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).

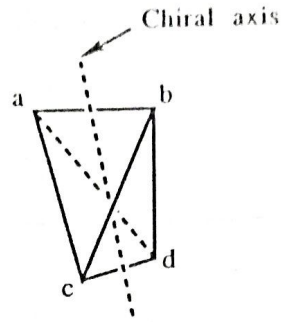


Figure 14.1. Chiral axis.

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

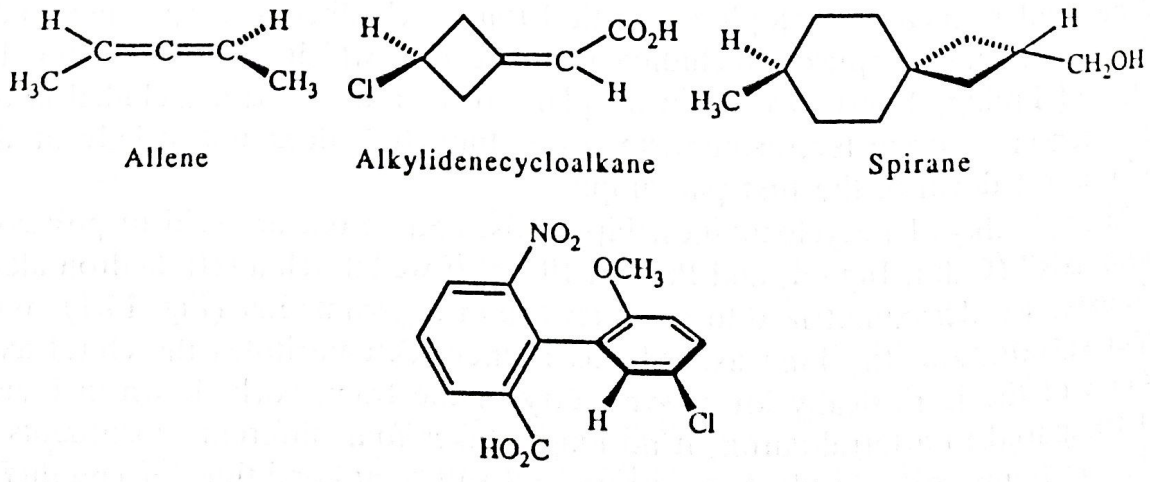


Figure 14.2. Molecules with chiral axes.

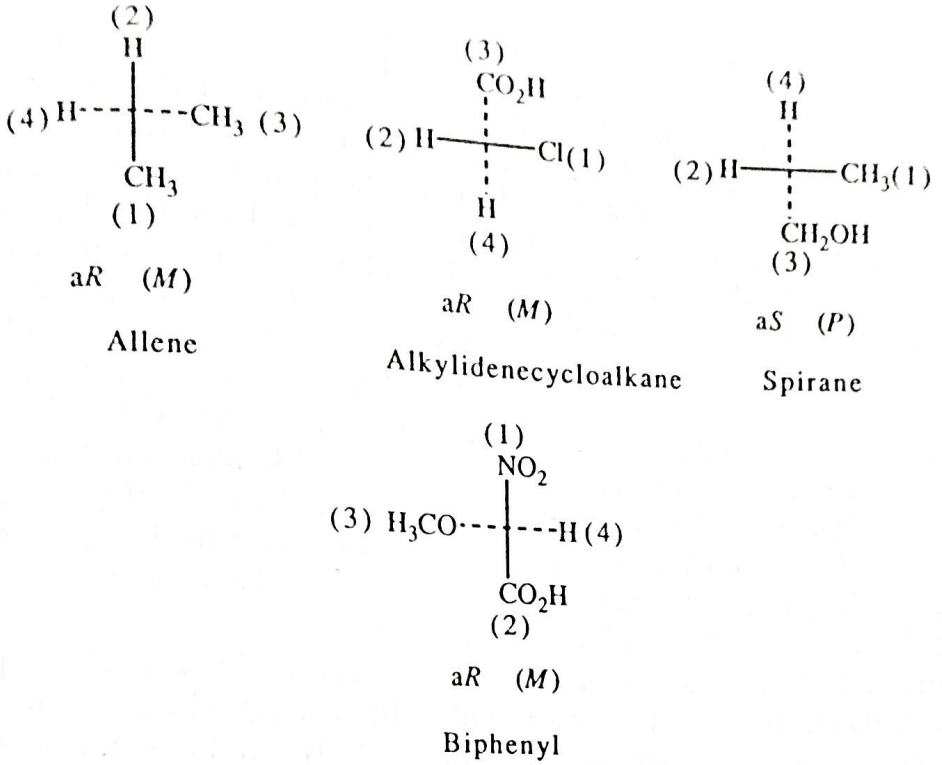


Figure 14.3. Descriptors for molecules with chiral axes.

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,

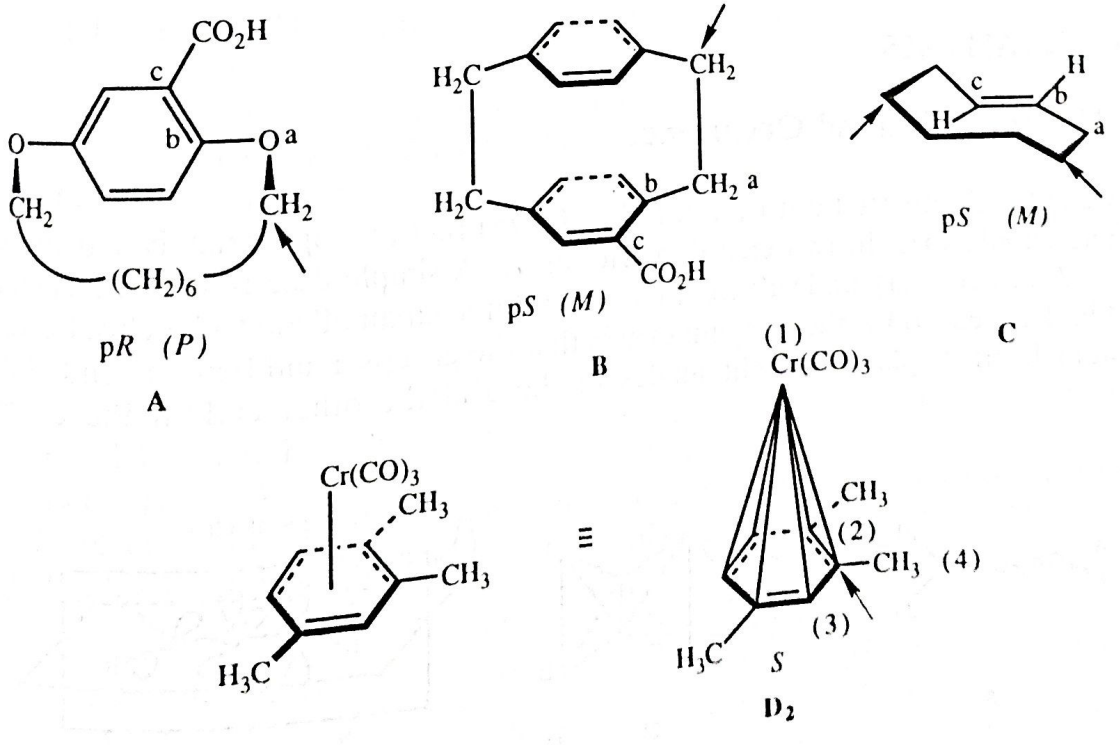


Figure 14.4. Molecules with chiral planes.

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 molecules 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 ≠ 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

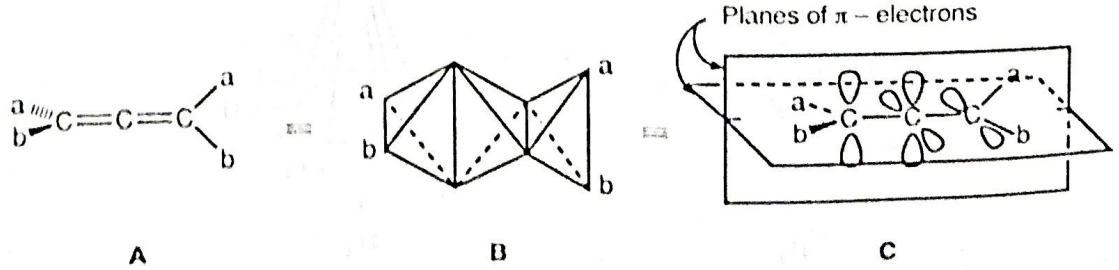


Figure 14.5. Dissymmetric allene.

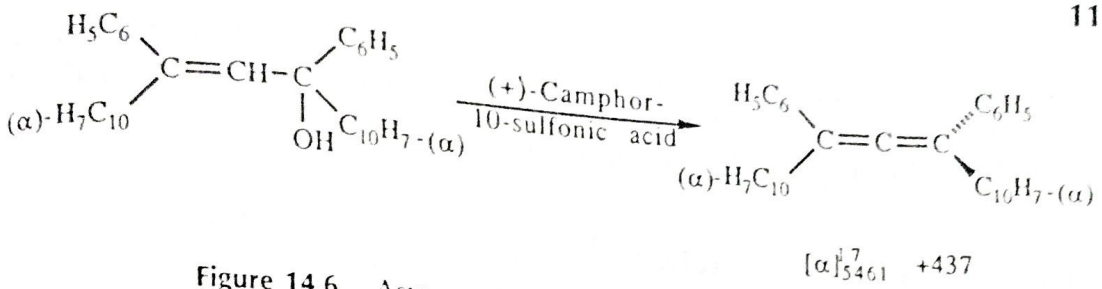


Figure 14.6. Asymmetric synthesis of optically active allene.

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-

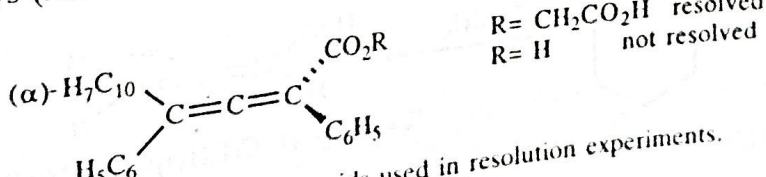


Figure 14.7. Allenic acids used in resolution experiments.

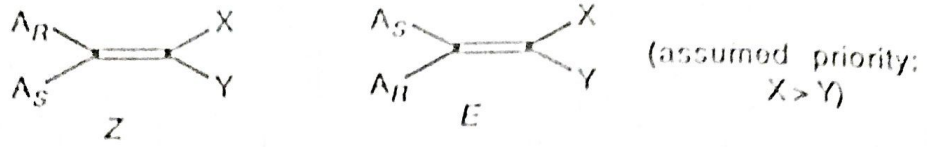


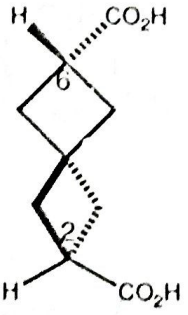
Figure 14.28. cis–trans Enantiomers.

It should be noted that, at least from the nomenclatural point of view, compounds **A** and **B** in Fig. 14.27 are *not* considered cases of axial chirality (Cahn, Ingold, and Prelog, 1966). To name such compounds one labels the chiral centers in the ring as *R* or *S*, as the case may be, and since $R > S$ in the sequence rules (other things being equal), the configuration is *Z*, the OH of the oxime being on the side of the *R* substituent on the ring. The type of chirality seen in Figure 14.27, originally called "geometric enantiomorphic isomerism" (Lyle and Lyle, 1959) and later "geometric enantiomerism" (Eliel, 1962, p. 320) should now be called cis–trans enantiomerism. In fact, it need not coincide with apparent axial chirality at all; a more general case is shown in Figure 14.28.

14-4. SPIRANES

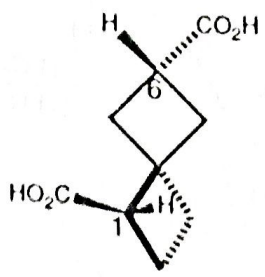
The name "spirane," from the Latin *spira* meaning twist or whorl implies that spiranes (cf. Fig. 14.2) are not planar; it is their nonplanarity that gives rise to their chirality.

Among the chiral spiranes (Fig. 14.29) one may discern three types: **A**, which definitely displays axial chirality similar to that of allenes and alkylidenecycloalkanes (see above); **B**, which, like corresponding alkylidenecycloalkanes (see above), displays central rather than axial chirality; and **C**, which conceptually would appear to display axial chirality but, for purposes of nomenclature, is considered to have a chiral center (Cahn, Ingold, and Prelog, 1966). Compound **A** is described as indicated in Figure 14.3, the descriptor is a*S* or *P*. Compound **B** has four stereoisomers (2 pairs of enantiomers); C(1) is a chiral center, whereas C(6) displays cis–trans isomerism and the stereoisomer shown is 1*S*,6-trans. To name **C** one arbitrarily gives one ring preference over the other; the more substituted branch in that ring then has priority 1 and the less substituted has



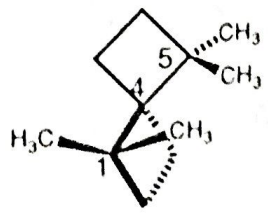
A

(*S*)-Spiro[3.3]heptane-2,6-dicarboxylic acid "Fecht acid" (*P*)



B

(1*S*, *t*-6)-Spiro[3.3]heptane-1,6-dicarboxylic acid



C

(*H*)-1,1,5,5-Tetramethylspiro[3.3]heptane

Figure 14.29. Types of spiranes.

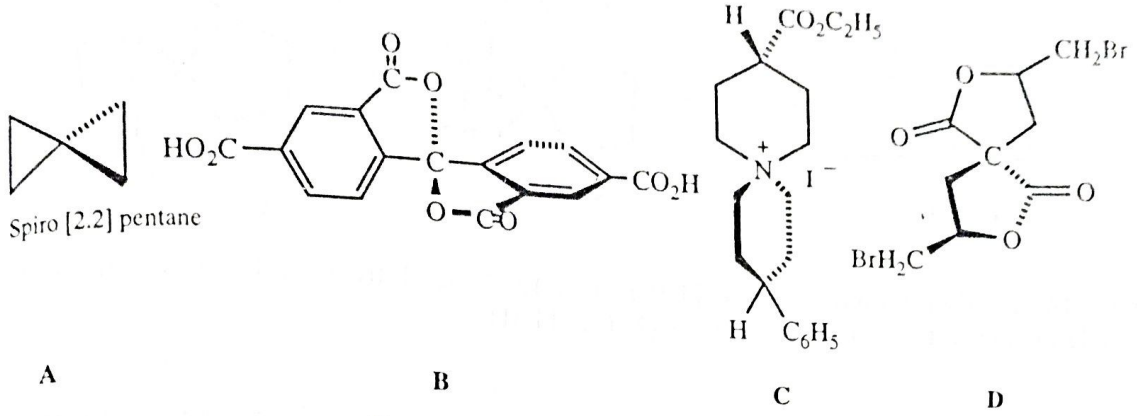


Figure 14.30. Examples of spiranes.

priority 3, whereas the corresponding priorities in the arbitrarily less favored ring are 2 and 4. The configuration is then 4*R*; the spiro center C(4) is considered a chiral center.

The most strained saturated spirane, spiro[2.2]pentane (Fig. 14.30, **A**), was apparently first synthesized in 1896 by Gustavson (q.v.) although it was not then recognized as such (cf. Applequist et al., 1958). Its strain of 65 kcal mol^{-1} (272 kJ mol^{-1}) is only about 10 kcal mol^{-1} (42 kJ mol^{-1}) greater than that of two isolated cyclopropane rings (Humphrey and Spitzer, 1950; Fraser and Prosen, 1955; for an interpretation, see Bernett, 1967). Chirality in spiranes, first recognized by Aschan (1902) was demonstrated in 1920 by Mills and Nodder (q.v.) by resolution of a spirodicarboxylic acid (Fig. 14.30, **B**). This compound is of type **C** in Figure 14.29; the central carbon atom can be described as a chiral center. However, a compound of type **A** in Figure 14.29 was resolved 5 years later (Mills and Warren, 1925); it is shown in Figure 14.30, **C**. It is of interest that the spiro center of compound **C** is a quaternary nitrogen rather than a carbon atom. Compound **D** in Figure 14.30 is also interesting; it has a spiro center and two conventional chiral centers; contemplation of models (cf. Fig. 14.31) indicates the existence of three diastereomeric racemates, which have, in fact, been isolated (Leuchs and Giesler, 1912).

Several assignments of absolute configuration of spiranes of type **C** in Figure 14.29 have been accomplished (see also Klyne and Buckingham, 1978, Vol. 2, p. 106; Buckingham and Hill, 1986, pp. 150–151). The first correct one (Gerlach, 1968) is concerned with the dione shown in Figure 14.32 and is based on that of its diol precursor shown in the same figure. The relative configuration of this diol had been established by the absence of intramolecular hydrogen bonding and by reductive correlation with a single one of the two diastereomeric mono-ols. The

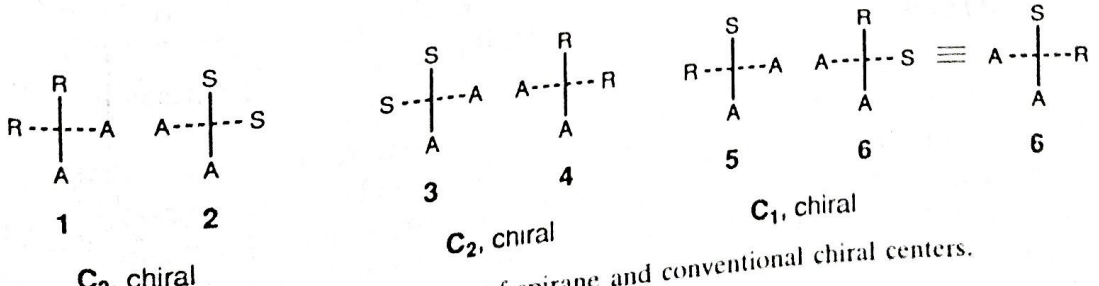
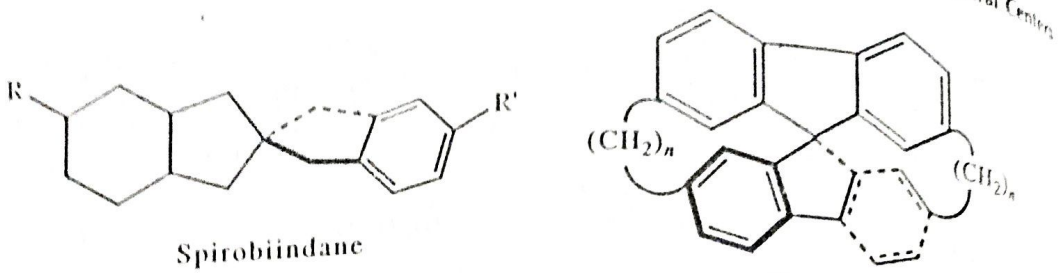


Figure 14.31. Combination of spirane and conventional chiral centers.



Spirobiindane
A

Vespirene
B

Figure 14.35. Spirobiindanes and vespirenes.

14-5. BIPHENYLS. ATROPISOMERISM

a. Introduction

In the examples given so far, the chiral axis is sustained (and the screw or helical sense of the molecule maintained) either by the "stiffness" (high barrier to rotation) of a double bond (allenes) or by the molecular framework as a whole (spiranes) or by a combination of the two (alkylidenecycloalkanes). We now come to molecules with a chiral axis whose helical sense is maintained through hindered rotation about single bonds, the hindrance in general being due to steric congestion. The classical examples of such molecules are the biphenyls (or biaryls in general) shown in Figure 14.36. If $X \neq Y$ and $U \neq W$ and, moreover, the steric interaction of X–U, X–V, and/or Y–V, Y–U is large enough to make the planar conformation an energy maximum, two nonplanar, axially chiral enantiomers (Fig. 14.36) exist. If the interconversion through the planar conformation is slow enough they may, under suitable circumstances, be isolated (resolved). This type of enantiomerism was first discovered by Christie and Kenner (1922) in the case of 6,6′-dinitro-2,2′-diphenic acid (Fig. 14.36, $X = U = CO_2H$; $Y = V = NO_2$), which they were able to resolve. It was later called (Kuhn, 1933) "atropisomerism" (from Greek *a* meaning not, and *tropos* meaning turn). (For references to the early history, see Eliel, 1962, p. 156.)

Reference to Chapter 10 suggests that atropisomerism is a type of conformational (rotational) isomerism in which the conformational isomers or conformers can be isolated. It is immediately obvious that the term suffers from all the problems discussed in Sections 2-4 and 3-1.b: How slow must the interconversion of the enantiomers be (i.e., how long is their half-life) before one speaks of atropisomerism? At what temperature is this measurement to be made? Does atropisomerism still exist when isolation of stereoisomers becomes difficult or impossible but their existence can be revealed by NMR (or other spectral) study,

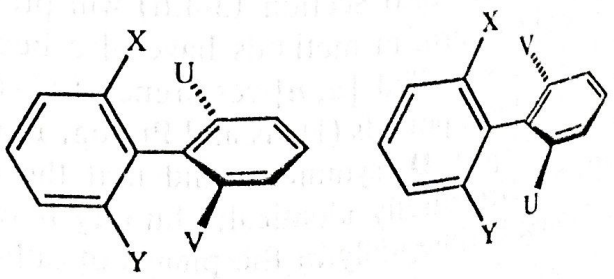


Figure 14.36. Enantiomeric chiral biphenyls.

and so on. Ōki (1983) arbitrarily defined the condition for the existence of atropisomerism as one where the isomers can be isolated and have a half-life $t_{1/2}$ of at least 1000 s (16.7 min). This value still does not define the required free energy barrier, which evidently now depends on temperature; it is 22.3 kcal mol^{-1} (93.3 kJ mol^{-1}) at 300 K, 26.2 kcal mol^{-1} (109.6 kJ mol^{-1}) at 350 K, and 14.7 kcal mol^{-1} (61.5 kJ mol^{-1}) at 200 K. Though this definition is entirely arbitrary, it is convenient and quite essential if the concept of atropisomerism is to be maintained at all.

b. Biphenyls and Other Atropisomers of the sp^2–sp^2 Single-Bond Type

General Aspects

Atropisomers are numerous in number and type and only a very brief treatment can be given here. Biphenyl isomerism has been extensively discussed earlier (Adams and Yuan, 1933; Shriner, Adams, and Marvel, 1943; Eliel, 1962, p. 156; Krow, 1970), especially in regard to the structural attributes needed to "restrict" rotation. Half-lives of racemization of numerous biphenyls have been determined with the following general findings:

1. Most tetra-ortho substituted biphenyls (Fig. 14.36, U,V,X,Y ≠ H) are resolvable and quite stable to racemization unless at least two of the groups are fluorine or methoxy.

A nonresolvable, tetra-ortho substituted biphenyl is shown in Figure 14.37, **A** (Adams and Yuan, 1933). It should be noted that although the condition U ≠ V and X ≠ Y is not fulfilled by this molecule, the perpendicular conformation lacks a plane of symmetry because of the meta substituents (Cl ≠ CO_2H).

2. Tri-ortho substituted biphenyls are readily racemized (short $t_{1/2}$ values) when at least one of the groups is small (CH_3O or F), otherwise racemization tends to be slow (but is possible, generally at elevated temperatures).
3. Di-ortho substituted biphenyls are generally resolvable only if the substituents are large. An interesting example is 1,1′-binaphthyl (Fig. 14.37, **B**), originally obtained optically active by deamination of the resolved 4,4′-diamino derivative (Cooke and Harris, 1963). The compound exists in

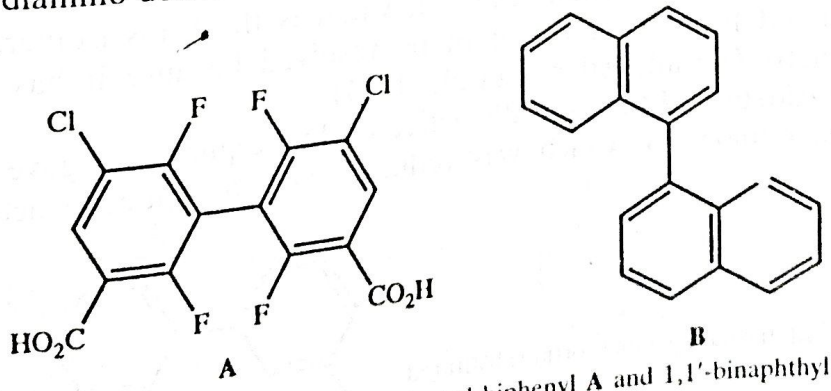


Figure 14.37. A tetra-*o*-fluorosubstituted biphenyl **A** and 1,1′-binaphthyl **B**.

two crystalline modifications, a racemic compound, mp 145°C and a conglomerate (cf. Section 6-3), mp 158°C. The latter is easily resolved either spontaneously or by seeding of the melt or solution (Wilson and Pincock, 1975; see also p. 317); above the melting point the enantiomers are in rapid equilibrium ($t_{1/2} \approx 0.5$ s at 160°C; $\Delta G^{\ddagger} = 23.5$ kcal mol^{-1} (98.3 kJ mol^{-1}).

4. Mono-ortho substituted biphenyls are, in general, not resolvable although the (+)-camphorsulfonate of the arsonium salt shown in Figure 14.38 shows mutarotation (cf. p. 750) suggesting that an interconversion of diastereomers occurs in solution because the two diastereomers are not equally stable (asymmetric transformation of the first kind, cf. Section 7-2.e).
5. Substituents in the meta position tend to enhance racemization barriers by what is known as a "buttressing effect," that is, by preventing the outward bending of an ortho substituent, which would otherwise occur in the transition state (coplanar conformation) for racemization. (This outward bending allows the ortho substituents to slip past each other more readily by energy minimization of the activated complex (cf. Section 2-6).
6. The apparent size of substituents (as gauged by racemization rates of differently ortho-substituted biphenyls) is $I > Br \gg CH_3 > Cl > NO_2 > CO_2H \gg OCH_3 > F > H$. This order roughly parallels van der Waals radii ($I > Br > C > Cl > N > O > F > H$; in polyatomic groups allowance must be made for the outer substituents) and is quite different from that of the ΔG^0 values in cyclohexanes (axial-equatorial equilibrium, Table 11.7) In contrast to synaxial substituents in cyclohexanes, ortho substituents on the two rings in biphenyls point at each other, so their interaction should increase with increasing van der Waals (and bond) radii.
7. Activation barriers to racemization can be calculated quite closely by molecular mechanics (cf. Section 2-6); in fact, calculation of barriers of this type constitutes the first application of what is now called the molecular mechanics or force field method (Westheimer and Mayer, 1946; cf. Westheimer, 1956). Semi-empirical methods have also been applied to the calculation of barrier height, with some success (Kranz, Schleyer, et al., 1993).
8. Diastereomers are found not only in biphenyls with chiral substituents but also in terphenyls. The compound shown in Figure 14.39, **A** is an example; the cis isomer has been resolved, whereas the trans isomer, which was separated from the cis, cannot be resolved because it has a center of symmetry (Knauf, Adams, et al., 1934).

Oxidation of the optically active cis hydroquinone **A** gave an optically active quinone **B**, which was reduced back to optically active **A**. This

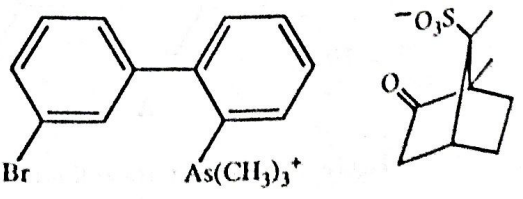


Figure 14.38. Mutarotating mono-orthosubstituted biphenyl.

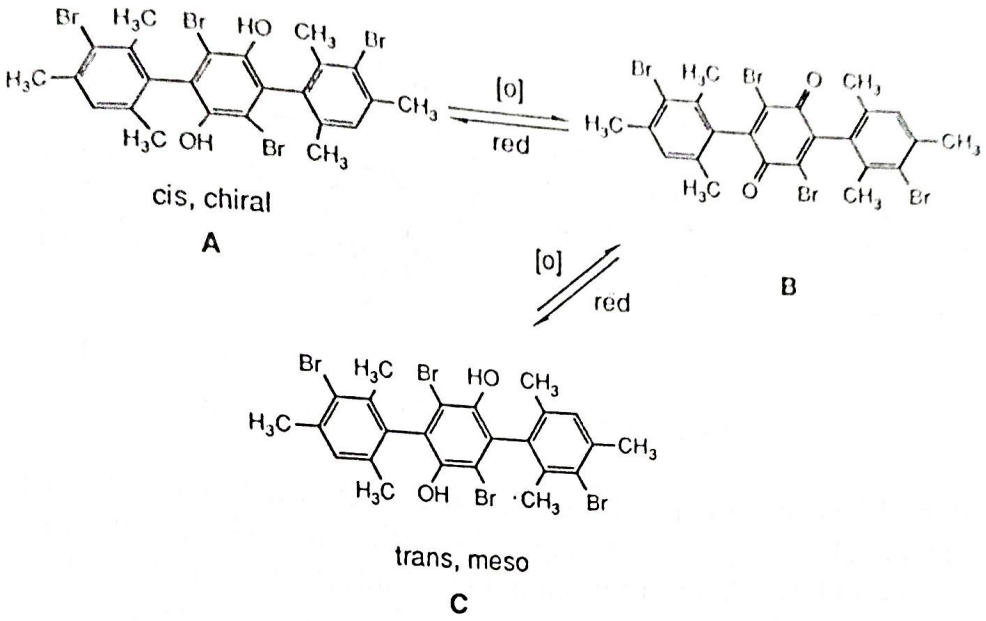


Figure 14.39. cis–trans Isomerism in terphenyls and diphenylquinones.

finding showed that atropisomerism is possible in structures other than biphenyls. Additional cases of resolvable atropisomers are shown in Figure 14.40 (Mills and Dazeley, 1939; Adams and Miller, 1940; Adams et al., 1941). Examples of thioamides were discussed earlier (Section 9-1.e; see also Ōki, 1983).

9. Noncoplanarity may be assisted or enforced by bridging (cf. Hall, 1969). Molecule **A** in Figure 14.41 is resolvable and moderately optically stable (Adams and Kornblum, 1941) even though *o,o'*-diphenic acid (Fig. 14.36, X = U = CO_2H, Y = V = H) is not. The ortho bridged **B** and doubly ortho bridged **C** biphenyls (Fig. 14.41) have been synthesized in optically active form by Mislow et al. (1964). The doubly bridged biphenyl enantiomers **C** with X = CO or S are quite stable but can be racemized thermally, whereas the compound with X = O is labile and racemizes with a half-life of only 54 min at 10.1°C. The enantiomers of the corresponding three-atom singly bridged species **B** (X = O) are much more stable (see also Iffland and Siegel, 1958). In contrast, the two-atom bridged compound **D** (Mislow and Hopps, 1962) has quite low enantiomeric stability ($t_{1/2}$ = 108 min at 28.1°C) contrary to the high stability of tetra-ortho substituted biphenyls in general (see above); it is thus clear that ortho bridging diminishes the enantiomeric stability of ortho-substituted biphenyls, presumably because

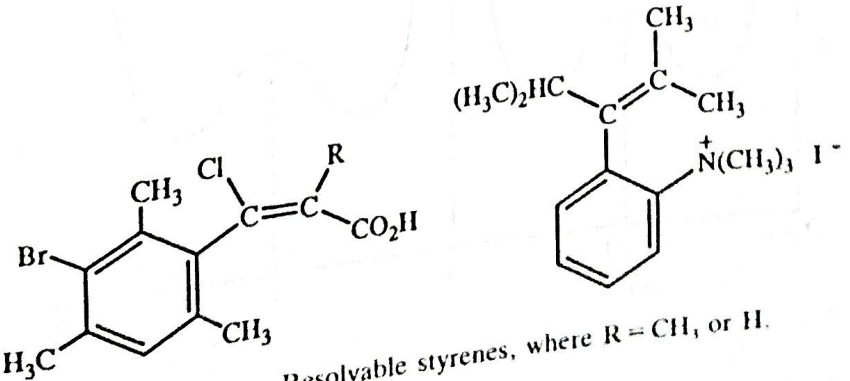


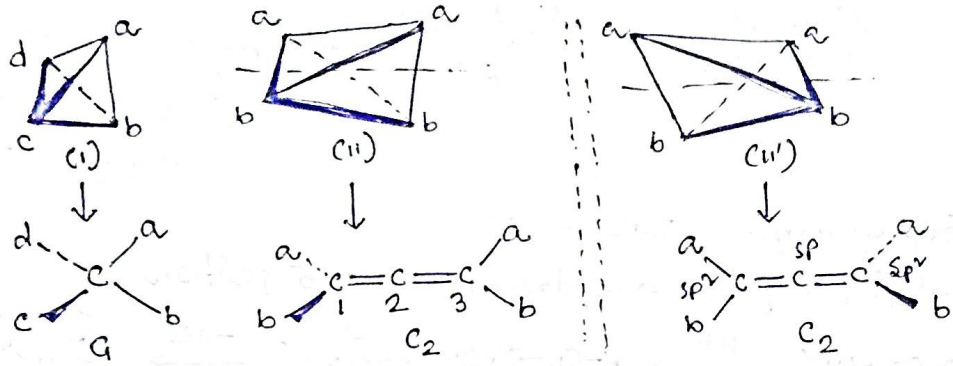
Figure 14.40. Resolvable styrenes, where R = CH_3 or H.

23/09/16: (KB)

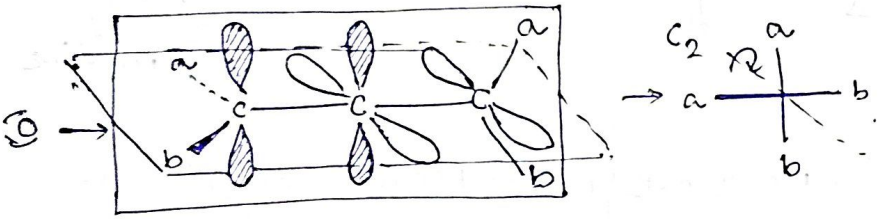
Axial chirality, Planar chirality. chiral centres (occasionally, pseudoasymmetric centres)

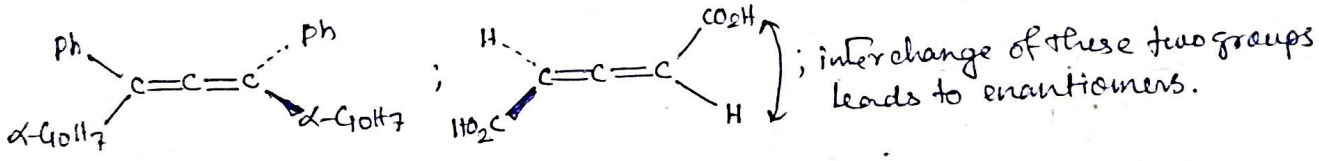
Two other elements of symmetry chirality → axes and planes

Biphenyl, spiranes, trans-cycloalkanes → No chiral centre (but having chiral planes or axis to exhibit chirality).

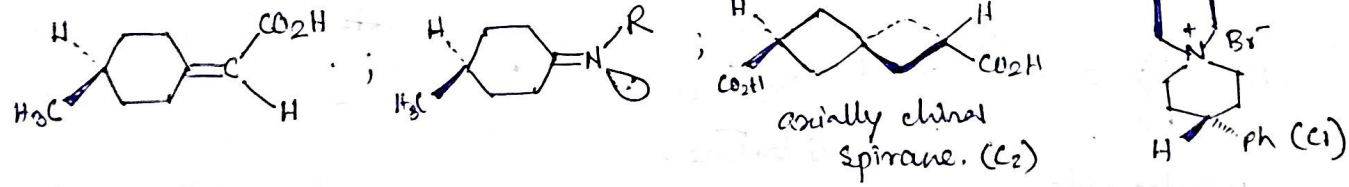


Elongated pyramid & chiral axis



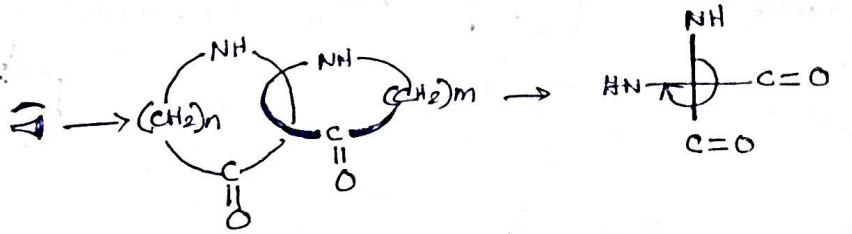


Optically active alkylidene cycloalkanes (heterospiranes):

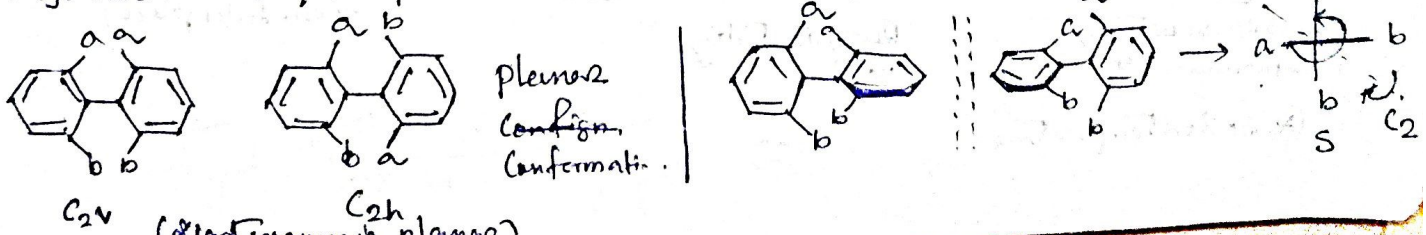


Optically active catenanes:

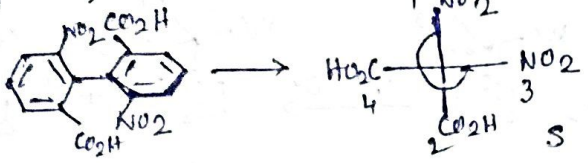
Two or more dissimilar rings interlinked with each other. (secondary structure).



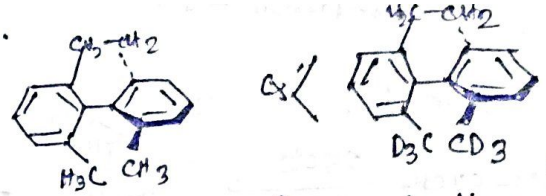
Biphenyl derivatives: / Atropisomerism:



Optically active biphenyls (D. Nasipuri 84).

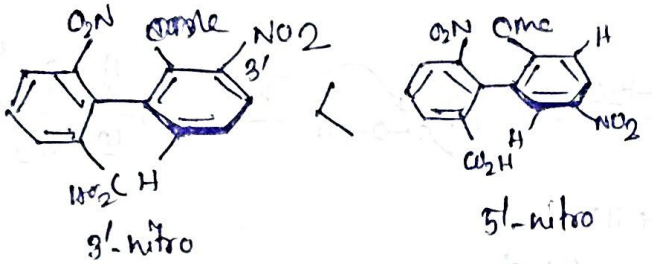


S



(I) (II)

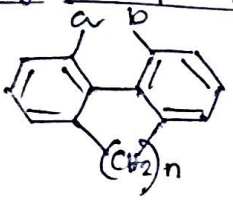
rate of racemization of (II) > (I)
due to small vanderwaal radii of D-atom
2ndary isotope effect.



3'-nitro 5'-nitro

(Rate of racemization)
A bulky gr. adjacent to o-position exerts a buttressing effect.

Bridged Biphenyls:



When n = 1
(disubstituted fluorene)
Planar: ~~does~~ No atropisomers

n = 2
(dihydrophenanthrene)
Non-planar
↓
Give Atropisomerism if o-substituents are bulky.

n > 2
Bridged biphenyls give atropisomers.