Resources for Student Assessment

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Through the Looking Glass and What Alice Ate There

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"How would you like to live in Looking-glass House, Kitty? I wonder if they'd give you milk, there? Perhaps Looking-glass milk isn't good to drink…"

Lewis Carroll

In a traditional discussion of optical isomerism at the general chemistry level, one typically notes that most biologically important molecules are chiral and points out that this means that they are therefore not superimposable on their mirror images. While one can explain the concept of and conditions necessary for optical activity in molecules and demonstrate the rotation of plane-polarized light by a glucose solution (*1*), the discussion tends to lack context. Even the relationship between the left hand and the right can be confusing, and demonstrating the relevance of this idea to molecules can be quite challenging. A recent article by Luján-Upton addresses this topic in the form of a mystery to be solved (*2*).

As another strategy for engaging the students in this topic and for relating it to the caloric value of food and the identity of organic functional groups, I have asked my students to consider the following open-ended test question. It was offered to them several days ahead of the test to allow them to think about it and with only the restriction that they could not ask me for the answer(s).[1]

In the book *Through the Looking Glass and What Alice Found There* by Lewis Carroll (*3*), Alice (of *Alice in Wonderland* fame) walks through a mirror into a mirror-image world. Assuming that she is not changed by this transition, her enzymes are still only capable of processing molecules of the handedness of her native world. In short, she has a problem that will severely curtail the duration of her stay because when she gets hungry she can eat, but her body cannot make use of most of the calorie-containing molecules such as L-glucose that exist naturally in the mirror image world. Her enzymes are designed for digesting its enantiomer, D-glucose. So the question is, what can Alice eat in the mirror-image world that provides nutritional value to her?

If this problem were posed to a high-level biochemistry class, the students might consider looking for those digestive enzymes that are sufficiently nondiscriminating to permit the metabolism of nonnative substrates. However, there is a much more clever answer that younger (general or organic chemistry) students could easily comprehend. As further explanation into the nature of the question and answer (without giving it away), one can point out that a compound absolutely necessary for her survival, water, is the same in both worlds. Water is an example of an achiral molecule; it is superimposable on its mirror image. Other necessary compounds such as sodium chloride and dioxygen are also achiral and readily used by her body.

One attractive aspect of this problem is that it draws on several other concepts presented in general chemistry. The caloric value of foods is usually described in the context of thermochemistry and the three major food components, carbohydrates, proteins, and fats (macronutrients [*4*]), which are discussed along with their respective calorie content. Most textbooks include some elementary biochemistry where the 20 amino acids are presented as the building blocks of proteins. Similarly, the structures of sugars and fats are given, along with a discussion of their organic functional groups. In the lab portion of my particular course, stearic acid (the saturated C_{18} fatty acid) was used for the experimental determination of Avogadro's number (*5*), so the students had additional familiarity with the concept of a fatty acid.

It is easy to show with models that of these three components, carbohydrates, typified by glucose (and its polymer, starch) and all but one amino acid, hence essentially all proteins, are not superimposable on their mirror images and are thus not of nutritional value to Alice. However, some fats are achiral, hence useful to Alice because they are exactly the same molecule in both worlds. These would be symmetrically substituted esters of glycerin (triacylglycerols) that possess an internal mirror plane (i.e., the fatty acids attached to carbons 1 and 3 of the glycerin molecule are the same). Obviously, this classification includes all those that have three identical fatty acid groups (simple triacylglycerols), such as tristearin, which has three stearate chains.

As an aside, a general triacylglycerol without a mirror plane, such as one prepared from three different fatty acids, is chiral, so its enantiomer in the mirror image world would, in principle, not be of use to Alice. This is simple to demonstrate with a model set. However, many of these enantiomeric pairs are not necessarily so different chemically from each other. A given compound can be related to its mirror image by the exchange of fatty acids on carbons 1 and 3 (Fig. 1), which might be structurally similar (e.g. stearate and palmitate, both saturated hydrocarbon tails of length 18 and 16 carbons, respectively).

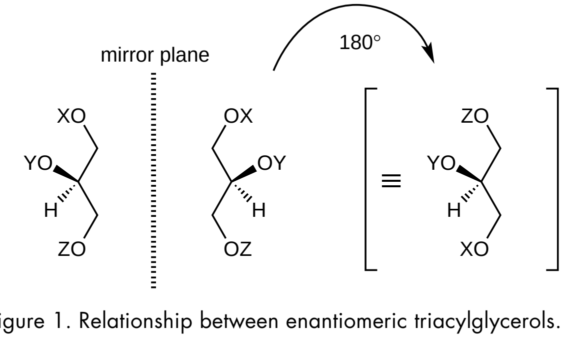

Figure 1. Relationship between enantiomeric triacylglycerols.

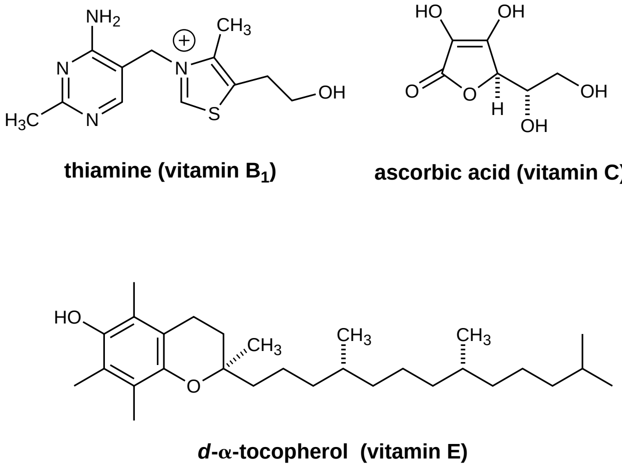

Figure 2. An example of an achiral and two chiral vitamins

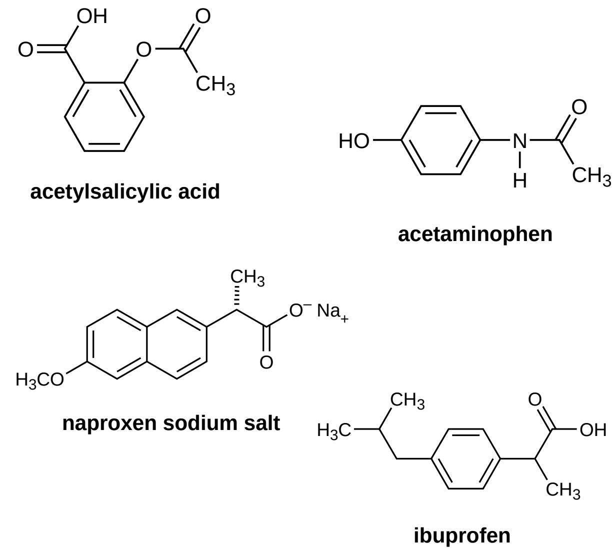

Figure 3. Common pain relievers.

One might even suppose that some concentration of each enantiomer exists in both worlds. But more importantly, one can infer that some of the enzymes responsible for ester hydrolysis in fats are sufficiently flexible to tolerate both substrates, which would make them both nutritionally valuable (*6*). Note that the glycerin molecule and each of the free fatty acids are individually achiral, so that after hydrolysis, stereochemistry is no longer an issue.

Several other solutions to the problem were accepted, including the achiral amino acid, glycine, and the most unequivocal and clever answer, ethanol. Consumption of the latter is, of course, a natural topic for college students but a particularly humorous answer considering that Alice is a young child. Vodka is a relatively unadulterated aqueous solution of ethanol, which might be an important consideration; other chiral compounds present of the wrong stereochemistry, such as flavorings and colorings, might happen to be toxic. A metabolic product of ethanol, acetic acid (vinegar), is also a correct answer. Finally, she could also eat other naturally occurring achiral compounds that we don't ordinarily think of as food per se, but which have caloric value—such as citric acid or glycerin, mentioned before.

To elaborate on this exercise, one could consider biochemical extensions of this question to vitamins that Alice might require. For instance, of those she needs, her own body synthesizes vitamin D, whereas β-carotene (a source of vitamin A) is achiral, as is thiamine (vitamin B_1, Fig. 2). However, ascorbic acid (vitamin C, Fig. 2) is chiral and there would presumably be no source of the enantiomer that she needs in the mirror-image world. Interestingly, whereas only a single stereoisomer of α-tocopherol (*d*-α-tocopherol) occurs naturally in our world (a form of vitamin E, Fig. 2), research with synthetic α-tocopherol, a mixture of all eight possible stereoisomers,[2] has shown that the enantiomer of the naturally occurring molecule is also somewhat efficacious (*7*). So Alice should be able to tolerate mirror-image vitamin E. This is, perhaps, not surprising because the antioxidant ability of vitamin E is associated with the bicyclic system, not the alkyl tail.

If Alice came down with a headache, acetylsalicylic acid (aspirin) and acetaminophen (Tylenol) are both achiral and hence useful, but naproxen sodium salt (Aleve) is chiral (and the other enantiomer, which would have been the one marketed in the mirror world, is reported to be a liver toxin [*8*]). Conveniently, ibuprofen (Advil or Motrin) is also chiral but is sold as a racemate (an equal mixture of the two enantiomers), so it would be an equally effective pain reliever for Alice in both worlds (Fig. 3) (*9*).

Fortunately for Alice, if she's addicted to her morning coffee, caffeine is achiral; but if it's cigarettes she's hooked on, she's in trouble because nicotine is chiral. In a fascinating twist, because the two enantiomers of carvone and limonene both exist in both worlds and are responsible for distinct flavors, smells (and perhaps tastes) will be inverted. To Alice in the mirror-image world, a caraway seed bagel will taste like spearmint and a stick of spearmint gum will taste like caraway (Fig. 4). Similarly, lemons will smell like oranges and oranges like lemons (*10*).

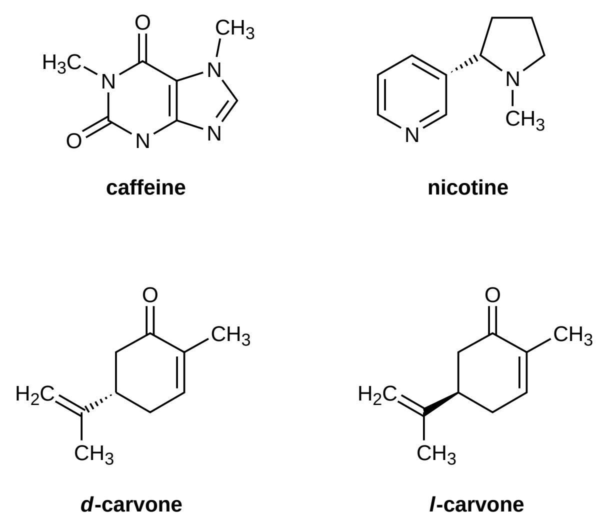

Figure 4. Other common chiral and achiral bioactive molecules.

Acknowledgments

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Notes

1. This question could also be used as a topic for class discussion.

2. Note that the molecule has three stereocenters, each of which can have two possible absolute configurations: $2^3 = 8$. Natural *d*-α-tocopherol has RRR absolute configuration.

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10. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 202; (*R*)-(+)-limonene smells like oranges, (*S*)-(–)-limonene smells like lemons.