Stereochemistry in a New Light

The unusual properties of the carbon atom have created much confusion in stereochemistry; a noted chemist tries to sort them out

Kurt Mislow would like to change the way chemists and biologists perceive stereochemistry. The Princeton University chemist thinks that at least part of the reason why many scientists have difficulty with stereoisomerism is that much of the nomenclature is imprecise, combining concepts that should be kept separate. In a new paper, Mislow and graduate student Jay Siegel attempt to clarify this nomenclature and to convey to others a new way to look at the problem.

Mislow has already been credited with bringing considerable order to the field of stereochemistry. He has, says Harry Mosher of Stanford University, "a deeper insight into stereochemistry than almost anyone else in the world." In his recent paper in the *Journal of the American Chemical Society,** adds Mosher, "he has put into words concepts that some experts have known intuitively for a long time, but haven't been able to verbalize as well."

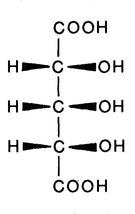
The development of stereochemistry has been based on the concept of the asymmetric or chiral carbon atom. That concept has provided a strong foundation for mainline organic chemistry, but it has been a source of confusion for certain types of organic chemicals and for many other compounds. Both the successes and the problems have arisen, says Mislow, because two separate and distinct properties have often been lumped together in the single property of chirality. Those properties are local geometry (symmetry) and stereoisomerism, which are often, but not always, linked. Because they are not always linked, ambiguities have arisen in the description of the stereochemical status of a molecule and the potential for changing that status.

The ambiguities derive from what Mislow terms "a remarkable coincidence." First, the building block of organic chemistry, the tetravalent carbon atom, can be represented as a tetrahedral bonding center. When four different substituents are attached to the carbon atom, it resides in a chiral environment. The Princeton chemists use the term chirotopicity to refer to this local geometry. Atoms that reside in a chiral environment are said to be chirotopic, while those that reside in an achiral environment are achirotopic. In the simple example of $CHBrClF$, for instance, all atoms and the spaces between them are chirotopic because the entire molecule is chiral. Chirotopicity is a general property of geometric objects.

Second, the regular tetrahedron is the only geometric skeleton in which every transposition of bonded atoms reverses the sense of chirality of the molecule. In a chiral molecule, therefore, transposition of two bonded atoms produces a new stereoisomer. Mislow and Siegel call this characteristic stereogenicity; any atom that displays it is termed stereogenic or a stereocenter. In that same $CHBrClF$ molecule, only the carbon atom is stereogenic. Stereogenicity, in contrast to chirotopicity, is closely associated with bonds and atoms.

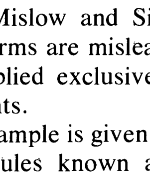
In most cases, when a tetrahedral bonding center is appropriately substituted with four different substituents, chirotopicity and stereogenicity are uniquely linked. The carbon atom in $CHBrClF$, for instance, is both chirotopic and stereogenic, while that in CH_2BrCl is achirotopic and nonstereogenic. "It is this coincidence that accounts for the enormous practical success of the concept of the 'asymmetric carbon atom,' " Mislow says. Unfortunately, he adds, the latter concept has often broken down when it is extended to organic chemicals with unusual characteristics and to organometallic complexes and inorganic chemicals. "Our system, in contrast, can be applied to any chemical compound," he adds.

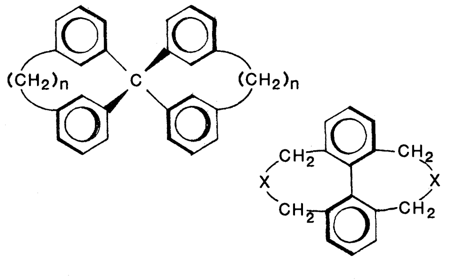
One of those unusual organic compounds is 2,3,4-trihydroxyglutaric acid (THGA). The central carbon atom (C-3) of one achiral diastereomer of THGA, for example, is attached to four substituents that differ in structure; it is thus, by definition, asymmetric. But there is also a plane of symmetry that passes through C-3. "The designation of C-3 as 'asymmetric' therefore seems to be inappropriate, if not actually contradictory," says Mislow. Some theorists have attempted to get around this problem by calling C-3 "pseudoasymmetric," but that term, he argues, "lacks any meaningful reference to symmetry and geometry."



But with the new nomenclature, the problem is resolved. The C-3 carbon of the achiral THGA is achirotopic because it has a plane of symmetry, but it is stereogenic because a transposition of two substituents produces a stereoisomer. The C-3 carbon of a chiral diastereomer of THGA, in contrast, is chirotopic because there is no plane of symmetry, but nonstereogenic because transposition of two substituents does not produce a stereoisomer.

Separating the concepts of local geometry and stereoisomerism becomes particularly important when chirality is not associated with a single atom. In their original 1956 paper on the specification of asymmetric configurations,† R. S. Cahn, C. K. Ingold, and V. Prelog stated that, in principle, three-dimensional space can be occupied asymmetrically around a point, a line, or a plane. This notion was embodied in their system by the terms "center of chirality," "axis of chirality," and "plane of chirality"—collectively referred to as "elements of chirality." Mislow and Siegel contend that these terms are misleading because they are applied exclusively to stereogenic elements.





A good example is given by two classes of molecules known as vespirenes (left, n = 6–8) and doubly bridged biphenyls (right, X = O, S, CO, or CH_2). The center of symmetry coincides with

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*J. Am. Chem. Soc. **106**, 3319 (1984).

†*Experientia* **12**, 81 (1956).

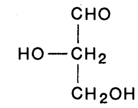
the central carbon atom in the vespirenes and with the center of the biphenyl bond in the doubly bridged biphenyls. Under the Cahn-Ingold-Prelog rules, the vespirenes are said to have a "center of chirality," but the doubly bridged biphenyls are said to have an "axis of chirality."

According to the Cahn-Ingold-Prelog conventions, however, a "center of chirality" does not necessarily have to coincide with an atomic center. The fact that investigators ignore this possibility and refer to an "axis of chirality" in the biphenyls, Mislow says, makes it clear that this term is being used exclusively to describe stereogenicity rather than local geometry. The revised nomenclature makes the distinction clear: the centers in both types of molecules are chirotopic, but only the vespirenes possess a stereocenter.

"It cannot be emphasized too strongly that the purely stereogenic character of 'elements of chirality' in a molecule must not be confused with the chirality properties of that molecule," Mislow adds. For example, a stereospecific rearrangement of a chiral molecule with a single stereocenter M to a chiral product with a single stereocenter N is commonly referred to as a "transfer of chirality from M to N." In fact, however, what is transferred in the process are stereocenters (M→N); chirality is retained throughout, not transferred. "It is equally misleading to speak of a molecule as being 'chiral (or optically active) at M' where the intent is to express M's property as a stereocenter in a chiral molecule," Mislow concludes. "Neither chirotopicity nor optical activity are *exclusively* attributable to individual atoms in a molecule."

The confusion of stereogenicity with local geometry has also been a problem with the related subject of prochirality. Prochirality has been conventionally defined as the capability of an achiral molecule to become chiral if one substituent is replaced by a new one. The carbon atom in CH_2BrCl is said to be "prochiral," for example, because replacement of one of the hydrogens with, say, fluorine produces a "chiral center" in CHBrClF. There is great interest today in prochirality because of the increasing importance of chiral natural products and related chemicals in chemistry and medicine and the need to synthesize chiral molecules from achiral substrates.

Ambiguity has arisen, Mislow and Siegel argue, because the term prochiral, like the term chiral, should have purely geometric connotations, yet by definition applies to the generation of a stereocenter—an operation for which the term prostereogenic would be more appropriate. An example of this ambiguity is provided by glyceraldehyde, in which

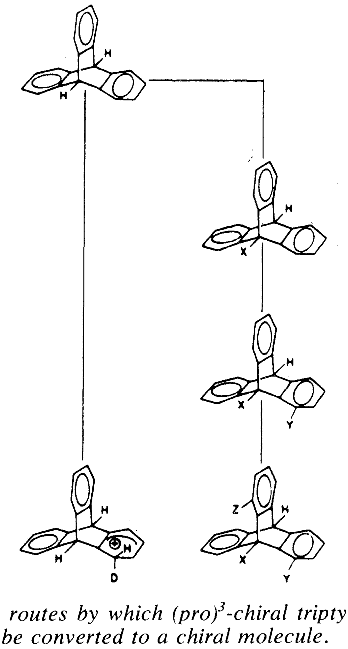


$$\begin{array}{c} \text{CHO} \\ | \\ \text{HO—CH}_2 \\ | \\ \text{CH}_2\text{OH} \end{array}$$

C-3 has been labeled prochiral because replacement of one of the hydrogen atoms at that carbon atom creates a stereocenter. But C-3 is chirotopic, and prochirality is explicitly defined as a property of an achiral assembly. This paradox is avoided, Mislow says, if C-3 is termed prostereogenic rather than prochiral. By making this distinction, chirotopicity and stereogenicity are again separated and there is no ambiguity.

In order to provide a purely geometric basis for the concept of prochirality, Mislow and Siegel have deduced three classes of achirality: $(\text{pro})^3$-chiral objects, which require three steps to become chiral, $(\text{pro})^2$-chiral objects, which require two, and $(\text{pro})^1$-chiral objects, which require one. Mislow illustrates this principle by reference to a series of three-dimensional objects. A sphere, for example, is $(\text{pro})^3$-chiral because it takes three steps to change it to a chiral object. First, it can be stretched into a cone, which is $(\text{pro})^2$-chiral. The cone can be bent into a horn, which is $(\text{pro})^1$-chiral. Finally, the horn can be twisted into a screw, which is chiral.

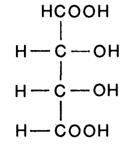
To illustrate this chemically, Mislow and Siegel use triptycene. "We chose it because it is a very rich molecule in this respect. It contains many symmetry elements and you can play all sorts of games." Triptycene is $(\text{pro})^3$-chiral because there exists a point in the molecule, the center of mass, which is equivalent to the center of a sphere. There are three planes of symmetry that go through the three benzene rings and a fourth at right angles to the three.



Two routes by which $(\text{pro})^3$-chiral triptycene can be converted to a chiral molecule.

If a substitution is made at one of the bridgehead carbons to give, for example, 9-chlorotriptycene, one plane of symmetry is destroyed and the molecule becomes $(\text{pro})^2$-chiral. If another halide is substituted for a hydrogen on one of the benzene rings, the molecule becomes $(\text{pro})^1$-chiral. And if a third halide is substituted on another ring, the molecule becomes chiral. "But the beauty of the scheme," Mislow says, "is that one or more of these steps can be short-circuited. If a metal atom is coordinated with one of the benzene rings or if a ring hydrogen is replaced by a halide, the molecule becomes $(\text{pro})^1$-chiral in one step. Or, if one of the ring hydrogens is attacked by deuterium to give a carbocation, then the molecule becomes chiral directly with no intermediate steps.

Freeing the concept of prochirality from its links to stereoisomerism actually broadens its applicability. *meso*-Tartaric acid, for example, is achiral, but it



$$\begin{array}{c} \text{HCOOH} \\ | \\ \text{H—C—OH} \\ | \\ \text{H—C—OH} \\ | \\ \text{H—COOH} \end{array}$$

would not normally be thought of as prochiral because there are no prostereogenic carbon atoms. But esterification of one of the carboxyl groups makes the molecule chiral. "We would have no hesitation about labeling this a $(\text{pro})^1$-chiral molecule," says Mislow. In general, he adds, "I think people will now feel more free to talk about prochiral molecules, and they will be more hesitant to talk about prochiral centers."

Mislow and Siegel's paper has created a great deal of interest among stereochemists. The chief criticism was perhaps best voiced by Ned Arnett of Duke University: "I thought it was so subtle and complicated that people would not spend much time studying it." Replies Mislow: "If it weren't subtle, it would have been pointed out a long time ago."

In general, however, the reactions have been favorable. "I may be somewhat prejudiced because I have published with Kurt, but I think it is a very important paper," says Frank Anet of the University of California, Los Angeles. "We're going to need many other papers, however, to flesh out the concept. The full revolution won't take place for 10 years."

—Thomas H. Maugh II