farmer, Zachary Sharrett is licensed [CC BY-SA 4.0](#).
- [3.12: Prochirality](#) by Tim Soderberg is licensed [CC BY-NC-SA 4.0](#). Original source: [https://digitalcommons.morris.umn.edu/chem\\_facpubs/1/](https://digitalcommons.morris.umn.edu/chem_facpubs/1/).