

Chapter 6. Ouellette, 2/e. Chemistry X402.

Ch 6. Stereochemistry.

Skip: none; we will cover the entire chapter.

Essays: The essay on p 186 is required reading for dog lovers. Otherwise, the essays are not assigned, but I think you will find them interesting biology.

Notes

Although we will cover the entire chapter, there are a couple of very clear top priority issues here. One is how to recognize chirality in organic compounds, and the second is to appreciate why it is important in biochemistry.

Recall that Sect 1.11 introduced the general topic of isomers, and we discussed some types in Ch 3-4. Here we introduce a new type of isomerism.

Models are very helpful in dealing with chirality. Even simple models made with grapes and toothpicks can help. You can also use RasMol. If you have a set of models, please bring them to class. Also, please bring a mirror.

The terminology of chirality can be confusing; be sure to distinguish your understanding of the phenomenon from your fluency with the terminology or your ability to visualize the structures. You should be able to demonstrate the phenomenon using models, and then with drawings on paper.

Epimer. An additional useful term with chiral compounds is epimer. Epimers are isomers that differ only in the configuration at one stereocenter. It's very useful with sugars; in fact, Ouellette introduces it in Ch 11, p 302. Example: Mannose is the 2-epimer of glucose; Table 11.1. That is, mannose and glucose differ only in their configuration at the 2-position. (An epimerase is an enzyme that changes the configuration at a particular position.)

Properties of enantiomers. Enantiomers (mirror image isomers) are absolutely identical in all properties, physical and chemical, except two:

- they have opposite directions of optical rotation (easily measured; Sect 3), and
- chiral molecules can distinguish other chiral molecules (which is behind Sect 8).

The latter issue of chemistry is especially important in biochemistry, because most of the major chemicals of life are chiral. This includes the enzymes, which catalyze most biological reactions.

Multiple stereocenters. If you find the opening paragraph of Sect 6 difficult, here is an alternative approach. Start with a simple view... If there are N stereocenters, then there should be 2^N stereoisomers. This should be "logical"; it helps to reinforce it with some examples. The catch is that sometimes two of the isomers you might draw on paper turn out to be identical, because of an overall symmetry in the molecule. This is the situation he calls "equivalent

stereocenters.” When this happens, the resulting isomer is called “meso”. Ouellette starts by distinguishing the two cases, equivalent vs non-equivalent stereocenters. But equivalent stereocenters are not very common (especially in biochemistry), so it is reasonable to start with the more common case, which is simpler, then treat equivalent stereocenters and meso isomers as a special case.

Describing chiral compounds. It is useful to think about three ways to describe (“name” -- though perhaps loosely) chiral compounds.

- The **R,S system** is rigorous IUPAC; it always works. I do expect you to learn the priority rules (recall the E,Z system, Ch 4), and to be able to figure out R and S. In this system, each stereocenter is described as R or S. Sect 5.
- The **+,- system** identifies two enantiomers based on a simple measurement of a physical property, the direction of rotation of polarized light. (In older literature, this is sometimes called d,l; p 177.) Sect 3.
- The **D,L system** is based on the appearance of the structural formula, drawn according to a special convention called a Fischer projection. Sect 4. Fischer projections and D,L nomenclature are common in biochemistry.

In Fischer projections the 3D geometry is implied; the groups to the sides are up (Fig 6.6). It is helpful to draw Fischer projections so that mirror image structures switch left and right substituents. (Remember that ordinary structural formulas do not convey 3D information.)

Important... There is no relationship between any of these naming systems. They are based on independent considerations.

Reactions. Sect 7-8 discuss reactions that make or use chiral compounds. There is one key principle... chiral objects recognize other chiral objects. This principle is important in biochemistry, since the catalysts (enzymes) are chiral. Fig 6.11 shows the idea. Note that Sect 7 introduces the term racemic mixture (or racemate), an equal mixture of two enantiomers. Otherwise, you are not responsible for any details from these two sections. Some of the articles listed below under Further Reading deal with issues of chiral synthesis.

Suggested problems

All the problems seem good, and relevant. 1-8 and 25-36 deal with the “top priority issues” noted above. Most of the rest are practice with the R,S system. This is “very important” if you are going on, moderately important if not. I suggest that you check yourself on each one as you go, and if you get bogged down check with me. If stuck, you need to distinguish whether you are confused by the rules, or merely having trouble visualizing the 3D structure. If necessary, use models, but then try to wean yourself from dependence on them.

Errata

p 183, Problem 6.2. Answer given is incorrect: the priority order of the middle two groups is reversed.

p 194, # 21-22. It should be “obvious” to you looking at these two questions that there is an error. What is it that is obviously suspect? E-mail/show me your discovery. (From reading the questions alone, you do not have enough info to figure out what is correct, merely to find that something must be wrong. If you are careful, you can sort this out from the chapter, but that is not important. Discovering the error does not substantively affect answering the questions.)

Further reading

G T Yee, Through the looking glass and what Alice ate there. *J Chem Educ* 79:569, 5/02. All the food there was presumably of the opposite handedness. What could she eat? Interesting reading; maybe worth reading after some of the more biochemical chapters. (Alice herself does note, “Perhaps looking-glass milk isn’t good to drink.”)

C Saxon et al, The world’s first “pastarimeter”: An analogous demonstration of polarimetry using pasta fusilli. *J Chem Educ* 79:1214, 10/02. A polarimeter (p 176) measures the rotation of light as it passes through a collection of right- or left-handed molecules. A pastarimeter measures the rotation of a stream of water as it passes through a collection of right- or left-handed pasta.

I Agranat et al, Putting chirality to work: the strategy of chiral switches. *Nature Reviews Drug Discovery* 1:753, 10/02. Review. The pharmaceutical industry has become increasingly aware of the desirability of producing enantiomerically pure drugs. The term “chiral switch” in the title refers to the switch from marketing a racemic drug to a pure enantiomer. Ibuprofen and Prilosec are examples that they discuss. They emphasize that each case must be considered on its own merits. For example, thalidomide is not a candidate for a chiral switch (even if one enantiomer is more toxic, as some evidence suggests), because the two enantiomers are readily interconverted within the body. (See Ito et al, 2010, below, for more about thalidomide.) The review starts with some simple discussion of chirality, and much of the article is on proprietary issues.

R Raval, Chemistry: Mirrors in flatland. *Nature* 425:463, 10/2/03. News. Common solid-phase catalysts are not chiral. This news item discusses how to make their surfaces chiral. For example, one can adsorb one enantiomer of a chiral compound to the surface; in favorable cases, it adsorbs in a regular pattern and the surface becomes chiral. This can even be observed by atomic force microscopy; for more on this observation method, see my web page for X11 Internet Resources. Also see Inoue (2005) and Diver (2008).

1) R E Gawley, Chirality made simple: a 1- and 2-dimensional introduction to stereochemistry. 2) P Lloyd-Williams & E Giralt, Stereogenic centers and axes: A comparison of the chiral topologies available to Cabcd and abC=C=C=cd. *J Chem Educ* 82:1009 & 1031, 7/05. #1 introduces the ideas of chirality using simpler examples. #2 introduces an interesting special case that does not involve our common “C with four different things attached”.

Y Inoue, Synthetic chemistry: Light on chirality. *Nature* 436:1099, 8/25/05. News. "Reactions that produce only one of two mirror-image forms of a molecule are a hot topic in organic synthesis. A light-driven catalyst provides good results, and the technique could be generally applicable." Also see Raval (2003) and Diver (2008).

R F Oliveira et al, Behavioural endocrinology: No hormonal response in tied fights. *Nature* 437:207, 9/8/05. The (male) fish studied here will attack their mirror image. However, their androgen levels do not increase in these encounters. It seems that the hormone response only occurs when the fish judges that it can win. One thing this work does is to separate the basic aggressive behavior from the hormone response. See Prior et al (2008) for a different type of response to a mirror.

D R Greenwood et al, Chemical communication: Chirality in elephant pheromones. *Nature* 438:1097, 12/22/05. They show that male elephants make both enantiomers of a pheromone, but in a ratio that varies with age. The enantiomer ratio seems to be a part of the signal.

M Hosoi et al, Right-handed snakes: convergent evolution of asymmetry for functional specialization. *Biol Lett* 3:169-172, 4/22/07. It is well known that most snails are coiled "right handed". Here, Hosoi et al show that some snakes specializing in eating snails have an asymmetric feeding apparatus ("mouth") that works best on right-handed snails.

E G Stephanou, Atmospheric chemistry: A forest air of chirality. *Nature* 446:991, 4/26/07. News. In the Ch 4 FR we introduced that plants emit isoprene derivatives known as terpenes. In the work reported here, they show that different enantiomers of some terpenes are produced by tropical and boreal (Northern) forests. They discuss both the reasons for and implications of the difference. Both light and temperature probably influence the product. It may well be that different parts of the same plant make different terpene enantiomers. Differences in terpene emissions have implications for the biology of the area; it is not clear that there is any implication for atmospheric chemistry.

H Prior et al, Mirror-induced behavior in the magpie (*Pica pica*): Evidence of self-recognition. *PLoS Biol* 6(8):e202, 8/08. The ability to recognize oneself in a mirror is a trait sometimes considered characteristic of only humans and apes. Over recent years, evidence accumulated that elephants and dolphins, too, show this aspect of self-recognition. Here is evidence that some birds recognize themselves in the mirror. Very readable paper, with interesting methodology. Contrast the magpie behavior here with the fish in Oliveira et al (2005). The paper is freely available online: OA: <http://www.plosbiology.org/article/info:doi/10.1371/journal.pbio.0060202>. A live link to the article is on the course web page of Internet Resources.

S T Diver, Organometallic chemistry: Catalyst takes control to heart. *Nature* 456:883, 12/18/08. News. Synthesizing a specific stereoisomer can be challenging. In the work discussed here, the chirality is imparted by a chiral Mo atom in the catalyst. Such asymmetric reactions occur in biology, too; the biological catalysts -- enzymes -- are chiral.

G Horváth et al, Polarized light pollution: a new kind of ecological photopollution. *Front Ecol Environ* 7(6):317-325, 8/09. Light reflected off surfaces is polarized. In fact, it seems that

many insects that land on water detect the polarization as the key to finding the water surface. In this review, they show that animals, including such insects and some birds, can be distracted by polarized light from manmade reflective structures. They refer to this as polarized light pollution. Whether it is a problem that should concern us may be open, but it is an interesting story, about light, engineering, and biology.

M M Green & V Jain, Homochirality in Life: Two Equal Runners, One Tripped. *Orig Life Evol Biosph* 40:111-118, 2/10. We understand that biological systems use one stereoisomer of a chiral compound; we call the phenomenon homochirality. The reason for the original choice is not understood. This article is part of a feature issue on the topic, and is something of an overview.

T Ito et al, Identification of a primary target of thalidomide teratogenicity. *Science* 327:1345, 3/12/10. Thalidomide is a classic example of the importance of having the correct enantiomer. It is likely that one enantiomer of this drug has the beneficial effects and the other enantiomer has the harmful effects. Unfortunately, the body probably interconverts the enantiomers sufficiently rapidly that this information is not clinically useful. However, thalidomide has made a comeback as a drug. Perhaps most importantly, research is developing derivatives of the original drug, with the goal of enhancing the usefulness. This article uncovers one key piece of information: the target of thalidomide action that leads to birth defects. Also see Agranat et al (2002).

Computer resources (See web page for details and links.)

Practice problems on stereochemistry (Dr Phil Bays). The structures are clear, and the questions appropriate. Instant feedback. (Also recommended for Ch 3, cycloalkanes.)

The 2001 Nobel prize in Chemistry was awarded for work in developing practical methods for making the correct stereoisomer of drugs, that is for doing chiral synthesis. Also see FR above, such as Diver (2008).

Everything has a mirror image? Even Google? (The story is that this was introduced as an attempt to circumvent censorship of search engines in certain countries. It worked.)

Ch 6 introduces the R,S system for naming chiral isomers. As noted, The E,Z system is a rigorous IUPAC system for naming alkene isomers, using the same general approach -- and same priority rules. See my E,Z system web page. (This was mentioned earlier, for Ch 4.)

You may also want to look at some stereoisomers of chiral compounds in RasMol. See my RasMol page.