14

Chirality in Molecules Devoid of Chiral Centers

14-1. INTRODUCTION. NOMENCLATURE

In Chapter 1 it was pointed out that a necessary and sufficient condition for a molecule to be chiral is that it not be superposable with its mirror image. The presence of a (single, configurationally stable) chiral center in the molecule (central chirality) is a sufficient condition for the existence of chirality but not a necessary one. In this chapter we shall turn our attention to chiral molecules devoid of chiral centers. We shall include some types of molecules (certain spiranes and metallocenes) in which, for nomenclatural purposes, a chiral center may be defined to exist (Cahn, Ingold, and Prelog, 1966) even though these molecules are closely akin to others in which no chiral centers can be discerned.

Classes of molecules to be discussed here (Eliel, 1962; Krow 1970) are allenes; cumulenes with even numbers of double bonds (cf. Chapter 9 for cumulenes with odd numbers of double bonds); alkylidenecycloalkanes; spiranes; the so-called atropisomers (biphenyls and similar compounds in which chirality is due to restricted rotation about a single bond); helicenes, propellerlike structures; and molecules, such as cyclophanes, chiral *trans*-cycloalkenes, ansa compounds, and arene–metal complexes including metallocenes, which are said (Cahn, Ingold, and Prelog, 1966) to contain a "plane of chirality." Also included is the phenomenon of cyclostereoisomerism, even though it does not strictly fit the condition set down in the first paragraph.

Allenes, alkylidenecycloalkanes, biphenyls, and so on, are said to possess a "chiral axis" (Cahn, Ingold, and Prelog, 1956). If we stretch a tetrahedron along its S_4 axis, it is desymmetrized to a framework of $\mathbf{D_{2d}}$ symmetry (Fig. 14.1). With proper substitution, the long axis of this framework constitutes the chiral axis. Because of the intrinsically lower symmetry of the framework shown in Figure 14.1 compared to a tetrahedron, it no longer takes four different substituents to make the framework chiral: A necessary and sufficient condition for chirality is that $a \neq b$ and $c \neq d$. Thus, even when $a = c$ and/or $b = d$, the framework retains chirality, for example, in abC=C=Cab (see below).

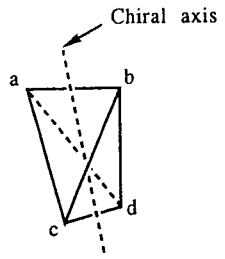
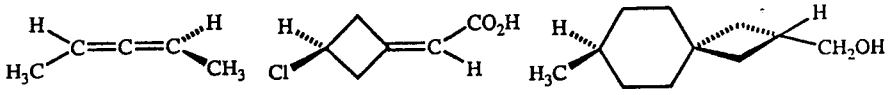


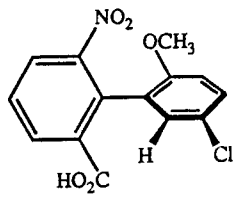
Figure 14.1. Chiral axis.

To specify the sense of chirality (i.e., configuration) of a molecule possessing a chiral axis (*axial chirality*, examples are shown in Fig. 14.2) an additional sequence rule is needed: Near groups precede far groups. The application of this rule to the molecules shown in Figure 14.2 is shown in Figure 14.3. In all cases the molecules in Figure 14.2 are viewed from the left. However, the reader should take note that the same configurational descriptor results when the molecules are viewed from the right, so no specification in this regard is needed. In the case of biphenyl it is important to note that the ring substituents are to be explored from the center on outward, regardless of the rule given above. Thus, in the biphenyl in Figure 14.2, in the right ring the sequence is C—OCH_3 > C—H; the chlorine atom is too far out to matter, a decision being made before it is reached in the outward exploration. The fiducial atoms (i.e. those that determine the configurational symbol, cf. p. 665) are the same when the molecule is viewed from the right. The descriptors a*R* and a*S* are sometimes used to distinguish axial chirality from other types, but the use of the a prefix is optional.

Molecules with chiral axes may alternatively be viewed as helices (in this respect they resemble the helicenes to be disussed below) and their configuration may be denoted as *P* or *M*, in a manner similar to that of conformational isomers (Chapter 10; Prelog and Helmchen, 1982). For this designation, only the ligands of highest priority in front and in the back of the framework are considered (ligands 1 and 3 in Figure 14.3). If the turn from the priority front ligand 1 to the priority rear ligand 3 is clockwise, the configuration is *P*, if counterclockwise it is



Allene Alkylidenecycloalkane Spirane



Biphenyl

Figure 14.2. Molecules with chiral axes.

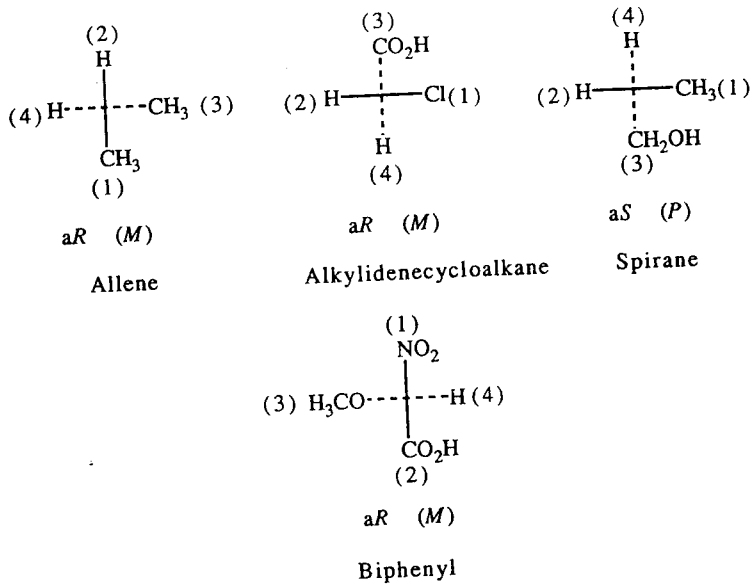


Figure 14.3. Descriptors for molecules with chiral axes.

M. Thus three of the four structures in Figures 14.2 and 14.3 are a*R* (chiral axis nomenclature) or *M* (helix nomenclature); the spirane is a*S* or *P*. (The correspondence of a*R* with *M* and a*S* with *P* is general.)

Figure 14.4 shows molecules with chiral planes. The definition of a chiral plane is less simple and clear-cut than that of a chiral center or axis. It is a plane that contains as many of the atoms of the molecule as possible, but not all; in fact,

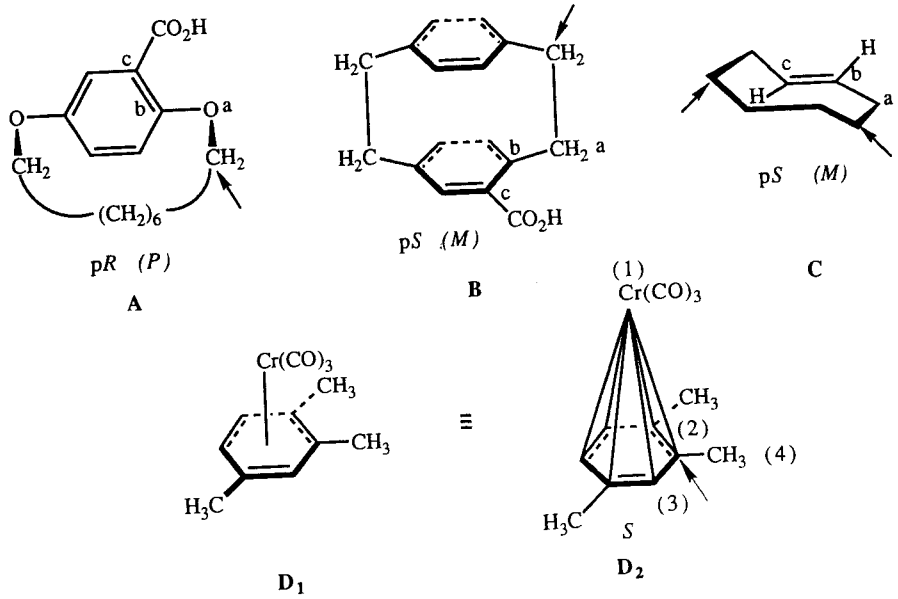


Figure 14.4. Molecules with chiral planes.

the chirality is due (and solely due) to the fact that at least one ligand (usually more) is *not* contained in the chiral plane. Thus the chiral plane of the "ansa compound" **A** (in which the alicyclic ring is too small for the aromatic one to swivel through) is the plane of the benzene ring; the same is formally true of the arenechromium tricarbonyl compound **D**; in the paracyclophane **B**, the more highly substituted benzene ring (bottom) is considered the chiral plane and in *trans*-cyclooctene **C** the chiral plane is that of the double bond. To find the descriptor for planar chiral moleules one views the chiral plane from the out-of-plane atom closest to the plane (if there are two or more candidates, one chooses the one closest to the atom of higher precedence according to the sequence rules, cf. Section 5-2). This atom, sometimes called the "pilot atom," is marked with an arrow in Figure 14.4 (for compound **C** there are two equivalent such atoms). Then, if the adjacent three atoms a, b, and c (again chosen by precedence if there is a choice) describe a clockwise array in the chiral plane, the configuration is p*R*, if the array is counterclockwise, the descriptor is p*S*. (The prefix "p" may be used to signal planar chirality.)

Compound **D**, although it would also appear to have a chiral plane, is conventionally treated as having chiral centers by replacing the η_6 π bond by six σ single bonds, as shown in structure $\mathbf{D}_2$. The (central) chirality is now determined for the atom of highest precedence (the ring carbon marked by an arrow) and the descriptor is thus found to be *S* (Cahn, Ingold, and Prelog, 1966; see also Schlögl, 1967; Klyne and Buckingham, 1978, Vol. 1, p. 222).

Planar chirality, like axial chirality, may alternatively be looked at as a type of helicity (Prelog and Helmchen, 1982). To determine the sense of the helix one uses the pilot atom plus atoms a, b, and c specified as above. It is then seen (Fig. 14.4) that p*R* compounds correspond to *P* and p*S* corresponds to *M*, opposite to the correlation in axial chirality (see above).

14-2. ALLENES

a. Historical. Natural Occurrence

It was already pointed out by van't Hoff (1875) that an appropriately substituted allene should exist in two enantiomeric forms. A simple case is shown in Figure 14.5, **A**; a necessary and sufficient condition for such an allene to be chiral is that $a \neq b$. The reason for the dissymmetry is that the groups a and b at one end of the system lie in a plane at right angles to those at the other end. If the doubly

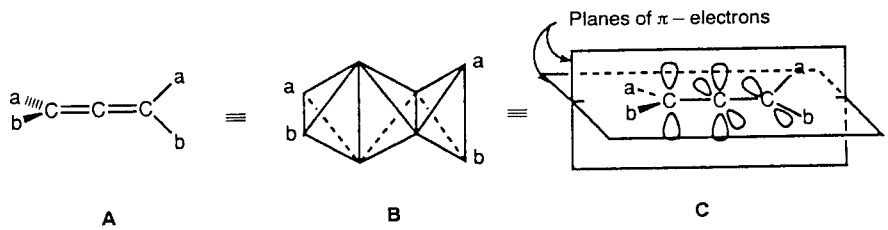


Figure 14.5. Dissymmetric allene.

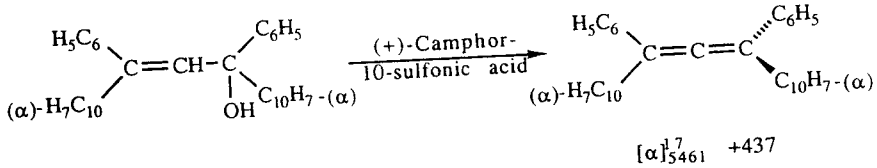


Figure 14.6. Asymmetric synthesis of optically active allene.

bonded carbon atoms are viewed as tetrahedra joined edge to edge, a view that was originally proposed by van't Hoff (see also Chapter 9), the noncoplanarity of the two sets of groups follows directly from the geometry of the system (Fig. 14.5, **B**). If, on the other hand, one views a double bond as being made up of pairs of σ and π electrons, orbital considerations indicate that the two planes of the π bonds attached to the central carbon atom must be orthogonal, and since the a and b groups attached to the trigonal carbon lie in a plane at right angles to the plane of the adjacent π bond, their planes are orthogonal to each other (Fig. 14.5, **C**).

The experimental realization of van't Hoff's prediction proved to be quite difficult, and 60 years elapsed before the first optically active allene was obtained in the laboratory (Maitland and Mills, 1935, 1936). The route chosen was one of asymmetric synthesis: Dehydration of 1,3-diphenyl-1,3-α-naphthyl-2-propen-1-ol with (+)-camphor-10-sulfonic acid gave (+)-1,3-diphenyl-1,3-di-α-naphthylallene (Fig. 14.6) in slight preponderance over its enantiomer [enantiomer excess (ee) ca. 5%]. Fortunately, the optically active allene forms a conglomerate (cf. Chapter 6) and the pure enantiomer could be separated from the racemate by fractional crystallization without excessive difficulty. The material has the high specific rotation $[\alpha]_{546}^{17} + 437$ (benzene), $[\alpha]_{D}^{20} + 351$ (cyclohexane). Use of (−)-camphor-10-sulfonic acid gave the enantiomer of $[\alpha]_{546}^{17} + 438$ (benzene). Shortly after this asymmetric synthesis was accomplished, the allenic acid shown in Figure 14.7 (R = CH_2CO_2H) was resolved by crystallization of the brucine salt (Kohler et al., 1935). Earlier attempts to resolve the simpler allenic acid shown in Figure 14.7 (R = H) had failed, but a quite similar acid of related type, $CH_3CH{=}C{=}C(n\text{-}C_4H_9)CO_2H$ was finally resolved by means of strychnine in 1951 (Wotiz and Palchak).

In 1952, it was recognized that optically active allenes also occur in nature. In that year Celmer and Solomons (1952, 1953) established the structure of the antibiotic mycomycin, a fungal metabolite, to be that of a chiral allene: $HC{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH_2CO_2H$. Since then a number of other chiral allenes have been found in nature (for tabulations see Rossi and Diversi, 1973, p. 27; Murray, 1977, p. 972; Runge, 1982, p. 595; see also Landor, 1982).

In recent years, numerous optically active allenes have been obtained in a variety of ways (resolution, transformation of chiral precursors, and enantioselec-

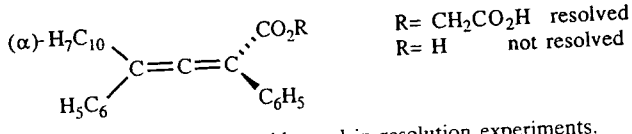


Figure 14.7. Allenic acids used in resolution experiments.