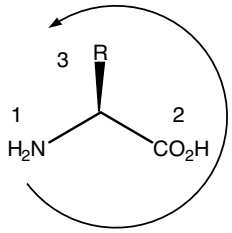
CHAPTER

6

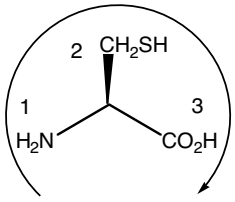
Stereochemistry

SOLUTIONS TO EXERCISES

1. Though all 19 chiral amino acids are homochiral (in other words, have the same side chain orientation, as shown below), the priority ordering is different for cysteine. In all other natural amino acids, the side chain has a lower priority than the carboxylate. In cysteine, however, the sulfur atom gives the side chain a higher priority, such that the stereochemical assignment switches to *R*. (Sulfur has a higher atomic number than oxygen.)

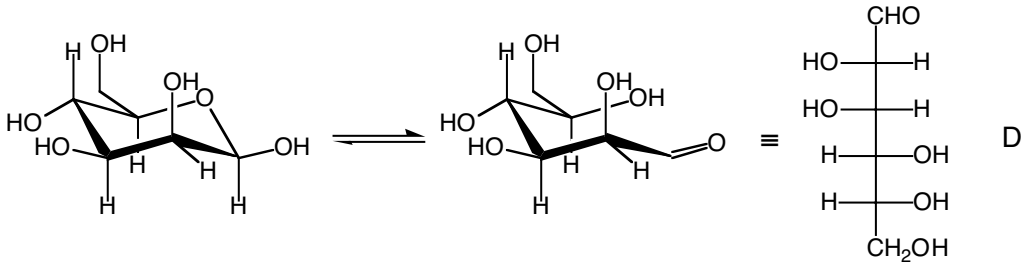


S

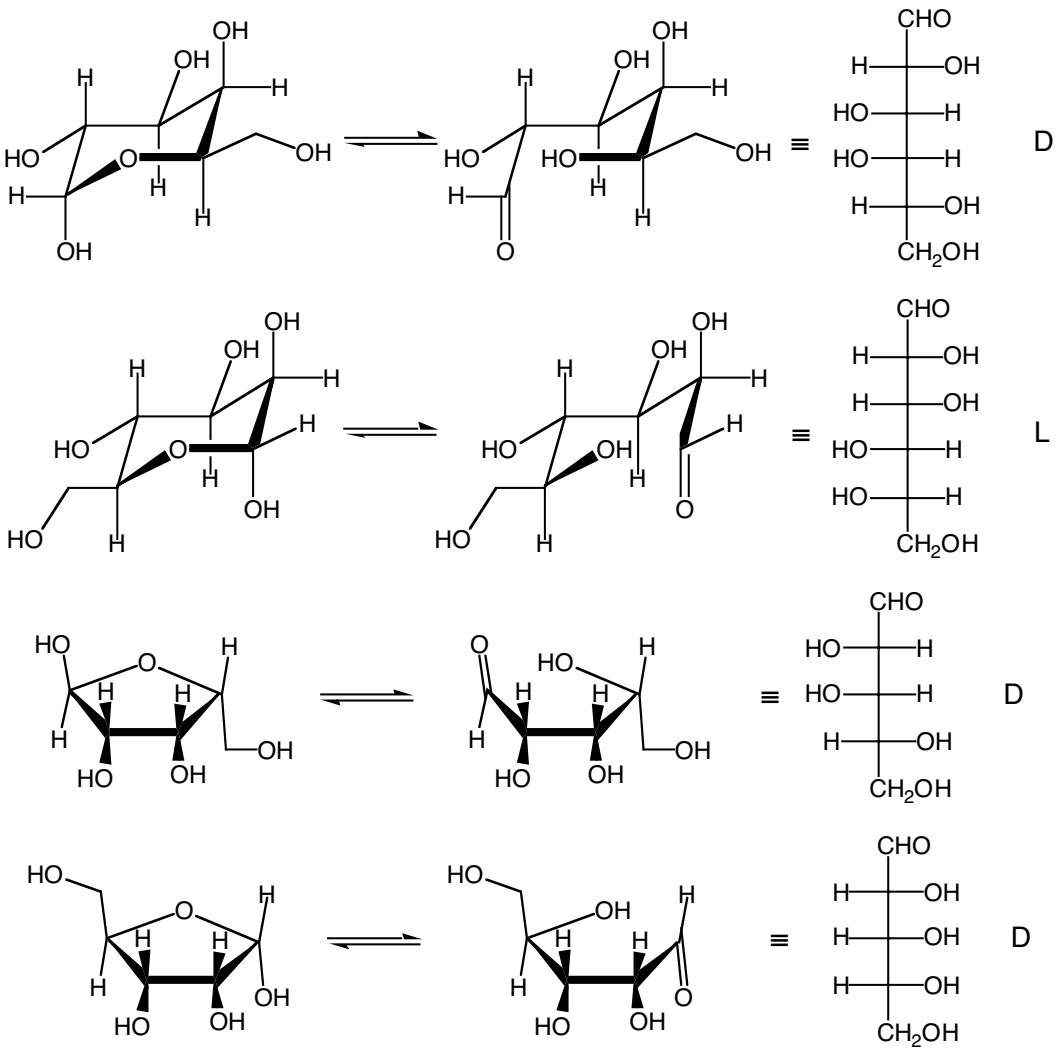


R

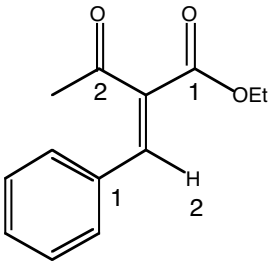
2. A sugar whose standard Fischer projection (with the carbonyl group at or near the top) has a hydroxy group to the right off the bottom stereocenter is designated as *D*.



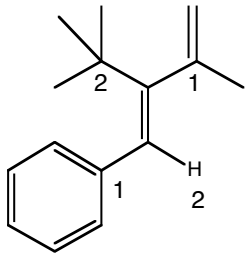
D



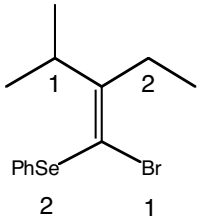
3. To determine *Z* and *E* labels, we need to determine the priority order at both ends of the stereogenic alkene.



E. In the top comparison, we find no distinction until the β position: C vs. O.

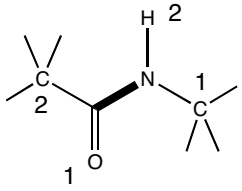


E. In the top comparison, we must go out three bonds to the γ position to find a difference. The attached atoms are both C, and each of these is attached three times to C. In the next step, we find only H's on the *t*-butyl CH_3 groups while the end C in the 2-propenyl group is attached to two H's and one C. Note that the double bond gives us an "extra" C on each end.

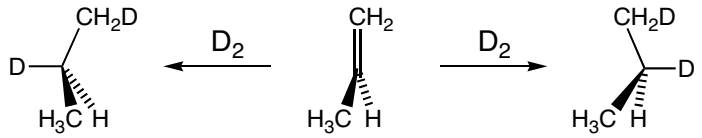


E. In the bottom comparison, Br has a higher atomic number (35) than Se (34).

4. Assigning priorities at both ends of the peptide bond (in bold), we can see that *Z* is the appropriate descriptor. Compared to H, C has higher priority, but compared to O, C has lower priority. So the higher priority groups are on the same side of the bond (*Z*), while the like groups (C) are on opposite sides (trans).



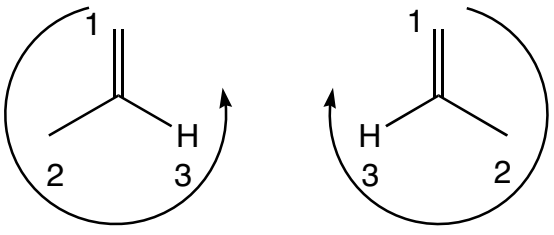
5. A trigonal C with three different ligands is prochiral, since attachment of a fourth different ligand will produce a tetrahedral stereocenter. Attachment from opposite faces will produce opposite configurations of the stereocenter, as shown:



R *S*

Also important in this case is that attachment of D onto the CH_2 group produces a labeled methyl group that is different from the existing methyl.

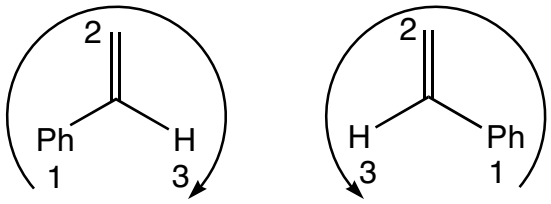
The *Re* and *Si* faces are assigned below, the labels referring to the faces in view. Priorities of groups attached to a trigonal atom are assigned with the usual priority rules. As described in Section 6.1.2, multiple bonds are treated as multiple ligands, so $=CH_2$ takes priority over methyl (CH_2C vs. CH_3).



Si *Re*

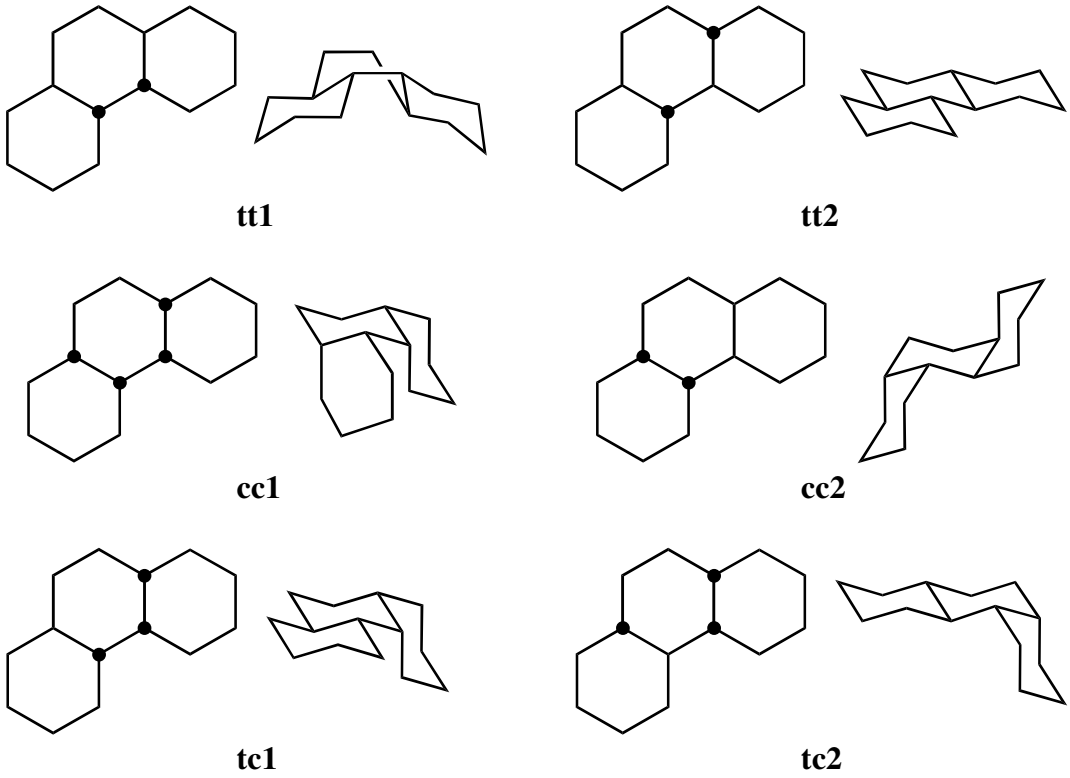
G O I N G D E E P E R

An additional example serves to show that the doubly-bonded ligand does not automatically take a higher priority. In styrene, Ph takes higher priority than $=CH_2$ (CC_3 vs. CH_2C).



Re *Si*

6. There are six diastereomers, shown below. One systematic way to classify and find all of these isomers is to note that each of the two ring fusions can be either trans or cis. Therefore, the possible diastereomers are *trans,trans*; *cis,cis*; and *trans,cis*. It turns out that there are two possibilities for each. The dot convention is a simpler way to show the isomers, but it does not convey the three-dimensional shapes very well. When we consider the chair cyclohexane structures, we find that one isomer, **tt1**, cannot have all three rings in the chair conformation. (Note that **cc1** does have three chairs, but no single vantage point shows this well.)



tt1 **tt2**

cc1 **cc2**

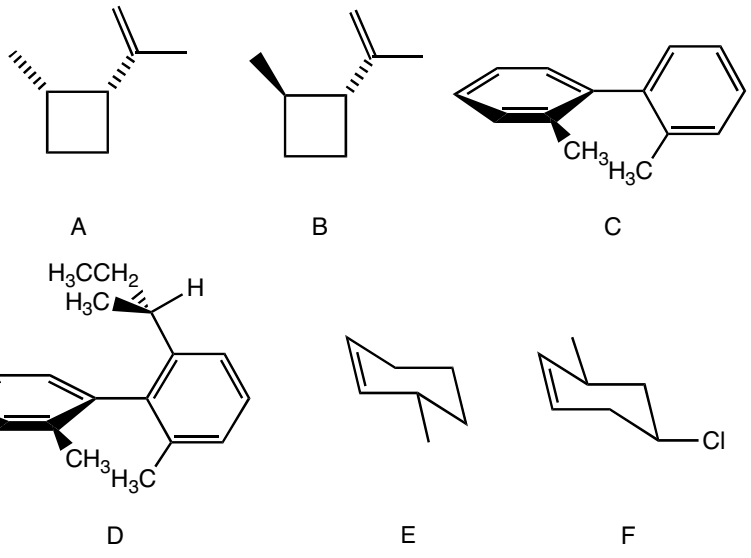
tc1 **tc2**

G O I N G D E E P E R

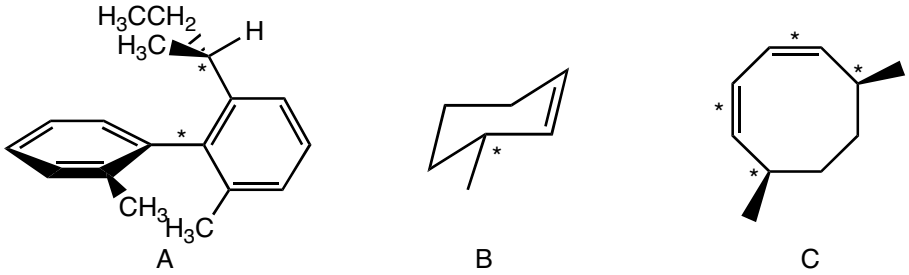
The answer of six diastereomers might seem surprising if you consider that the maximum number of stereoisomers for a compound with four stereocenters is $2^4 = 16$. Looking at the above six compounds, we can spot two that are *meso* isomers (**tt1** and **cc1**), leaving four that are chiral, representing pairs of enantiomers. (Isomer **cc1** is chiral in the chair conformation shown, but may be considered as a conformationally averaged *meso* isomer, as suggested by the dot-convention structure.) That gives a total of 2 + 4(2) = 10 stereoisomers. Since each *meso* compound represents two potential "stereoisomers" (*SRSR* and *RSRS* for **tt1** and *RRSS* and *SSRR* for **cc1**), that brings us to a total of 12 of the possible 16 combinations that are accounted for. What happened to the other four?

This apparent conundrum is solved by realizing that there are more possibilities that happen to be identical represented by the two *trans,cis* diastereomers. Just as the end-to-end symmetry makes the *meso* configurations *SRSR* and *RSRS* identical, the chiral structure **tc2** represents the identical possibilities *RSSS* and *SSSR*, along with their enantiomers, *SRRR* and *RRRS*. In this way, each of the two *trans,cis* diastereomers represent 4, not just 2, of the 16 possible configurations. Our accounting is thus complete! (If you still find this confusing, try drawing all 16 possibilities. You will find that 6 of these can be generated from 6 others just by flipping the molecule over, leaving only 10 unique stereoisomers.)

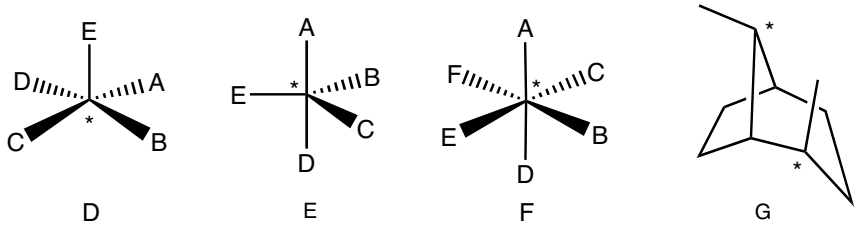
7. For some structures, such as A and B, making the enantiomer is simply a matter of reversing the configuration of *every* stereocenter. For structures C-F, the better approach is to reflect the molecule through an imaginary mirror plane. This naturally reverses any sense of twist and inverts each stereocenter, creating the enantiomer. Note that simply changing the configuration of the stereocenters by switching two groups in E and F would give the enantiomers, but in different conformations. Your drawings need not look exactly like those below to be correct.



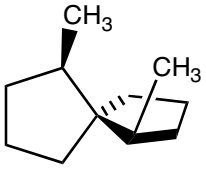
8. In A, the biphenyl ring system is viewed as a stereogenic unit as discussed in text; reversing its sense of twist produces a new stereoisomer. The C2 of the 2-butyl substituent is a conventional stereogenic center. The molecule thus has two stereogenic units and four stereoisomers. In B and C, the methyl-substituted carbons are conventional stereocenters. The alkene of cyclohexene might be considered a stereogenic unit in some contexts, but the trans isomer would be so high in energy that we can reasonably think of the cis as the only isomer. The alkenes in the cyclooctadiene, on the other hand, should be considered as stereogenic units, since *trans*-cyclooctenes are stable at ambient temperature.

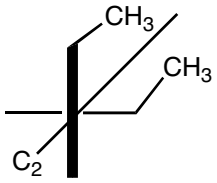


The central atoms in the square pyramidal (D), trigonal bipyramidal (E), and octahedral (F) structures with all different substituents are all stereocenters. (In fact, switching *any* two ligands produces a stereocenter, though the requirement is only that one such transposition be possible.) In the bicyclo[3.2.1]octane (G), the bridgehead C's may also be considered stereocenters, although again the diastereomers arrived at by switching two ligands would be unreasonably strained. (Such isomers are known for larger bicyclics, however, and are known as *in,out* and *in,in* isomers, having bridgehead hydrogens that point toward the interior of the molecule. The normal isomers, the only reasonable possibilities for smaller bicyclics, are *out,out* isomers.)



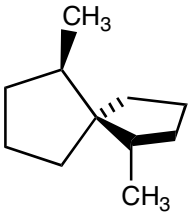
9. To determine topicity of the methyl groups, we need to determine if and how they are related by symmetry. This can be difficult to see from drawings on paper. Models can be very helpful, as can redrawing the structure in an orientation that makes the symmetry more obvious. (Models can make this redrawing easier also.) The left structures below are copied from the exercise, and the right structures represent the same molecules viewed from the left, such that the C's in the two five-membered rings appear as perpendicular lines.

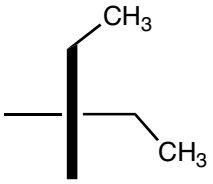




Homotopic methyls.

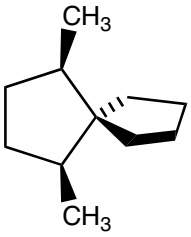
The methyl groups are related by a C_2 rotation axis.

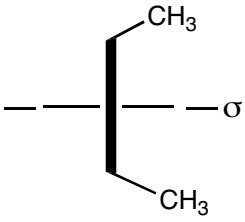




Diastereotopic methyls.

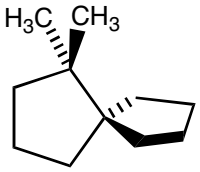
The methyl groups have the same connectivity but are not related by symmetry. We can tell by looking at either structure that they different, since one CH_3 points roughly towards the other, while the other CH_3 points roughly away from the other.

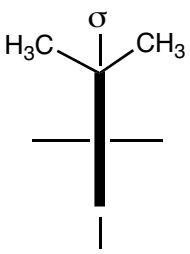




Enantiotopic methyls.

The methyl groups are related by a horizontal mirror plane.

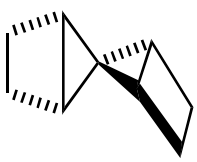


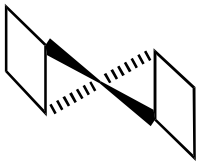


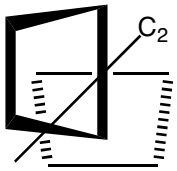
Enantiotopic methyls.

The methyl groups are related by a mirror plane that is roughly the plane of the paper in the left structure and vertical in the right structure.

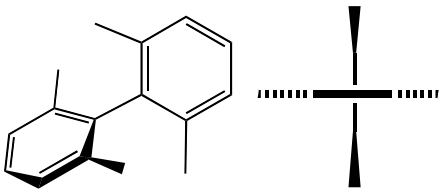
10. The compound is chiral but not asymmetric. It has a C_2 axis, as shown by the middle perspective, viewed along the C_2 axis. The right drawing is similar to those in exercise 9, drawn from a left-hand viewpoint of the left structure, such that the C's in the three-membered rings appear as perpendicular lines.



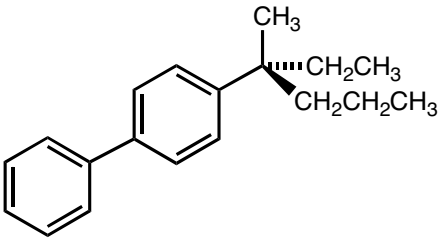




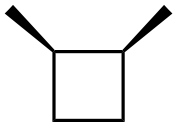
11. Achirotopic points are those that reside on molecular mirror planes or at the center point of a molecule that has an S_n axis. (The vast majority reside on mirror planes.)



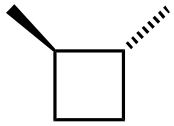
All atoms are achirotopic. Viewing down the axis of the C–C bond that links the two rings, we can clearly see two mirror planes that contain all of the C atoms and the H atoms on the rings. (Note that the mirror planes require a 90˚ dihedral angle between the rings.) The H atoms on the CH_3 groups can also be considered achirotopic, since the time scale for their rotation in and out of the mirror planes is very fast.



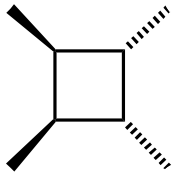
All atoms are chirotopic. The presence of a single stereogenic center makes this a chiral compound, such that all atoms are in a chiral environment. There are no achirotopic points in a chiral molecule.



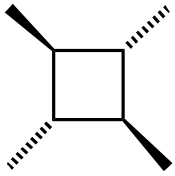
This *meso* compound has a single mirror plane (vertical), so there is a plane of achirotopic points. However, none of the atoms reside on the plane, so all atoms are chirotopic.



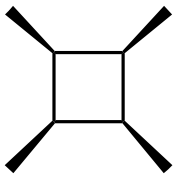
This is the *d* or *l* isomer of the last compound. Since it is chiral, no points are achirotopic.



This is another *meso* compound, possessing one mirror plane (horizontal). Like the earlier *meso* example, the mirror plane contains no atoms, all of which are therefore chirotopic.

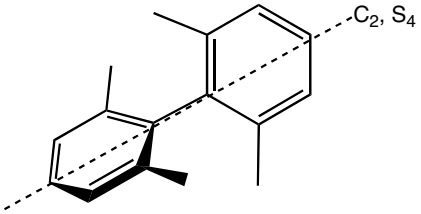


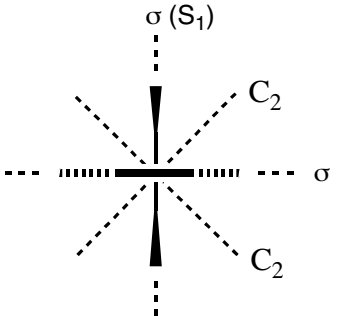
All atoms are achirotopic. This compound has two mirror planes, each angled at 45˚ from vertical. These planes contain all atoms except for some of the CH_3 H atoms, which rotate into the planes on a very short time scale.



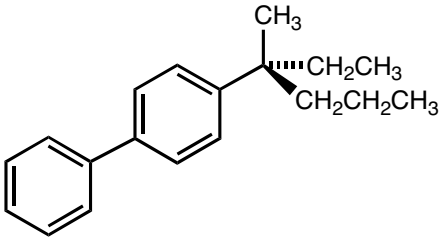
All atoms are achirotopic, just like the last example, due to two mirror planes angled at 45˚ from vertical. This molecule has two additional mirror planes (vertical and horizontal) containing additional achirotopic points.

12.

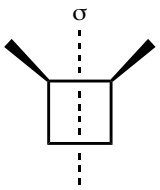




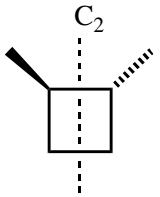
This biphenyl has three axes and two mirror planes.



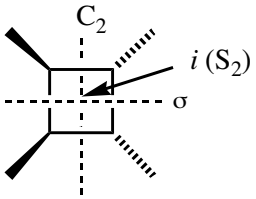
No symmetry elements.



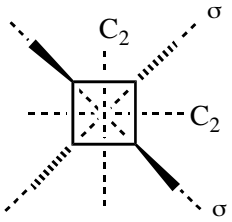
Only one mirror plane.



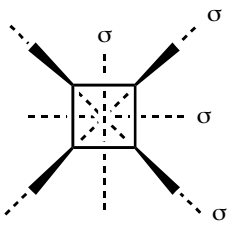
Only one C_2 axis.



This molecule has one C_2 axis, one mirror plane, and a center of inversion (*i*). An S_2 axis is equivalent to *i*, and an axis in any direction will work, as long as it contains the center point.

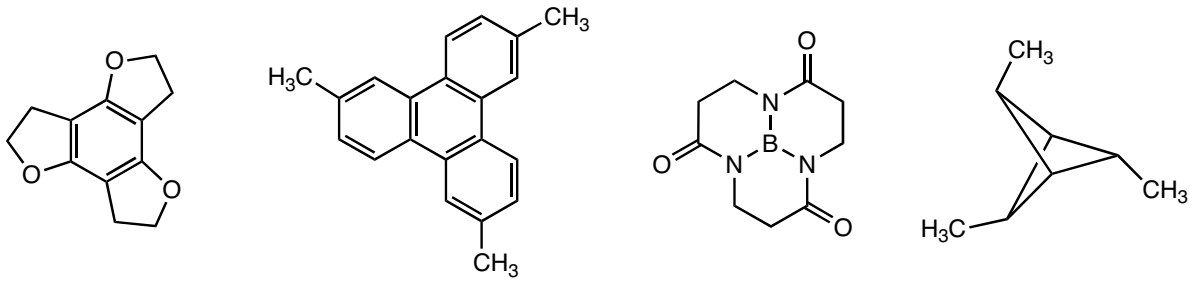


This molecule has three C_2 axes and two mirror planes. Two C_2 axes are shown; the viewing axis is also a C_2 axis.



This molecule has one C_4 axis (the viewing axis) and four mirror planes.

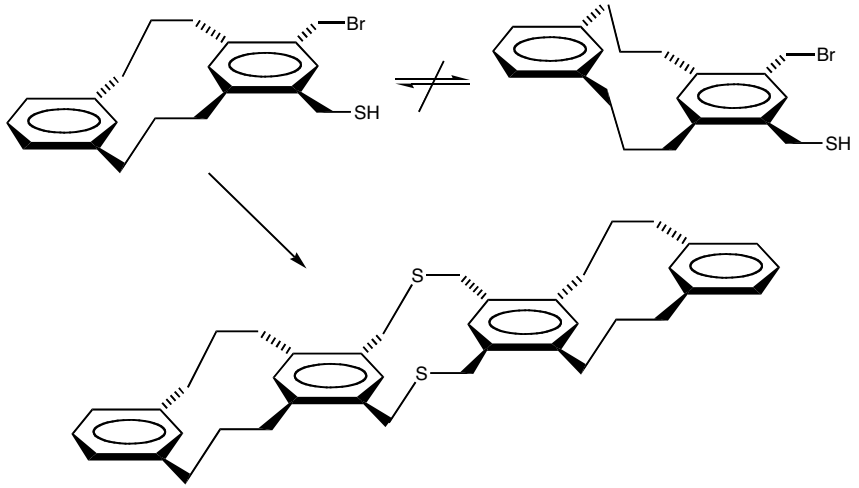
13. While it is easy to think of molecules with a C_3 axis and three mirror planes (CH_3F, for example), molecules with a C_3 axis and only one mirror plane are less common. In this case, the mirror plane must be perpendicular to the axis; if parallel, the axis would generate two more mirror planes. Four examples are shown:



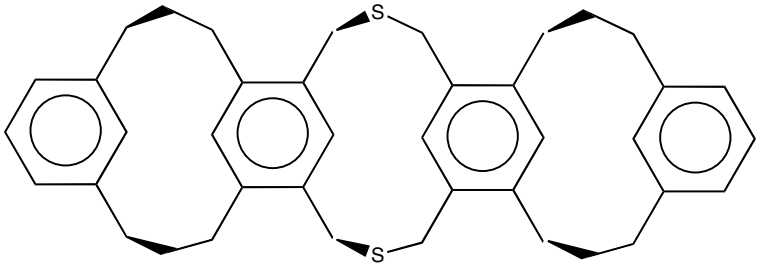
These molecules have C_{3h} point group symmetry, while CH_3F has C_{3v} point group symmetry. Though not included in the scope of this text, point groups are very useful for classification of molecular symmetry.

14. This cyclophane thiol has no symmetry in the conformation shown and is therefore chiral. It can be converted to its enantiomer by rotation about single bonds, but given the observation that its solutions are optically active, we can conclude that the compound is an atropisomer.

Two molecules of this compound can react through two S_N2 steps to give a polycyclic cyclophane product.



This product, shown both above and below, is achiral. In the lower view, a horizontal mirror plane is apparent. The increase in symmetry, and destruction of chirality, occurs because the two different substituents, CH_2Br and CH_2SH, become equivalent CH_2SCH_2 bridges in the product.

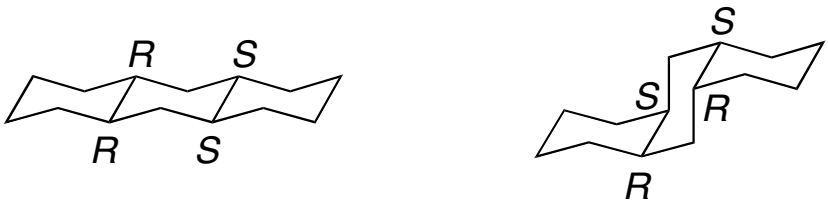


This is a novel process, in that two chiral molecules of the same handedness are combining to make an achiral molecule. The general requirement for a similar result in any system is that the reaction must lead to new symmetry – a mirror plane or other S_n – in the joined product. The reverse process is a molecular realization of a famous parlor trick, "la coupe du roi," in which an apple (achiral) is cut into two identical, chiral pieces. See: F. A. L. Anet, S. S. Miura, J. Siegel, K. Mislow, *J. Am. Chem. Soc*. **1983**, *105*, 1419-1426.

15. An epimer is defined as a diastereomer that differs from a reference compound in the configuration of only one of two or more stereocenters. Therefore, for example, *trans*- and *cis*-decalin are epimers, having two stereocenters and differing at only one. In the tricyclic compound of this exercise, we must change the configuration of two of the four stereocenters to go from the *trans,trans* isomer to the *cis,cis* isomer, so these diastereomers are not epimers.

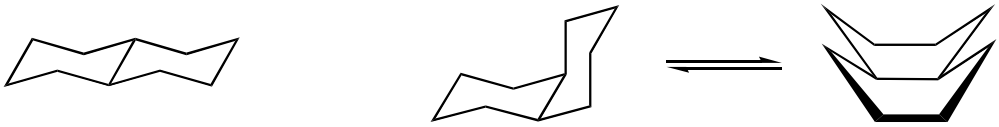
G O I N G D E E P E R

If we assign *R* and *S* labels to the isomers above, we can see from the labels alone that the configurations of two of the four stereocenters have been changed.



If, however, we go back and consider the simpler case of *trans*- and *cis*-decalin, we have trouble doing the same thing. When we attempt to assign priorities, we find that our rules do not allow us to prioritize the two $(CH_2)_4$ chains that lead to the other stereocenter. So how can the C atoms at the ring fusion be stereocenters if two of the attached groups are the same? In fact, we know that these are stereocenters, because we can interconvert the trans and cis diastereomers by switching two ligands at one of

these centers. The answer is that the two $(CH_2)_4$ groups really are different, even though their connectivity is the same. In *trans*-decalin, the two chains are enantiotopic (mirror images, *i.e.*, not the same), and in *cis*-decalin, they are also enantiotopic in several intermediate conformations between the two chair-chair forms (such as the boat-boat conformation shown) as well as in the time-averaged conformation. But with prioritization rules based on connectivity, we are unable to assign *R* and *S* labels.

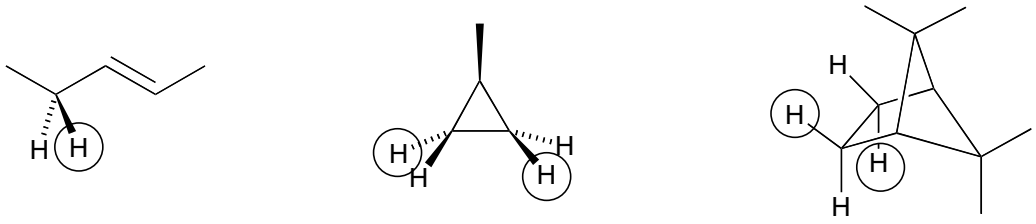


Be assured that those who thought up the prioritization rules took cases like this into account. Although textbooks only give two sequencing rules (atomic number, then atomic mass number to distinguish isotopes), there are indeed three additional rules in the Cahn-Ingold-Prelog (CIP) system. Use of the remaining three rules is not at all trivial, and it is not recommended that you look these up unless you really need them or find such things interesting. If you do need them, they are explained in detail in a 17-page article: V. Prelog and G. Helmchen, *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 567-583.

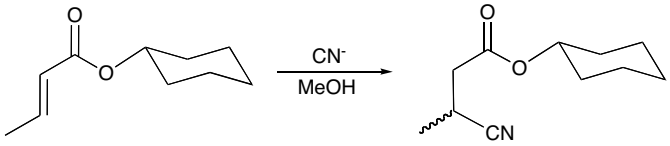
Knowing that stereochemical descriptors can be assigned for the decalins leads us to another question. We can reason that the two descriptors for *trans*-decalin must be the same, since the stereocenters are homotopic (interchanged by a horizontal C_2 axis in the drawing above). Likewise, the stereocenters are also homotopic in *cis*-decalin in the boat-boat and time-averaged conformations, so the two descriptors must also be same in this case. Further, the descriptors must be different for the cis and trans isomers, since these are stereoisomers that differ in the spatial arrangement at the stereocenters. But here's the problem: the cis and trans isomers differ by spatial arrangement at only *one* of the two stereocenters (*i.e.*, they are epimers), yet these arguments show that *both* of the descriptors must change in going from trans to cis. How is this contradiction resolvable?

It turns out that both stereocenters in *trans*-decalin are designated r_n, while the stereocenters in *cis*-decalin are s_n. (The lower case descriptors indicate that these are special cases that require rule number 5!) The contradiction is resolved by noting that as a single stereocenter is inverted in going from trans to cis, the descriptor changes not only for that stereocenter, but also for the other. The reason the other one changes has to do with priority rules that are based on things other than connectivity. The moral of this story is that stereochemical analysis of some simple molecules can be complicated. Fortunately, the simple rules work for the vast majority of molecules!

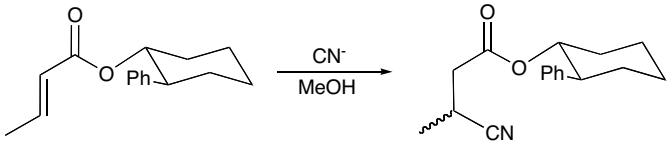
16. Prochiral hydrogens are labeled as "H", and Pro-*S* hydrogens are circled.



17. A 50/50 ratio will be expected if and only if one or more of the species present (including reactants, catalysts, solvent, etc.) are chiral and non-racemic.

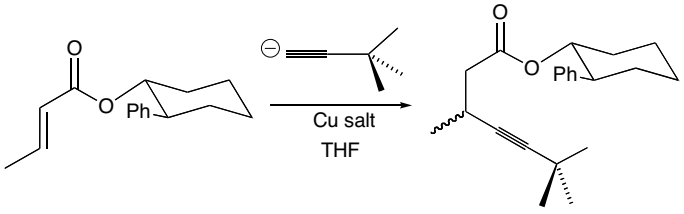


Since all species present are achiral, a 50/50 mixture is expected. (The squiggly bond in the product indicates a mixture of configurations.) Another way to think about it: the transition states leading to the two configurations of the new stereocenter are enantiomeric, having the same energy, so the rates of formation of the enantiomeric products are the same. Yet another approach: the faces of the alkene are enantiotopic (related by a mirror plane of the molecule), so there is no preference in the attack of an achiral nucleophile.

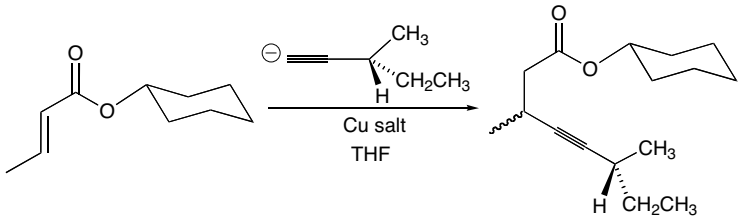


Due to the Ph group, the reactant is chiral and the faces of the alkene are diastereotopic. (The mirror plane in the first reactant is destroyed by the Ph.) Thus the attack of any nucleophile on either face leads to diastereotopic transition states (having different energy). The product ratio will not be 50/50.

(Note that we are assuming that the drawing of a single enantiomer actually represents a single enantiomer. In some contexts, the drawing of a single enantiomer can represent a racemic mixture, such as when a chiral product is obtained in an achiral environment, as in the first reaction above. In cases like this, chemists are expected to realize that the compound must be racemic even if a single enantiomer is drawn. In the absence of any notation or context implying that the compound is racemic, the best interpretation is generally that a single enantiomer is implied.)

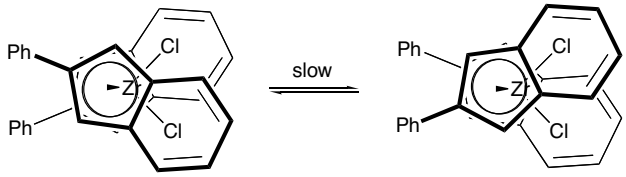


This is the same chiral reactant and a different nucleophile. By the reasoning above, the product ratio will not be 50/50.

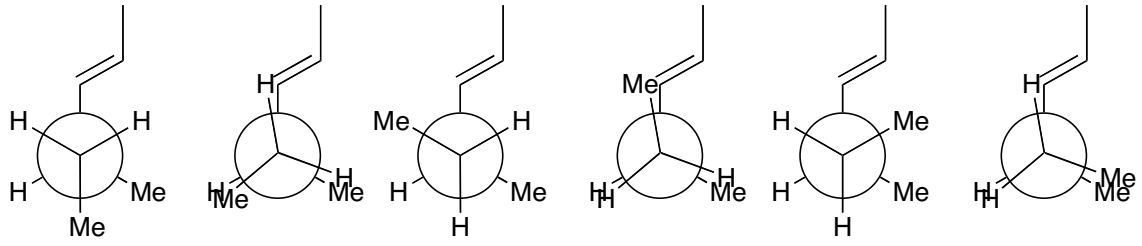


The unsaturated ester is achiral in this case, but the nucleophile is chiral. Even though the alkene faces are enantiotopic, the chiral nucleophile leads to diastereomeric transition states. The product mixture will not be 50/50.

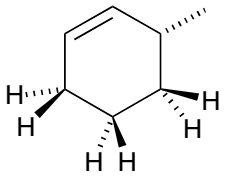
18. This catalyst, in a sense, is an atropisomer. In its most stable conformation it has C_2 symmetry, but it can racemize through rotation of the aromatic ligands such that the Ph groups pass each other. Apparently, this racemization is slow in the active catalyst relative to the polymerization propagation step. Thus, like the C_2 catalysts discussed in the chapter, this one produces isotactic polypropylene, but the sense of the chirality of the catalyst occasionally switches, causing a switch also in the polymer stereochemistry from one block to the next.



19. Both compounds are asymmetric, possessing no symmetry elements. Therefore, *no* hydrogen atoms in these molecules are ever equivalent. Nonetheless, it is a good exercise to prove to ourselves that rotation about bonds is ineffective at making the CH_2 hydrogens equivalent. We can do this by drawing sets of limiting conformations.

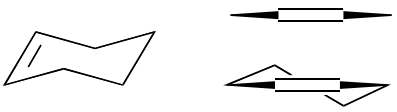


The first Newman projection above represents the conformation shown in the exercise, with the CH_2 hydrogens of interest on the front C of the projection. In this conformation, the two H's are clearly different, as one is *anti* to Me and the other *anti* to H. Likewise, in the other two staggered conformations, the two H's are *anti* to different groups. In all three eclipsed conformations, the two H's are eclipsing different groups. It is also clear that rotations around other bonds starting from any of these conformations will not help to make the H's equivalent.



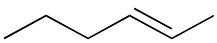
For 3-methylcyclohexene, we could also draw possible conformations. (To be complete, we might include chair, boat, twist-boat, etc.) Fortunately, we can easily see that for each CH_2, one H will always be cis to the Me, while the other will always be trans to the Me for any conformation.

20. To determine topicity of the faces, we need to determine any symmetry relationships between the faces.

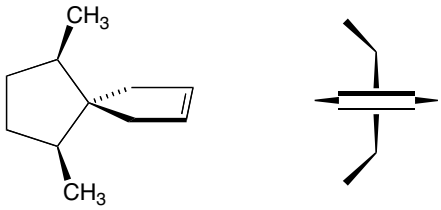


Homotopic faces. Whether a planar or twist geometry is taken, a C_2 axis interchanges the two faces of the alkene. The axis is made obvious by viewing the molecule down the axis. (The faces are also interchanged by a mirror plane in the planar geometry, but this does not alter the homotopic relationship.)

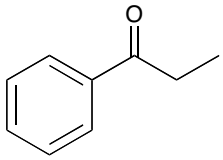
Diastereotopic faces. In any conformation, the Me group is cis to one alkene face and trans to the other. There are no symmetry elements.



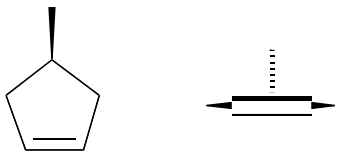
Enantiotopic faces. The plane of the paper is a mirror plane that interchanges the faces.



Enantiotopic faces. A horizontal mirror plane in the right view interchanges the two alkene faces.

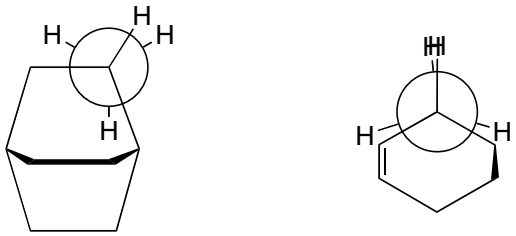


Enantiotopic faces. The plane of the paper is a mirror plane that interchanges the faces. The *Si* face is in front of the paper, and the *Re* face is behind the paper.



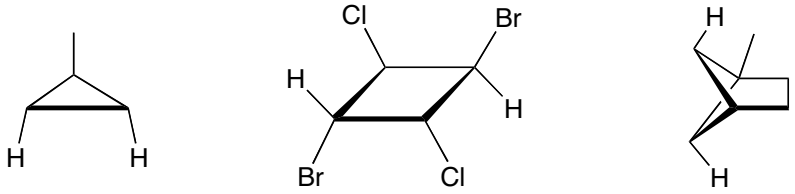
Diastereotopic faces. The only symmetry element is a vertical mirror plane in both views, and this plane does not interconvert the faces.

21. The two compounds are redrawn from new perspectives as Newman projections. The left structure shows the view of the original drawing from the top of the page, while the right structure shows the view of the second molecule from the left side of the page. In both cases, the new vantage point makes it clear that the methyl hydrogens are all inequivalent in these static structures. However, two 120˚ rotations about the C–CH_3 bond are sufficient to interchange the hydrogens, placing each of the three hydrogens in the same three locations.

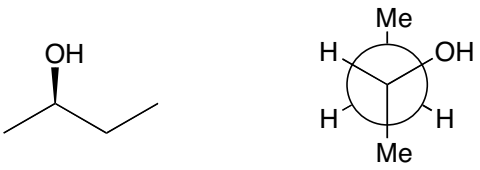


22. A. Both reactions are 100% stereoselective, and the bromination is 100% stereospecific. There is no selectivity for *d vs. l* – nor could there be, since both reactants are achiral.
    B. Identical product mixtures are obtained from the isomeric reactants, so there is no stereospecificity. Since the mixtures are 60% *d,l* and 40% *meso*, we can say that there is a 60% stereoselectivity for the *d,l* isomer.
    C. The product mixture for maleic acid is the same as in B: 60% stereoselective for *d,l*. Higher stereoselectivity for *d,l* is observed for fumaric acid: 80%. Since the shift in product percentage with the change in reactant isomer is only 20%, the bromination can be called 20% stereospecific.
    D. Since different diastereomers of the reactant give different diastereomers of the product, each reaction is 100% stereoselective, and the thermolysis is 100% stereospecific.
    E. In this case, the thermolysis is 71% stereoselective but is not stereospecific.
    F. Since the reactant has no stereoisomer (at least not in a practical sense – the *E* isomer is very high in energy, such that it cannot be studied in this reaction), the reaction cannot be stereospecific. The reaction *is* stereoselective. Even though the product isomers are produced in low yield, the stereoselectivity relates only to the selectivity among these products. Therefore, the product percentages should be scaled such that they sum to 100% for computing the selectivity. Thus, the reaction is 65% stereoselective.

23. The possibilities are limitless; three examples are shown. In the first and third molecules, the labeled H's are related by a mirror plane and not by any rotation. In the second molecule, the H's are interchanged by a center of inversion, the only symmetry element of this molecule. In each of the cases shown, there exists one additional pair of enantiotopic H's that are not attached to the same atom.



24. The two H's attached to C_3, the back C in the Newman projection shown, are diastereotopic in all conformations. In the conformation shown, for example, one of the H's is anti to OH and the other is anti to H. Indeed, the H's of *any* CH_2 in an asymmetric molecule (including any molecule that has a single tetrahedral stereocenter) are diastereotopic. See exercise 19.



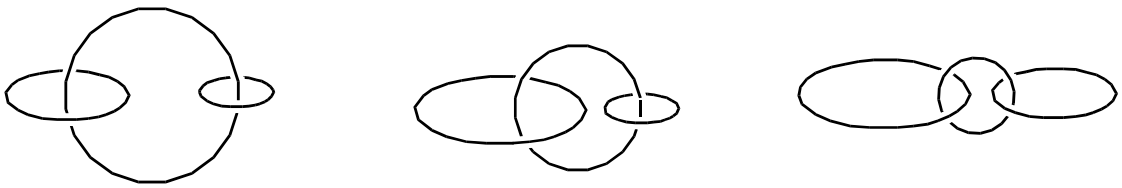
25. It helps to realize first that there are only two stereoisomers for a [2]catenane with directional rings, even if the rings are different (shown as different sizes). These isomers are enantiomeric. We denote the left isomer *R*, since each ring has a clockwise orientation when viewed from the other ring as it enters the center (in the direction indicated by the arrow). Likewise, we denote the right isomer as *S* for its counterclockwise orientation.

R *S*

a. For a [3]catenane with identical and directional rings, each of the two linkages can be either *R* or *S*. Four permutations of *R* and *S* are possible, just as in molecules with two tetrahedral stereocenters. The first and third structures are enantiomers, but the second and fourth are identical, due to the equivalency of the end rings. This isomer may be considered a *meso* isomer, possessing a topological center of inversion. Therefore, with identical and directional rings, there are three stereoisomers, an enantiomeric pair and a *meso* isomer.

RR *RS* *SS* *SR*

b. For a [3]catenane with different and non-directional rings, three linkage isomers exist, since each of the three rings can be in the center, as shown below. All three topological isomers are achiral, as the plane of the central ring can be a mirror plane.

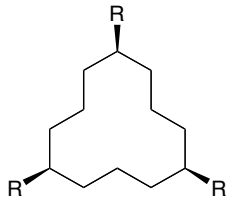


c. For a [3]catenane with different and directional rings, both types of isomerism exist simultaneously. For each of the three linkage isomers of part b, the four directionality isomers of part a would exist, for a total of twelve isomers (six enantiomeric pairs). Note that no *meso* isomer is possible in this case, since the end rings are different.

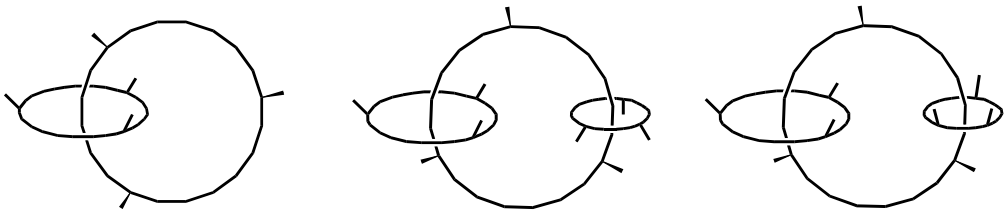
G O I N G D E E P E R

The exercise instructed us to presume that the individual rings are achiral, and further that the ring plane is a mirror plane. If we remove these restrictions, a new form of topological chirality appears, and the number of possible isomers increases dramatically.

We first allow for the possibility that the individual ring planes are not mirror planes. The rings can still be achiral if a mirror plane perpendicular to the ring plane exists. The presence of such a mirror will also make the ring non-directional, so this change does not apply to parts a or c. An example of such a ring is shown:



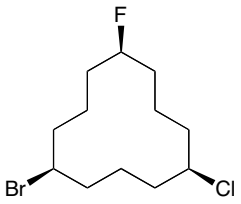
Linking two such rings, whether identical or different, leads to chiral [2]catenanes (at left below), since all mirror planes of the individual rings are destroyed by the linkage. Like the linkage and directional isomerism discussed above, this is a form of topological isomerism, arising from a different type of directionality. For [3]catenanes like those in part b, two diastereomeric pairs of enantiomers will be formed for each linkage isomer. The diastereomers could be called head-to-tail and head-to-head, referring to the relative directions of the end rings.



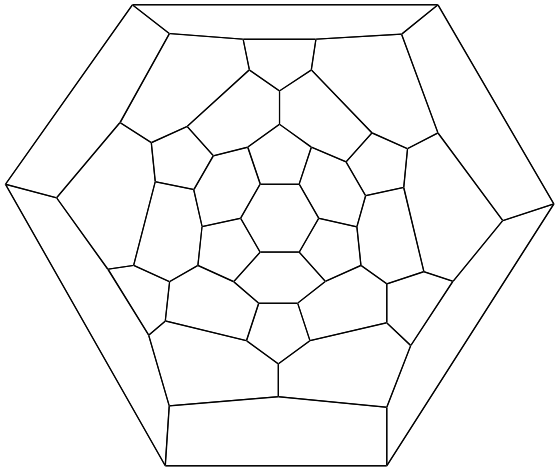
head-to-tail head-to-head

If the individual rings are chiral, then isomerism arises that is similar to that associated with the presence of multiple stereocenters. If each ring exists as two enantiomers, then a [2]catenane will exhibit two diastereomeric pairs of enantiomers (2^2 isomers), and a [3]catenane will exhibit 4 diastereomeric pairs of enantiomers (2^3 isomers).

Expanding on part c, what happens if we make [3]catenanes with rings that are different, directional in both senses, and chiral? An example of such a ring is shown below. The types of directionality are interdependent, since both senses are switched by flipping the ring over. So the number of possible isomers is $3 \times 4 \times 8 = 96$. Clearly, these issues must be considered when designing a catenane synthesis!

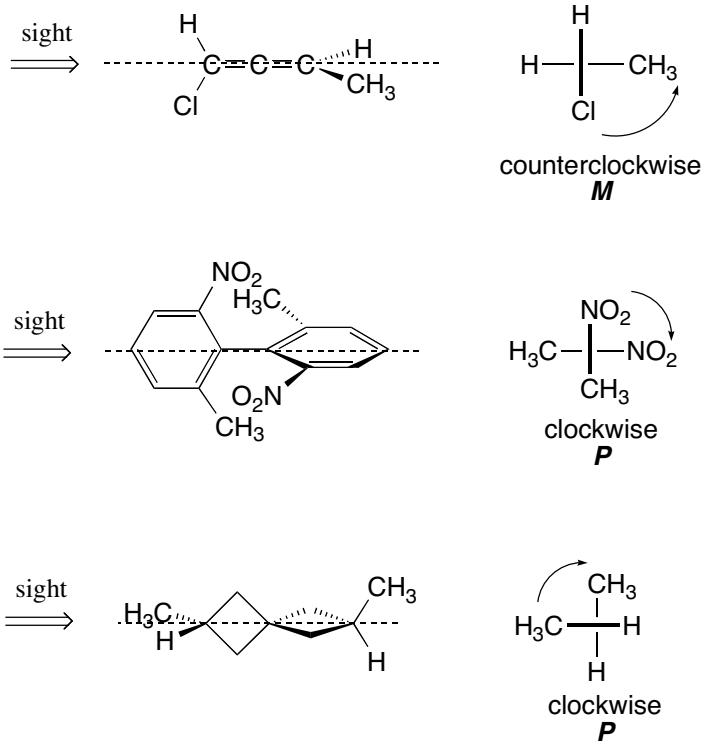


26. It may seem surprising at first that C_{60} has a planar graph, given that there are so many crossed bonds in the diagram. But imagine viewing the molecule from the inside — there would be no crossed bonds! This surrounding shell is not planar, but we can make it planar by stretching bonds and flattening the molecule. Imagine standing inside the sphere and placing your fingers into one of the six-membered rings overhead and pushing to the sides to stretch all six bonds. Keep stretching these bonds while flattening the molecule until this large ring surrounds the rest of the molecule on the floor. A planar graph would be obtained (π bonds omitted):



27. The product would be a [2]catenane.

28. In the text, the descriptors were determined by sighting from right to left. Here, sighting from left to right, we obtain the same descriptors:

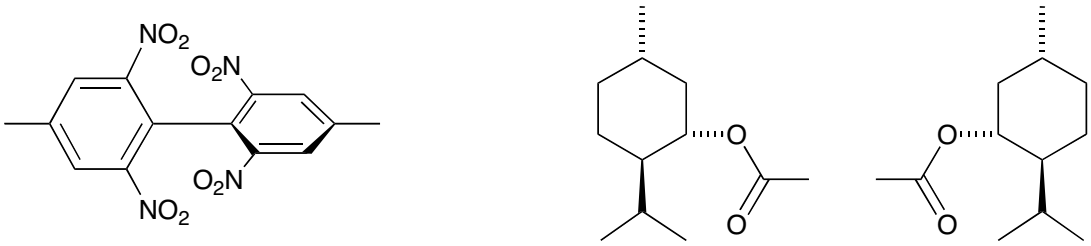


29. The number of possible arrangements of five different rings in five possible positions is 5! (five factorial). This result from probability theory is easy to understand. There are 5 possible places for the first ring. For each of these, there are 4 remaining possibilities for the second ring, and so on. However, this will lead to a double counting, since, for example, 1-2-3-4-5 is the same as 5-4-3-2-1. So the number of isomers is 5!/2 = 60.

30. The eclipsed form has a C_5 axis and a perpendicular mirror plane, and in combination these constitute an S_5 axis. The staggered form has a C_5 axis but no perpendicular mirror plane; the C_5 axis is also a S_{10} axis. Both conformations are shown as viewed along the axis.

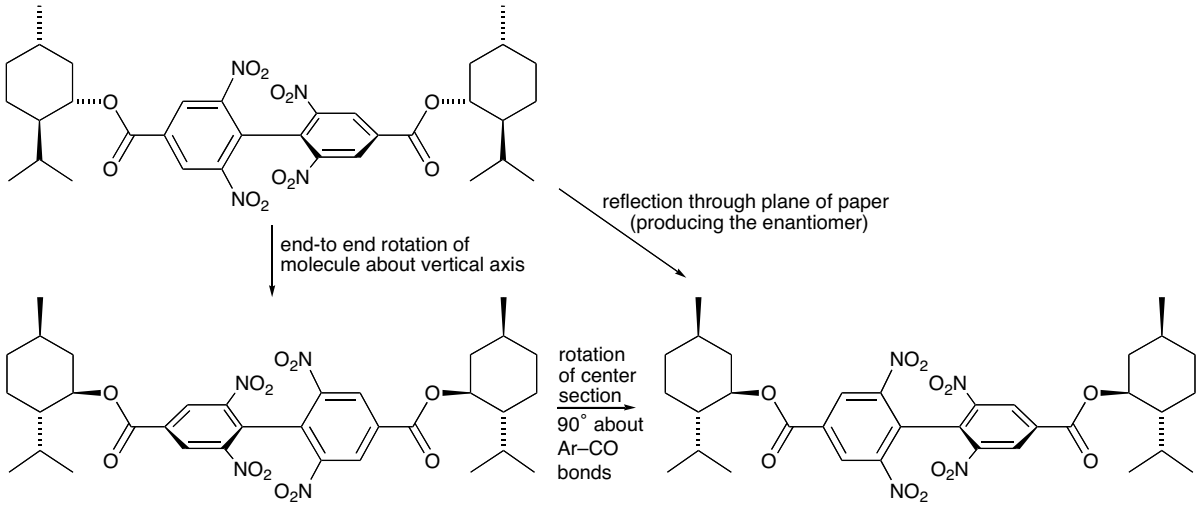
The Cp–Fe rotation has a five-fold barrier. (One might be tempted to say that ferrocene should have a 25-fold barrier, since it has two five-fold rotors. However, all C's become eclipsed at the same time, reducing the foldedness.)

31. a. We can most easily analyze the symmetry of this molecule by considering the center and the ends of the molecule separately. The center section, shown at the left below, is achiral, having two mirror planes and an S_4 axis. The mirror planes contain the central C–C axis and one of the aromatic rings, and the S_4 axis is coincident with the central C–C axis. The end groups taken together, shown at the right, are also achiral, having a vertical mirror plane. If one of the ends were rotated 180° with respect to the other, there would be a center of inversion (*i* or S_2).



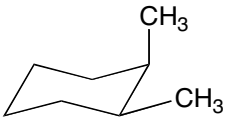
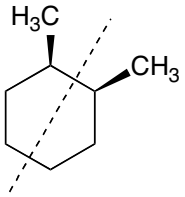
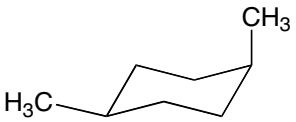
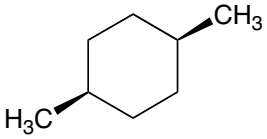
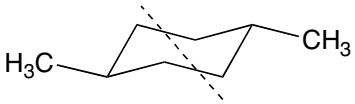
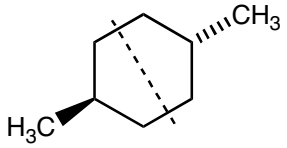
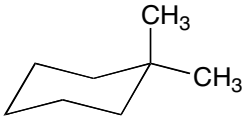
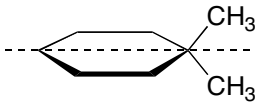
The center and ends of the molecule have no symmetry elements in common. Thus, when the components are put together, there is no symmetry. The molecule is therefore chiral.

b. We can draw the enantiomer by reflection of the molecule through any mirror plane. For convenience, we will choose the plane of the paper (see scheme). We can also convert one enantiomer as drawn to the other by two rotations: a rotation of the entire molecule followed by an internal rotation about two single bonds.

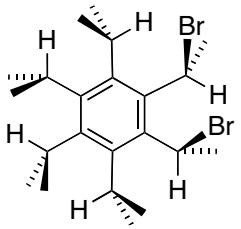


c. Using the reasoning of part a, we can see that the only way this molecule can become achiral, in other words, to possess a mirror plane or other improper rotation, is to rotate about the central C–C bond to make the Ar rings coplanar. This would potentially give the molecule a vertical mirror plane that bisects the central C–C bond or a center of inversion. However, since the nitro groups prevent this from happening, the molecule must always be chiral.

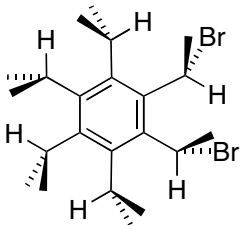
32. For the timescale where ring inversion is slow, we can think of the molecules, for symmetry purposes, as rigidly locked in one chair conformation. For fast inversion, we can treat the molecule as if the six ring carbons lie in a single plane. We should realize, however, that neither the planar conformation nor any other symmetric conformer need participate in the inversion process to enforce the topicities we determine this way (a situation similar to that presented in exercise 31).

Slow inversion	Fast inversion
 Diastereotopic (one CH_3 axial, one equatorial but same connectivity)	 Enantiotopic (related by mirror plane)
 Diastereotopic (one CH_3 axial, one equatorial but same connectivity)	 Homotopic (related by C_2 axis – molecule viewed along axis)
 Homotopic (related by C_2 axis)	 Homotopic (symmetry cannot be decreased by inversion process)
 Diastereotopic (one CH_3 axial, one equatorial but same connectivity)	 Homotopic (related by horizontal C_2 axis)

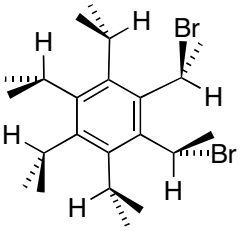
33. Replacing an isopropyl CH_3 with Br produces a stereocenter. With two such substitutions, the molecule has two stereocenters and $2^2 = 4$ possible stereoisomers: *RR*, *SS*, *RS*, and *SR*. Since the two stereocenters have the same connectivity, an achiral *meso* isomer (*RS* = *SR*) is a possibility, but in fact, the two stereocenters are not related by symmetry in the geared conformation. (They are obviously different: one points into the back of the other.) Therefore, there are four isomers and all are chiral: two diastereomeric pairs of enantiomers (*RR*, *SS* and *RS*, *SR)*.



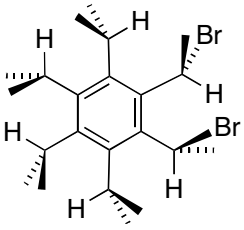
RR



SS



RS



SR

The consequences of correlated 180˚ rotation of the six groups depends on the isomer. The *RS* and *SR* isomers are interconverted by this process. The *RR* isomer is converted into itself, as is the *SS* isomer. (For the *RR* and *SS* isomers, 180˚ rotation of the whole molecule about a horizontal axis produces a structure equivalent to that produced by the correlated rotation.)

34. Showing that the metal centers are chirotopic is simple. Since each complex has a C_2 axis as the only element of symmetry, each complex is chiral and all atoms in the complexes are chirotopic. To show non-stereogenicity, we must show that stereoisomers are not produced upon switching of any two ligands. The first two complexes, having tetrahedral metal centers, would need to have four different ligands in order to be stereogenic. Both have pairs of identical ligands, and switching any two produces the same complex. The third complex has an octahedral nickel atom with a meridional tridentate ligand. Several possible ligand swaps could produce a diastereomeric complex with a facial tridentate ligand, but this complex would be considerably higher in energy due to the rigidity of the tridentate ligand. So practically speaking, this nickel center is also non-stereogenic. In all three complexes, the stereogenic atoms are carbon atoms in the ligands.

35. This probability can be calculated by realizing first that each product molecule has a 50% chance of being either enantiomer. We will assume a 100% yield – that is, every molecule of starting material is converted to product. (Note that if only one molecule, or any other odd number of molecules, is not converted to product, the probability for an exactly 50:50 ratio will be zero!) This question then becomes a classic problem from probability theory called an

equipartition problem. The probability is the same as the probability that in n flips of a coin, heads will be obtained exactly $n/2$ times.

$$\text{probability of exact } 50:50 \text{ ratio} = \frac{\text{number of } 50:50 \text{ combinations}}{\text{number of total possible combinations}}$$

Let us number the molecules from 1 to n. The numerator above represents all possible ways that half of the molecules could be one enantiomer, say (+). For example, for $n = 2$, there are two possible combinations: either molecule 1 or 2 could be (+). For $n = 4$, there are six combinations: (12, 13, 14, 23, 24, 34). In general, the number of combinations of k items selected from a set of n items is $n!/k!(n\text{-}k)!$ In our case, $k = n/2$, so the expression reduces to $n!/((n/2)!)^2$. The denominator above represents all possible combinations, whether 50:50 or not. Since each molecule has two possible states, (+) and (-), that are determined independently of the other molecules, the total number of combinations is 2^n.

$$\text{probability of exact } 50:50 \text{ ratio} = \frac{n!/\left(\frac{n}{2}!\right)^2}{2^n}$$

Plugging in some values for n (including 10 and 1000, which were asked for in the exercise):

n	2	4	6	8	10	34	100	340	1000
prob.	0.5	0.375	0.313	0.275	0.246	0.136	0.080	0.043	0.025

Whether using a calculator or computer, we find that we cannot go much further. Both the factorials of the numerator and the exponential of the denominator get very big as n increases, and even with 15-digit number precision (allowing numerator and denominator to approach 10^{308}), the highest n we can use is 1022. However, we can do better by using Stirling's approximation for factorials, which is very accurate for large n:

$$\ln(n!) = \left(n + \tfrac{1}{2}\right)\ln(n) - n + \ln\sqrt{2\pi}$$

To use this approximation, we first take the logarithm of the probability and then substitute, expand, and simplify:

$$\ln(\text{prob. } 50:50) = \ln\left(\frac{n!/\left(\frac{n}{2}!\right)^2}{2^n}\right)$$

$$= \ln(n!) - 2\ln\left(\tfrac{n}{2}!\right) - n\ln 2$$

$$= \left(\left(n + \tfrac{1}{2}\right)\ln(n) - n + \ln\sqrt{2\pi}\right) - 2\left(\left(\tfrac{n}{2} + \tfrac{1}{2}\right)\ln\left(\tfrac{n}{2}\right) - \tfrac{n}{2} + \ln\sqrt{2\pi}\right) - n\ln 2$$

$$= n\ln(n) + \tfrac{1}{2}\ln(n) - n + \ln\sqrt{2\pi} - (n+1)\left(\ln(n) - \ln 2\right) + n - 2\ln\sqrt{2\pi} - n\ln 2$$

$$= n\ln(n) + \tfrac{1}{2}\ln(n) - \ln\sqrt{2\pi} - n\ln(n) - \ln(n) + n\ln 2 + \ln 2 - n\ln 2$$

$$= -\tfrac{1}{2}\ln(n) - \ln\sqrt{2\pi} + \ln 2$$

$$= \ln\left(\frac{2}{\sqrt{2\pi n}}\right) = \ln\sqrt{\frac{2}{\pi n}}$$

$$\text{prob. } 50:50 = \sqrt{\frac{2}{\pi n}}$$

This equation reproduces the above-calculated probabilities with increasing accuracy as n increases (2.5% error for $n = 10$ and 0.025% error for $n = 1000$). With this equation, we can directly calculate the probability for $n = 10^{21}$ to be 2.5×10^{-11}. Clearly, the probability of an exact 50:50 ratio will be vanishingly small.

G O I N G D E E P E R

Even though the chance of an exact 50:50 ratio of enantiomers for any laboratory sample is extremely small, the probability that the ratio will be experimentally indistinguishable from 50:50 is very large. Let's first investigate the trend for small n. We will calculate the probability that the ratio will be between 48:52 and 52:48.

A convenient and intuitive way to address this problem is to use Pascal's triangle. This mathematical construct, shown below, is generated line by line by placing "1" on the outside edges and taking each interior number as the sum of the two adjacent numbers above it. It turns out that Pascal's triangle directly shows us the number of combinations needed for our probability calculations. (Completely analogously, Pascal's triangle shows the number of possible spin-state combinations contributing to an NMR multiplet and therefore predicts the relative intensities.)

```
                                    1
                                  1   1
                                1   2   1
                              1   3   3   1
                            1   4   6   4   1
                          1   5   10  10  5   1
                        1   6   15  20  15  6   1
                      1   7   21  35  35  21  7   1
                    1   8   28  56  70  56  28  8   1
                  1   9   36  84  126 126 84  36  9   1
                1   10  45  120 210 252 210 120 45  10  1
```

The 1's on the left of the triangle will represent the single combination with all (-) molecules, and the 1's on the right will represent the single combination with all (+) molecules. (There's only one way each can happen, no matter how many molecules there are.) To analyze what can happen with n molecules (or flips of a coin), we look at row n+1 of the triangle. For $n = 2$, row 3 shows us that there is 1 way to have zero (+) molecules, 2 ways to have one (+) molecule, and 1 way to have two (+) molecules. The probability of a 50:50 mixture is therefore the center number (2) divided by the sum of the whole row (4), giving a probability of 0.5. For $n = 4$, row 5 shows us that there is 1 way to have zero or four (+) molecules, 4 ways to have one or

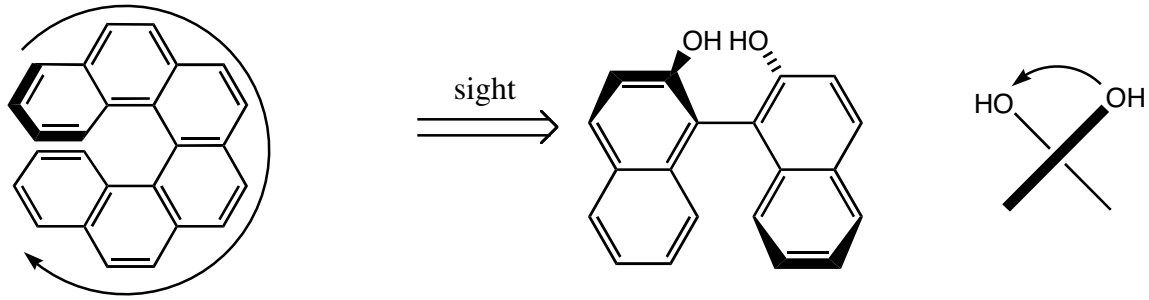
three (+) molecules, and 6 ways to have two (+) molecules. The 50:50 probability is 6/(1+4+6+4+1) = 0.375. Look at the triangle and note how quickly the numbers near the center get large as *n* increases. Nonetheless, the sums of the rows get large a bit faster, leading to a decrease in the 50:50 probability as *n* increases, as seen above.

For neither *n* = 2 nor 4 are there any possibilities to be within the 50±2% range without being exactly 50:50. The first opportunity for this occurs at *n* = 50, where we can have 24 and 26 molecules of each enantiomer. In row 51 of Pascal's triangle, the center number is 1.264×10^{14} and the sum of the row (*i.e.*, 2^{50}) is 1.126×10^{15}, giving a 50:50 probability of 0.112. The numbers on either side of the center, representing the 24:26 and 26:24 combinations, are both 1.216×10^{14}. So the probability of having 50±2% of the (+) enantiomer is $(1.264 + 2(1.216))\times10^{14}/1.126\times10^{15} = 0.328$, approximately three times that for the 50:50 ratio.

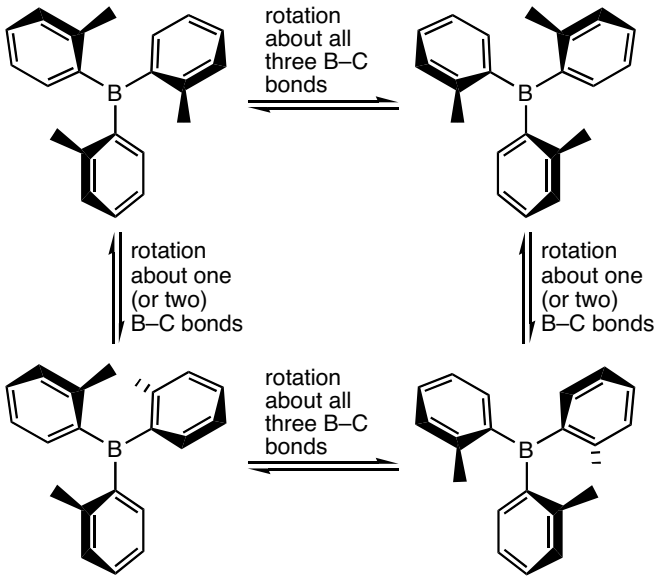
As *n* gets larger and more possible combinations fall within the ±2% range, the probability increases further. For *n* = 100, the number of (+) molecules can be 48, 49, 50, 51, or 52, and the probability of this is 0.383. For *n* = 1000, the number of (+) molecules can range from 480 to 520, and the probability increases to 0.805. The probability for *n* = 10,000 is 0.99994, while the probability for *n* = 100,000 is 0.999999999999999999999999999999999999. In other words, the probability that the ratio would fall *outside* the 50±2% range would be 10^{-36}, less than your chances at winning the lotto jackpot five weeks in a row (after buying only one ticket each week)!

The answers to this problem may be calculated also by using Stirling's approximation or by using binomial distributions, which for large *n* are accurately approximated by the normal distribution (see any probability and statistics textbook). Using this method, we can calculate that for $n = 10^{21}$, the probability that the number of (+) molecules will fall outside the 50±0.00000002% range is similar to the five-jackpot probability mentioned above. Thus, we can feel quite assured that in any racemic laboratory sample, the enantiomer ratio will fall close enough to 50:50 that we will be unable to tell otherwise by even our most sensitive of methods.

36. The helicene is *P* (right-handed). The binaphthyl is *M* (left-handed). Note that for a true helix like the helicene, prioritization of groups is not required – the arrow should just follow the helix.



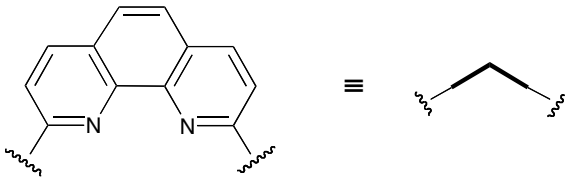
37. Four propeller-shaped stereoisomers exist: two diastereomeric pairs of enantiomers:



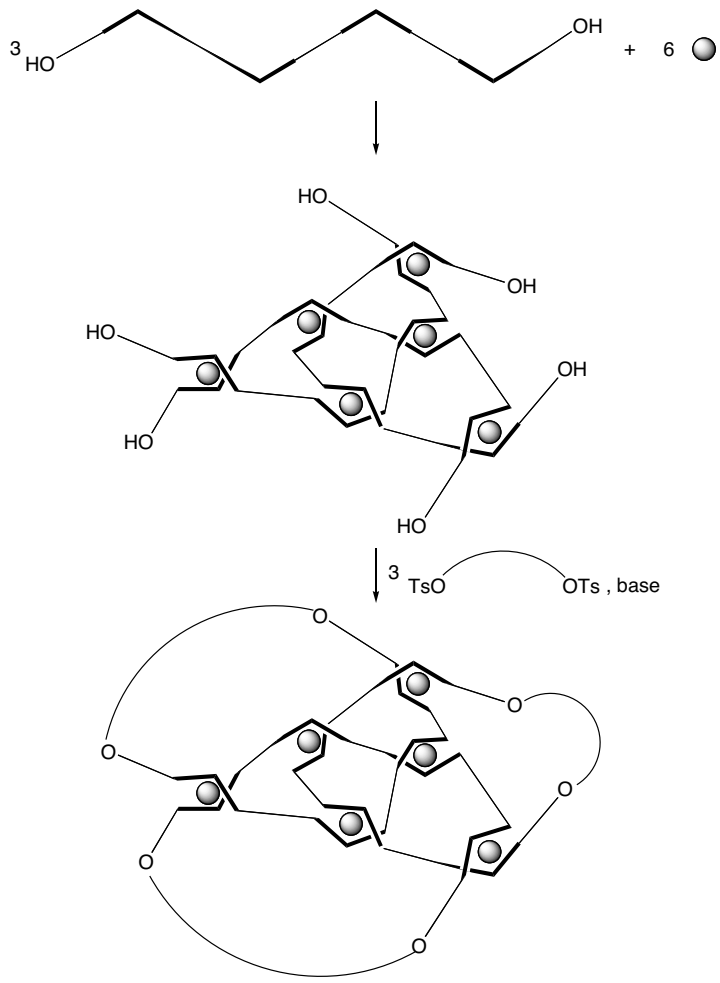
The enantiomers at the top have a C_3 rotation axis, while the two at the bottom have no symmetry. Interconversion of enantiomers requires rotation of all three aryls groups, switching the helicity from *M* (at left) to *P* (at right). None of the rings need rotate through the BC_3 plane, so the racemization is expected to be fast. Interconversion of diastereomers requires rotation of either one or two aryl groups through the plane, and this might be slower due to steric hindrance. For either interconversion, steric crowding can be best avoided through coupled rotations. For racemization, the three rings best avoid each other by rotating at the same time. For interconversion of diastereomers, two rings can best allow the third to rotate through the plane by rotating to become perpendicular to the plane.

38. Since there are no stereoisomers of phenylacetylene, the reaction cannot be stereospecific.

39. We can make use of the synthetic strategy illustrated in Figure 4.15 to make catenanes by coordination of phenanthroline ligands to preorganize the units before cyclization. To make the highly interwoven Borromean rings we have a big organizational job to do, but in principle, each crossing can be accomplished by a separate coordination. Drawing the very large molecules required will be much easier if we use a schematic notation:



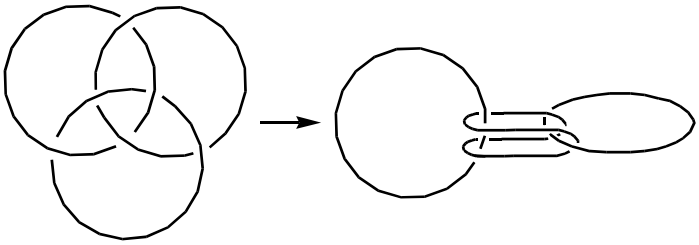
Each ring needs to make four crossings, so we need chains with four ligand units. We need not specify the details of the linking pieces.



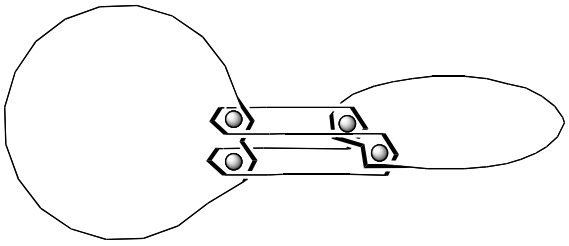
Removal of the metal atoms from the structure above will provide a Borromean ring structure.

It is probably wishful thinking to expect that the complexation of tetraligand units will actually provide the desired trimer shown unless we expend considerable effort in designing linkers that will promote this structure over the myriad of other possibilities. Such a design, to be successful, would likely require computational modeling to analyze the energy changes that come with various complexation options. The goal would be to find linkers that would give the desired supramolecular structure by thermodynamic control.

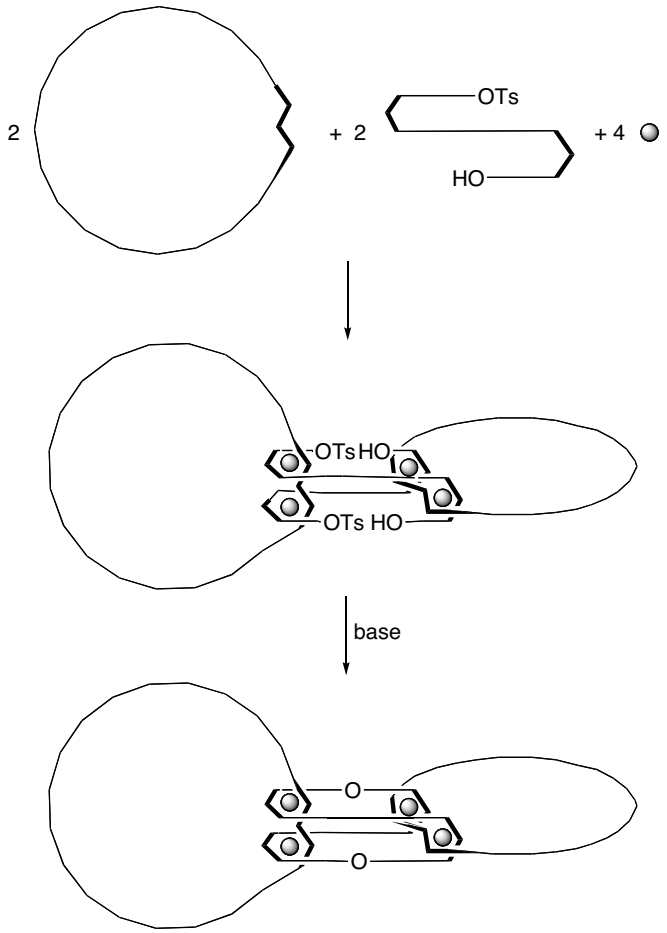
To illustrate that the strategy above is not the only one possible, we will present one alternative. Remember that topology is completely insensitive to any operations that do not break bonds — we can stretch or fold the desired ring structure any way we want. Let's pursue the strategy of making two of the rings simple and flat, leaving all the contortions for the third ring. Since no two rings are linked to each other, we can take two and pull them apart, letting the third ring stretch. The resulting structure is shown below. (It can be challenging to visualize what happens as we do this. A simple way to work it out is with a physical model, such as two key rings and a loop of string.)



Applying the same synthetic strategy, our target structure becomes



It's interesting (and fortunate) to note that this strategy requires only eight phenanthroline units and four metal atoms. A synthetic sequence to this target can make use of preformed rings:



Though this strategy may also suffer from other possible complexes and linkages, it appears to be simpler than the previous strategy. The number of possibilities (and therefore, the reduction in entropy) is greatly decreased. If our linker in the TsO-linker-OH component is rigid and gives the component a 90˚ twist, the desired product might be preferred over alternatives. Removal of the metal atoms would give a Borromean ring structure.

The successful synthesis of a Borromean ring structure by Stoddart and coworkers used a strategy similar in some ways to the first one described above but aimed at the orthogonal geometry shown below. These researchers describe the thermodynamically driven, one-pot assembly of 18 components (12 organic components of two types plus 6 zinc ions) in essentially quantitative yield! Also worth noting is the prior construction of DNA-based Borromean rings by Seeman and coworkers (C. Mao, W. Sun, and N. C. Seeman, *Nature* **1997**, *386*, 137).