REVIEW

Organic Stereochemistry

Part 3[1])

Other Stereogenic Elements: Axes of Chirality, Planes of Chirality, Helicity, and (*E*,*Z*)-Diastereoisomerism

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In this third review, our series on Organic Stereochemistry continues with further stereogenic elements [1–14]. Indeed, the presence of a stereogenic center is not a necessary condition for a molecule to be chiral, and a given structure may contain other elements leading to molecular chirality. According to the *factorization rule* [15–19], overall chirality can be factorized into three elements, namely *stereogenic centers* , *axes of chirality*, and *planes of chirality*. The first step in the procedure for specifying chirality is to factorize the overall chirality of a given molecule into as many stereogenic centers as are present. Should this specification leave the description of the overall chirality of a molecule incomplete, factorization into axes of chirality, or planes of chirality, or both is pursued as far as necessary. It is also relevant to consider another element of chirality, namely *helicity*.

In addition to these elements of chirality, another stereogenic element is included in our presentation, namely *stereoisomerism about double bonds* [20][21]. Except in a few cases such as allenes, this is not an element of chirality that allows the compound to exist as two enantiomers, but its presence allows for the possibility of *diastereoisomers*. In other words, it is an element of *diastereoisomerism*. Stereoisomerism about double bonds has also been known as *cis*/*trans* isomerism, although this term is abandoned given that it is mainly used to characterize diastereoisomers having two stereogenic centers, particularly in cyclic systems. As a result, the term π-diastereoisomerism has been proposed but is seldom used. As we shall see, the most frequently used term is *(*E,Z*)-diastereoisomerism* based on the specific (*E*)- and (*Z*)-convention.

As in *Part 2*, the main focus in this review are the *convention systems* used to describe the *absolute configuration in 3D space* of compounds characterized by the presence of an axis of chirality, a plane of chirality, helicity, or a stereogenic double bond.

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[1]) For the other *Parts*, see. *Helv. Chim. Acta* **2013**, *96*, 1–3.

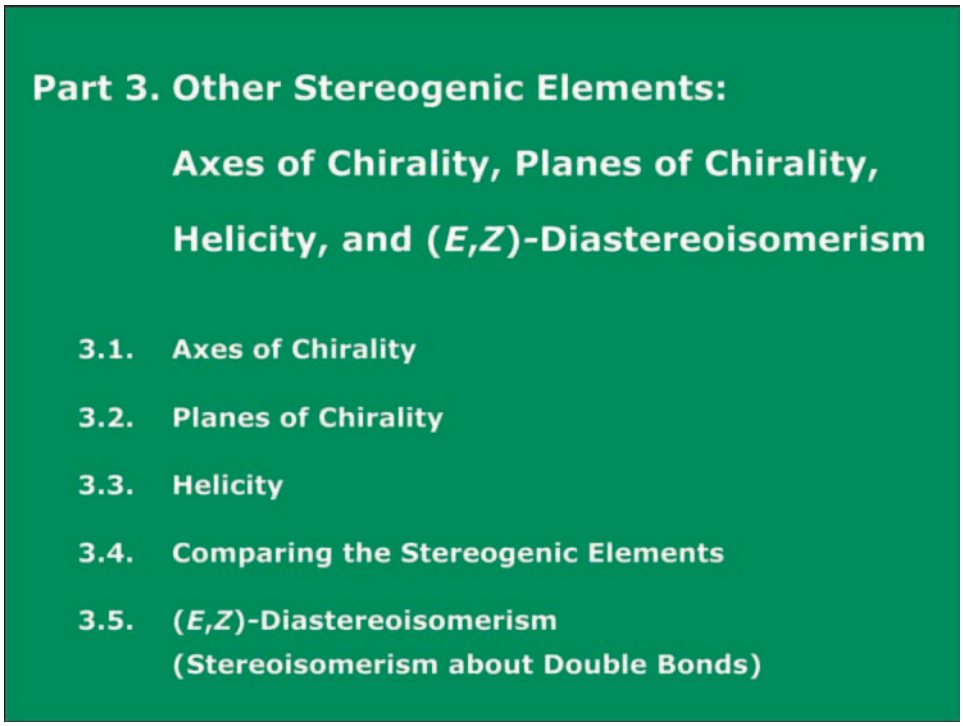

Fig. 3.1. The *layout* of this *Part* is summarized here and follows the sequence outlined in the *Introduction* above. The fact that an *axis of chirality* can be envisaged as formed by elongation of a 'center' of chirality facilitates understanding and the relevant extension of the sequence rule. The concept of the *plane of chirality* is more difficult to grasp in its principle and related conventions, and this is not simplified by divergent views expressed in the literature. In contrast, *helicity* is intuitively and pictorially easy to envisage; its significance in biochemistry cannot be over-emphasized, as our examples will demonstrate.

The fourth stereogenic element is different from the others, as its presence in a molecule is a sufficient condition for diastereoisomerism but does not necessarily imply chirality. It appears under a variety of terms in the literature, namely torsional isomerism about double bonds, *cis/trans* isomerism, geometrical isomerism, and π-diastereoisomerism, none of which is fully satisfactory in our view. Thus, the terms *(*E,Z*)-diastereoisomerism* (in accordance with the IUPAC Recommendations), and occasionally stereoisomerism about double bonds, will be used.

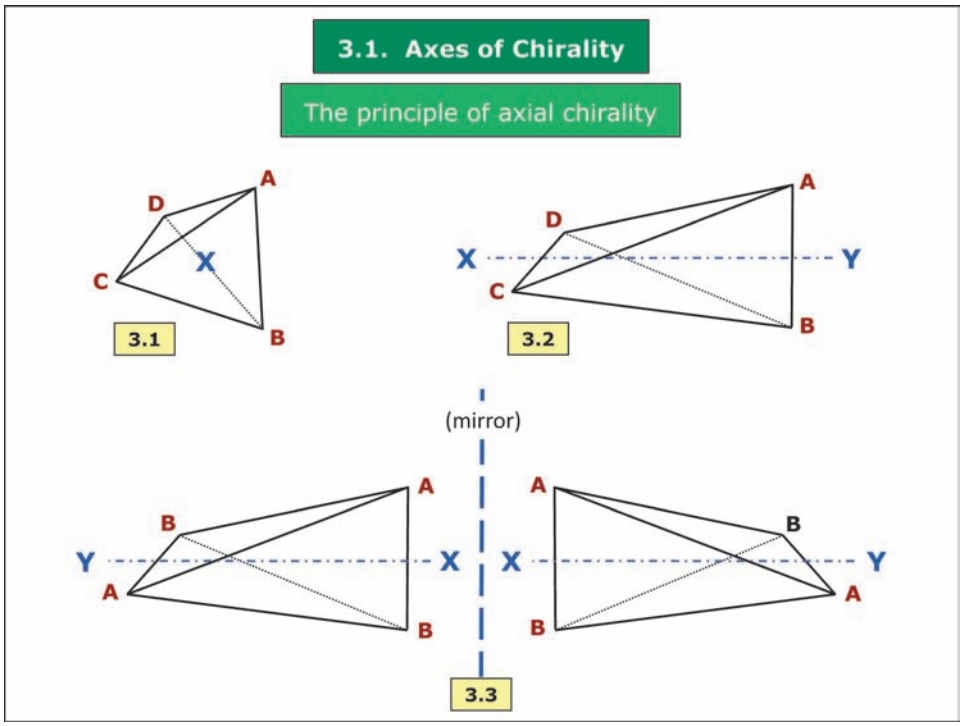

Fig. 3.2. The *regular tetrahedron* **3.1** symbolizes a central atom X with its four substituents A, B, C, and D located at the vertices. As we saw in *Part 2*, a stereogenic center exists when these four substituents are different from each other. If we now *elongate the tetrahedron* as shown in **3.2**, the stereogenic center X is extended into an *axis of chirality* X–Y. In such a structure, the conditions for chirality are less stringent than in a regular tetrahedron. This is seen in **3.3** where the two elongated tetrahedra are *enantiomers* despite having two A and two B substituents, the minimal condition for chirality here being simply A ≠ B. In other words, X–Y will be an axis of chirality if the pair of substituents at the X end and the pair of substituents at the Y end are each formed by two different substituents. How the *Cahn–Ingold–Prelog* (*CIP*) convention can be extended to such a situation is explained in the next *Figure*.

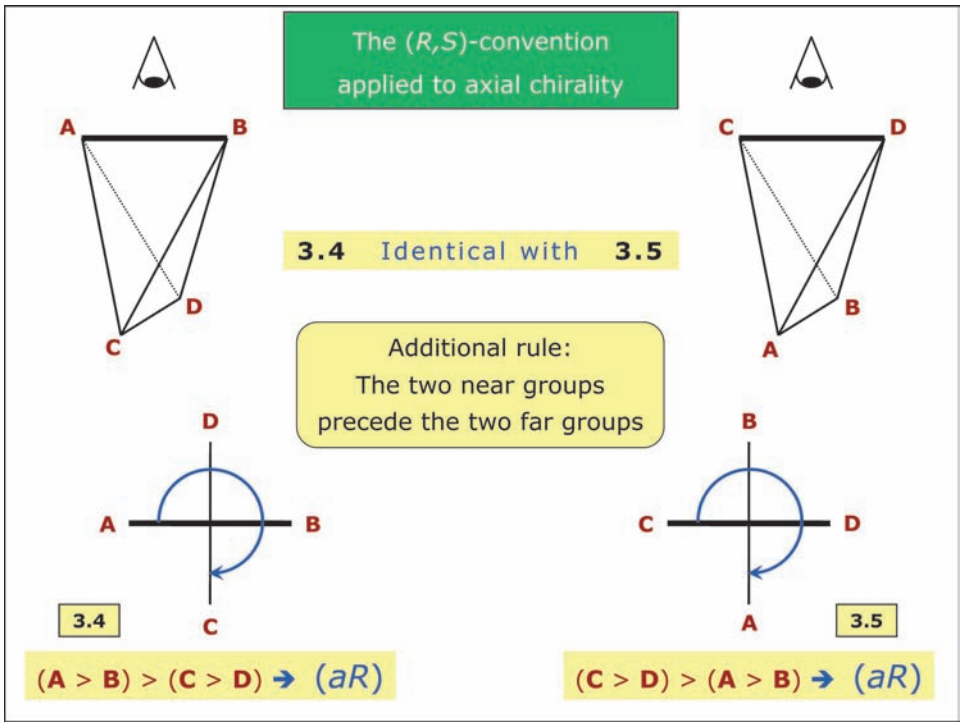

Fig. 3.3. When applying the sequence rule to axial chirality [1–8][11–13][15–18], a new rule is added such that *the two near groups have priority over the two far groups.* As a consequence of this additional rule, the (*R*)- and (*S*)-designation *no longer depends on the end from which the axis is viewed*, as demonstrated here. Indeed, viewing the tetrahedron from the A–B edge (as shown in **3.4**) and taking A > B and C > D, plus the new rule that (A > B) > (C > D), yields the sequence shown on the lower left quadrant and resulting in an (*R*)-configuration. As shown, the italic letter *a* can be added before the configurational descriptor to indicate *axial* chirality.

If we now view the tetrahedron from the C–D edge (as shown in **3.5**) and again take C > D and A > B, plus the new rule that (C > D) > (A > B), an (*R*)-configuration is found again as illustrated in the lower right quadrant. In other words, *models* **3.4** *and* **3.5** *are identical.*

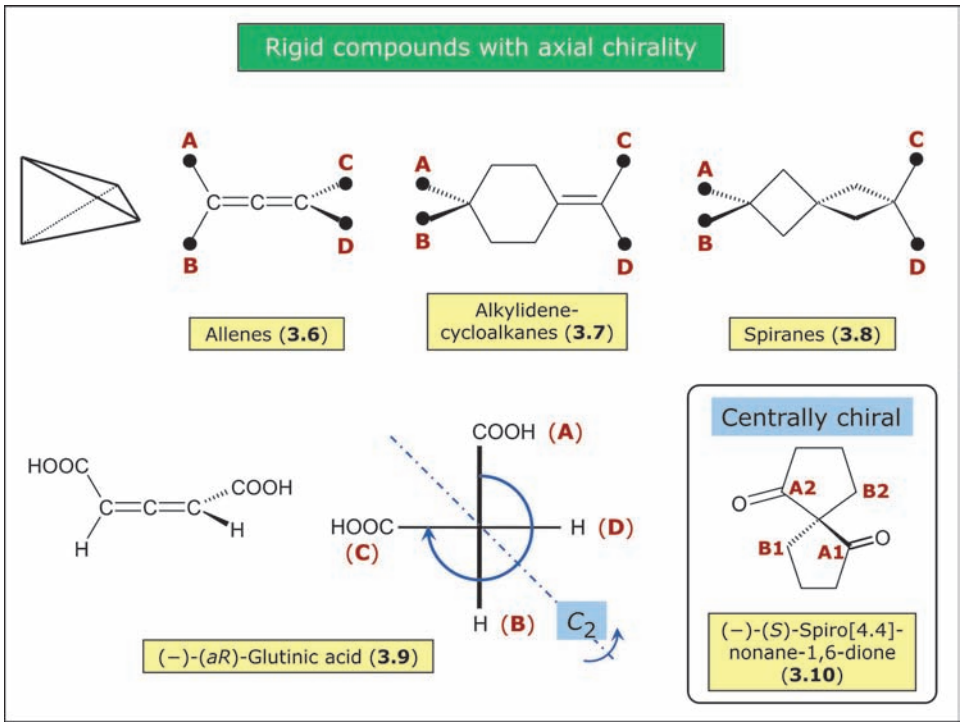

Fig. 3.4. This *Figure* presents a few examples of *rigid* chemical structures exhibiting axial chirality. Note that in each case, A ≠ B and C ≠ D. A well-known class is that of *allenes* (**3.6**), whose four substituents A, B, C, and D are confirmed here to occupy the vertices of an elongated tetrahedron. Other examples include some *alkylidene-cycloalkanes* (**3.7**) and a few *spiranes* (**3.8**). When A = C and B = D, a C_2 axis of symmetry exists as the sole element of symmetry, meaning that such structures belong to point group C_2. This is demonstrated here with the allene *(−)-(*aR*)-glutinic acid* (**3.9**) [1].

A note of warning is given with *spiro[4.4]nonane-1,6-dione* whose (*S*)-enantiomer is shown as **3.10**. This compound and analogs are considered to be *centrally chiral*, namely to have a stereogenic center, in accordance with the *factorization rule* [1][15–19]. The prioritization of the four substituents at the central C-atom follows the order A1 – A2 – B1 – B2, or alternatively A2 – A1 – B2 – B1, with both sequences yielding the (*S*)-configuration for **3.10**.

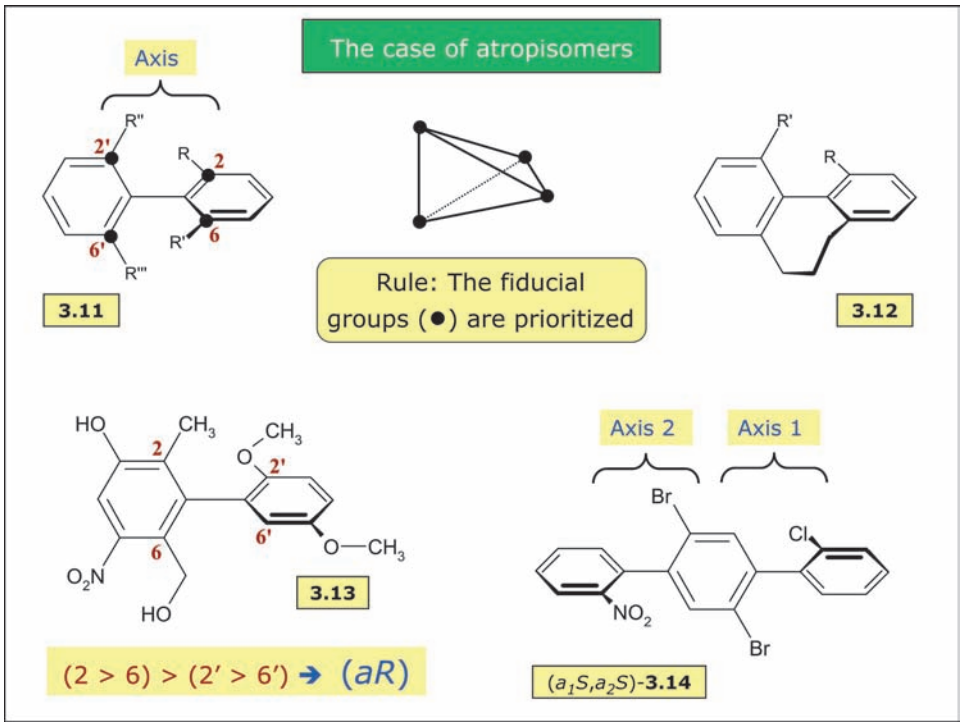

Fig. 3.5. *Atropisomers* are stereoisomers characterized by *axial chirality along a rotatable single bond*, as exemplified with the *biphenyl* **3.11** and the related *tricyclic structure* **3.12**. Here, defining the vertices of the virtual tetrahedron may be ambiguous, hence the subrule that the four vertices should correspond to so-called '*fiducial groups*'. These are defined as the pairs, nearest together, of groups which are directly bonded to atoms *on the axis*, and which lie pairwise in each of the planes of atoms that intersect along the axis [1][16]. To take the example of the biphenyl **3.11**, the fiducial groups are *C(2)* and *C(6)* for one pair, and *C(2′)* and *C(6′)* for the other. How these fiducial groups trace a tetrahedron is also shown on the *Figure*.

Assigning priority within each pair of fiducial groups is accomplished simply by exploring the atomic neighborhood of each fiducial group. In the biphenyl **3.13**, for example, a straightforward application of the sequence rule implies that, due to the vicinal phenolic group, C(2) has priority over C(6) despite their adjacent groups [16]. The preference of C(2′) over C(6′) is easier to recognize.

One implication of the definition of fiducial groups is that only a limited segment of the chirality axis is used in defining that axis. This becomes critical in the para-*terphenyl* **3.14** which features *two chirality axes* as indicated. To give an unequivocal description of its configuration, the *italic letter* a *(for axial)* plus the axis number are specified before the descriptor *R* or *S*.

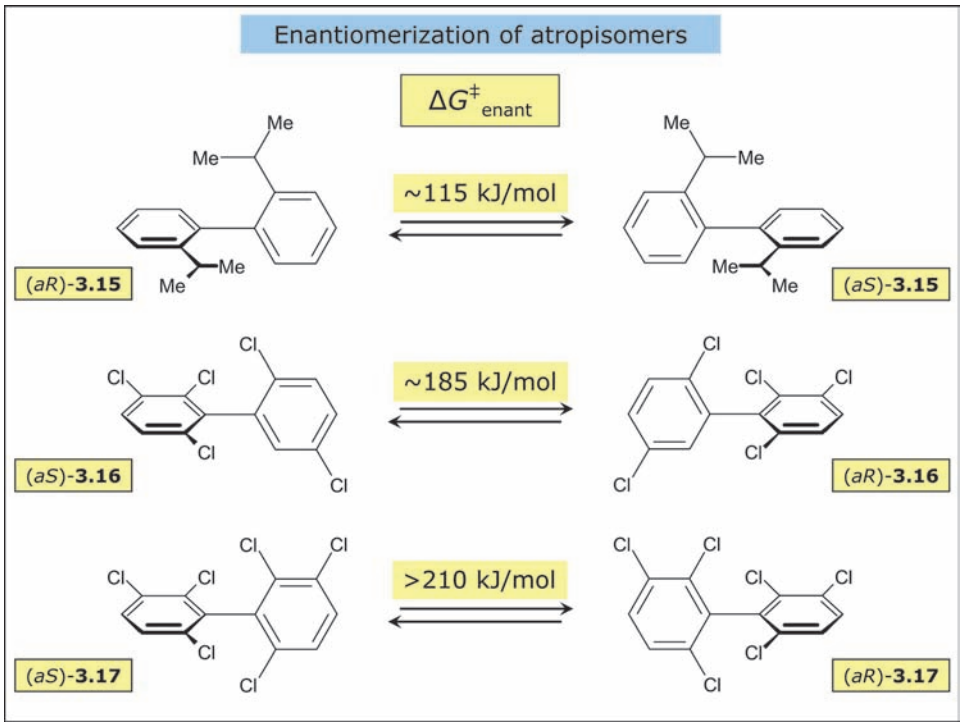

Fig. 3.6. As stated above, the chirality axis of atropisomers contains a *rotatable, single bond*. While rotation must necessarily be restricted, the Gibbs *free-energy barrier of enantiomerization* ($\Delta G^{\ddagger}_{enant}$), or racemization depending on the method used, can be markedly different from one compound to the other. In some biphenyls, enantiomerization is so fast that the two enantiomers cannot be isolated. In other compounds, especially in highly hindered ones, racemization is practically impossible. The main factor influencing the barrier of racemization is the *presence and size of substituents* at the four fiducial centers C(2), C(6), C(2′), and C(6′) [22].

Three examples have been selected to illustrate the energy barrier that separates their two enantiomeric forms; absolute configurations are also indicated for didactic reasons. As expected, the energy barrier increases with increasing degree of substitution on the fiducial C-atoms. *2,2′-Diisopropyl-1,1′-biphenyl* (**3.15**) thus has a half-life of enantiomerization of *ca.* 2 h at 80° [23]. *2,2′,3,5′,6-Pentachloro-1,1′-biphenyl* (PCB 95; **3.16**) is more hindered due to three of the four fiducial C-atoms bearing Cl-atoms, and indeed its barrier is markedly higher [24–26]. As for *2,2′,3,3′,6,6′-hexachloro-1,1′-biphenyl* (PCB 136; **3.17**), its enantiomerization was so slow due to strong steric hindrance (> 5% at 320° for 3 h) that it could not be measured and just assigned a lower limit [24]. Given the environmental concern with halogenated biphenyls and the possibility of enantioselective toxicity (see *Parts 5* and *7*), their configurational stability, or lack thereof, may be a relevant issue.

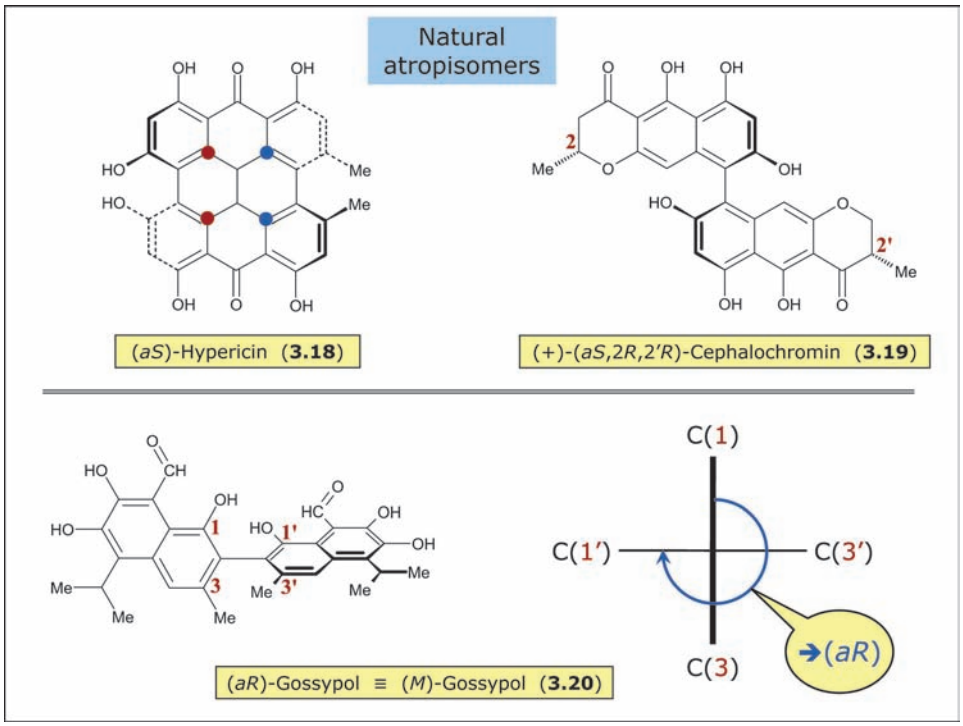

Fig. 3.7. This *Figure* shows *three natural products* each characterized by the presence of an axis of chirality and associated with some stereochemical issue. *Hypericin* (**3.18**), one of the main active components of *Hypericum* (Saint John's wort), has a complex polycyclic structure often regarded as planar. This is not the case, however, due to steric hindrance between two OH groups and two Me groups. The resulting *twisted structure* allows for enantiomerism, the free-energy *barrier of enantiomerization* being close to 98 kJ/mol [27]. The two senior fiducial C-atoms are indicated in red, the two junior ones in blue, making it easy to assign the (*S*)-configuration to the enantiomer displayed.

Cephalochromin (**3.19**), a natural compound produced by some fungi, has three stereogenic elements. The axial (*S*)-configuration accounts for its dextro-rotation, but it took a combination of methods to establish the (*R*)-configuration at C(2) and C(2′) [28]. As mentioned in *Fig. 3.5*, the *italic letter a* serves to avoid confusion between the descriptors.

Gossypol (**3.20**) is a potent antispermatogenic agent isolated from the cotton plant. Its 2,2-binaphthyl structure and steric hindrance allow for two stable enantiomers, with a free-energy barrier of enantiomerization of *ca.* 200 kJ/mol [29–31]. The more active enantiomer is the (−)-(*R*) one. However, the literature also mentions its absolute configuration as (*M*), the descriptor of the configuration of left-handed helixes, which will be explained in *Fig. 3.13*.

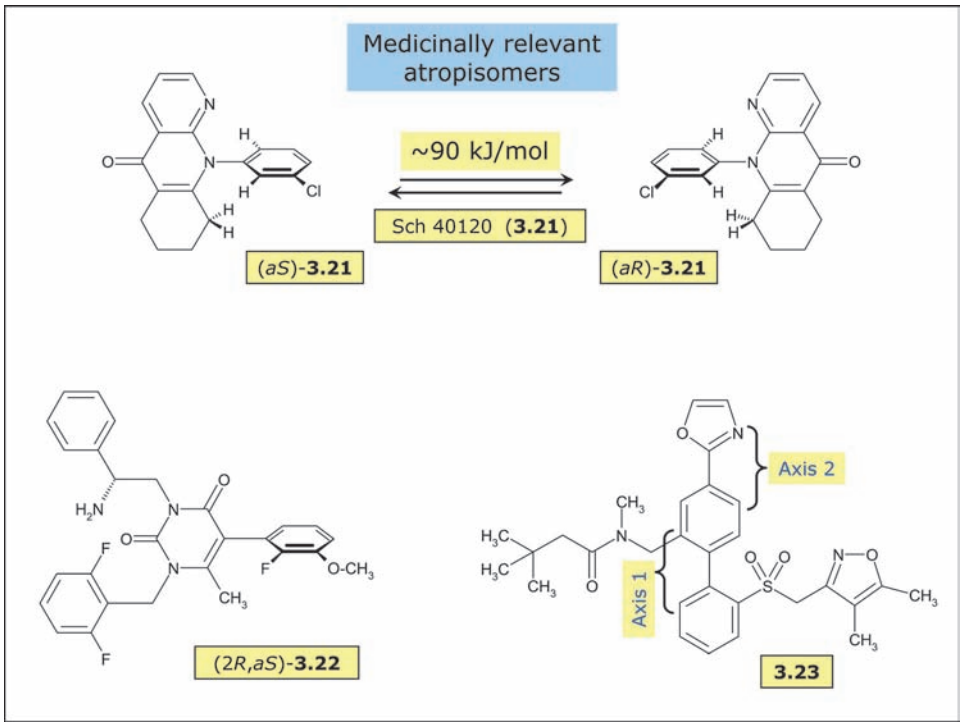

Fig. 3.8. Atropisomerism is also of relevance in medicinal chemistry, as illustrated here with a few examples. *Sch 40120* (**3.21**) is an antipsoriatic agent whose molecule features an axis of chirality [32]. Steric hindrance along the axis appears modest, being due to the H-atoms shown explicitely in the *Figure*. In other words, *fast enantiomerization* is expected, as was indeed found with a *Gibbs* free-energy barrier of enantiomerization of 90 kJ/mol corresponding to half-lives of *ca.* 7 and 3.2 min at 25 and 37°, respectively.

A markedly slower rate of interconversion at the chirality axis was found for *1-(2,6-difluorobenzyl)-3-[(2*R*)-2-amino-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-6-methyluracil* (*NBI 42902*; **3.22**), an antagonist of the human gonadotropin-releasing hormone receptor [33]. The compound also contains a *stereogenic center* of (*R*)-configuration which does not influence rotation along the axis of chirality due to the large distance separating them. Here, the *Gibbs* free-energy of interconversion (more specifically diastereoisomerization) was found to be 96 kJ/mol, with an equilibrium very close to 50 : 50 and a half-life of 46 min in aqueous media at 37°.

The endothelin receptor antagonist *BMS-207940* (**3.23**) contains two axes of chirality, one of which (*Axis 2*) is free-rotating (presumably 10^3 – 10^6 rotations per s) and of no relevance here. In contrast, the high steric hindrance at *Axis 1* allows for the occurrence of two relatively stable atropisomers. Interconversion in aqueous media followed first-order kinetics with a half-life close to 16 h (temperature and pH not specified) [34]. Intriguingly, interconversion was found to be much faster in blood plasma.

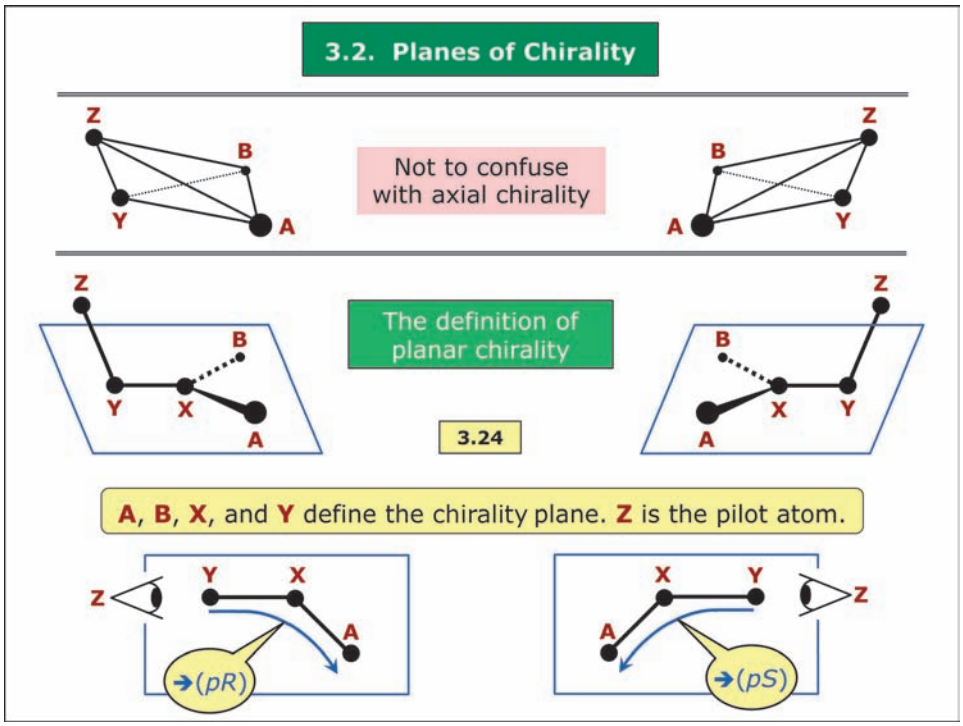

Fig. 3.9. The *plane of chirality* is a further stereogenic element. The conditions for the existence of a plane of chirality are the presence of *four coplanar atoms* (labeled A, B, X, and Y in **3.24**; with A ≠ B), plus a *fifth center* Z located above (or below) the ABXY plane, and restricted in its rotation around the X–Y axis [1][16–18][35]. As shown by the two distorted tetrahedra in the upper part of the *Figure*, there is some geometric analogy with the chirality axis (*Figs. 3.2–3.5*), calling for care to avoid confusion.

The five atoms ABXYZ in **3.24** are characterized by means of an *expansion of the sequence rule* to include cases of stereoisomerism involving a chirality plane. The atom Z is thus defined as the *sequence-rule-preferred atom directly attached to the plane*, and it is called the *pilot atom*. Starting from this pilot atom and looking at the plane, one classifies the atoms in the plane in the order of their encounter along the bonds. When a *branching* creates ambiguity, the sequence rule is applied. Thus, the path explored from the pilot atom takes its order from the *sequence-rule-preferred path Y–X–A*, and this allows either a clockwise, (*R*), or counterclockwise, (*S*), rotation to be traced from the pilot atom. This is illustrated in the lower left and right corners of the *Figure* for the two enantiomers of **3.24**, respectively. For the sake of clarity, the prefix '*p*' can be used to indicate that the configuration refers to *planar chirality*, *i.e.*, (*pR*) and (*pS*).

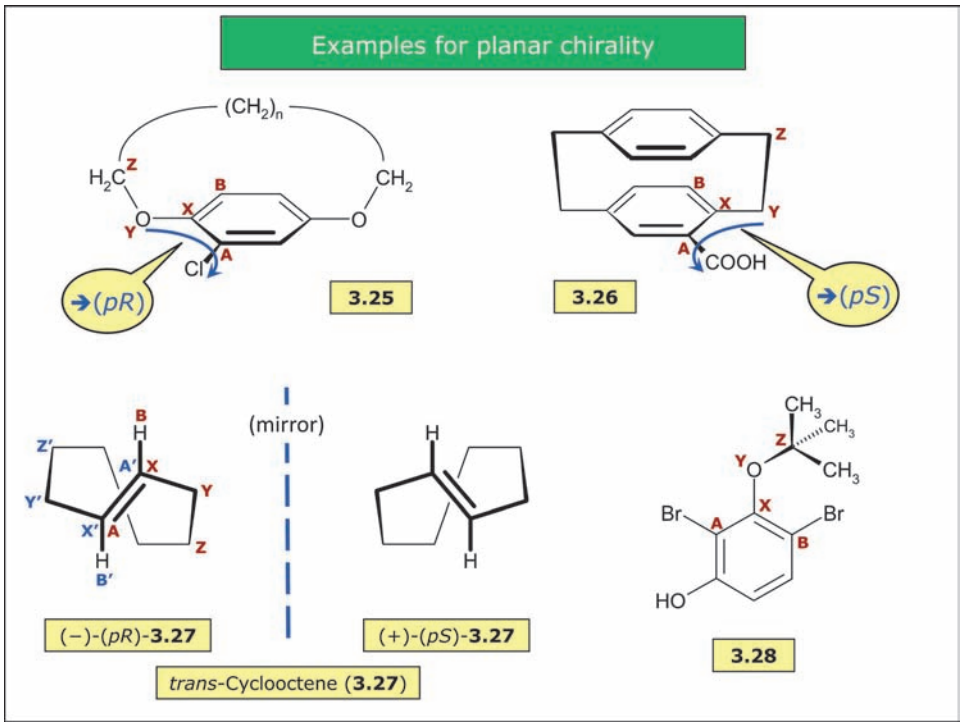

Fig. 3.10. Compounds such as *quinol polymethylene ethers*, **3.25**, contain neither a stereogenic center nor an axis of chirality, but when the number of CH_2 groups is small, restricted rotation about the O–phenyl–O axis results in the occurrence of two enantiomers. Here, the *plane of chirality is defined by the atoms ABXY*, and *Z is the pilot atom*, while the *sequence-rule-preferred path Y–X–A*, traces a clockwise rotation, *i.e.*, the (*pR*)-configuration. In *[2.2]paracyclophanecarboxylic acid* (**3.26**), *the sequence-rule-preferred plane* (*i.e.*, the one bearing the C=O group) is the plane of chirality, again defined here by ABXY. The pilot atom is Z, and here the preferred path traces a counterclockwise rotation, *i.e.*, the (*pS*)-configuration. Compound **3.26** has been resolved; it is optically stable, and its dextrorotatory enantiomer is the one having the (*pS*)-configuration as shown [1][16]. The higher homolog [4.4]paracyclophanecarboxylic acid could not be resolved, while the [3.4]-homolog racemized at high temperature.

Another case of planar chirality is provided by *trans*-cycloalkenes as exemplified with trans-*cyclooctene* (**3.27**). Here, it is necessary to recognize *two partly overlapping chirality planes* defined by the atoms labeled ABXY and A′B′X′Y′, respectively. The *pilot atoms* of these planes are Z and Z′, respectively; the preferred paths Y–X–A and Y′–X′–A′ both trace *the same direction of rotation*, meaning that the two planes of chirality are sterically constrained to be of identical configuration.

Yet another case is provided by the *imagined compound* **3.28** [35]. Its plane of chirality, pilot atom, and sequence-rule-preferred path are identified by the same labels as above. This example may help when dealing with some complex drug molecules.

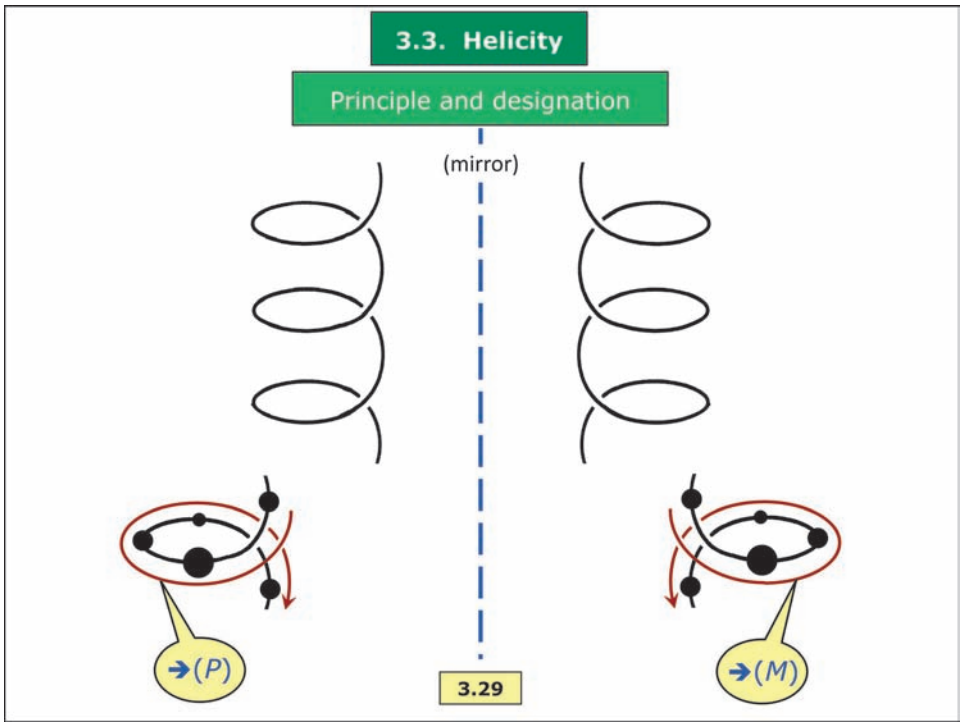

Fig. 3.11. A *helix* is a smooth curve in three-dimensional space, being characterized by the fact that the tangent line at any point makes a constant angle with its axis [36]. A helix can be *circular* (*i.e.*, having a constant radius) or *conical* (*i.e.*, being like a spiral on a conical surface). Another key parameter of helices is their pitch, namely the width of one complete turn, measured parallel to the axis of the helix. Most importantly in our context, helices are chiral objects as illustrated with the two enantiomeric circular helices **3.29**.

A helix is said to be *right-handed* if it shows a clockwise rotation when viewed along its axis and moving away from the observer; its absolute configuration is designated as (*P*) ('plus'). The corresponding enantiomeric helix is then said to be *left-handed* and its configuration is (*M*) ('minus') [1][6][8]. There are a number of helical (and hence chiral) molecules. Helical molecules exhibit *axial dissymmetry*, as they are a particular category of structures with a chirality axis. But rather than describing the absolute configuration of helical molecules using the (*aR*)- and (*aS*)-convention, it may be easier and more convenient to treat them for what they are, namely helices, and apply the *(*M*)- and (*P*)-convention* to designate their sense of chirality. As we shall see in *Fig. 3.13*, this ease and convenience goes far enough to allow some molecular geometries with axial chirality to be described with the (*M*)- and (*P*)-convention.

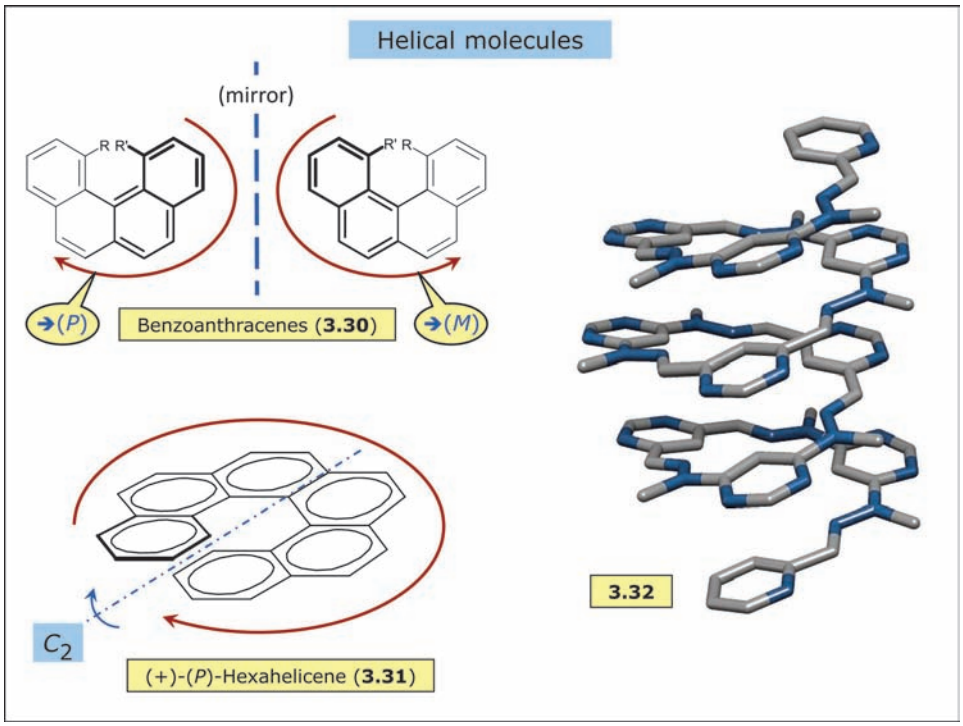

Fig. 3.12. Helical molecules can be rigid (configurational helices) or flexible (conformational helices; see *Parts 1* and *4* for the concept of *conformation*). An example of *configurational helices* is illustrated by *benzophenanthrenes* such as **3.30**, provided the substituents R and R′ are bulky enough to prevent the two terminal benzo rings from flipping over each other except under extreme conditions of temperature. Of marked interest to chemists is the class of polycyclic aromatic hydrocarbons known as *helicenes*, as exemplified here with *hexahelicene* (**3.31**) [1][37]. As can be seen, strong steric hindrance at the two terminal benzo rings twists the molecule into a helical structure. Hexahelicene has a C_2 axis of symmetry as its sole element of symmetry, and the barrier of racemization is *ca.* 150 kJ/mol. It has been resolved and its absolute configuration determined, the dextrorotatory enantiomer shown here having (*P*)-helicity.

A beautiful example of an oligomer crystallizing in the shape of a *conformational helix* is provided by the *foldamer* **3.32** [36][38]. *Foldamers* are discrete chain molecules or oligomers that adopt a secondary structure stabilized by noncovalent interactions [39]. Compound **3.32** is seen to contain two terminal pyridine rings and nine pyrimidine rings joined by –C=N–N(Me)– linkers. The molecule folds spontaneously into a $3^1/_3$-turn helix stabilized by π–π staking among its heterocycles. Each unit cell in the crystallized foldamer **3.32** contained one pair of enantiomeric helices, the form with (*P*)-configuration being shown here.

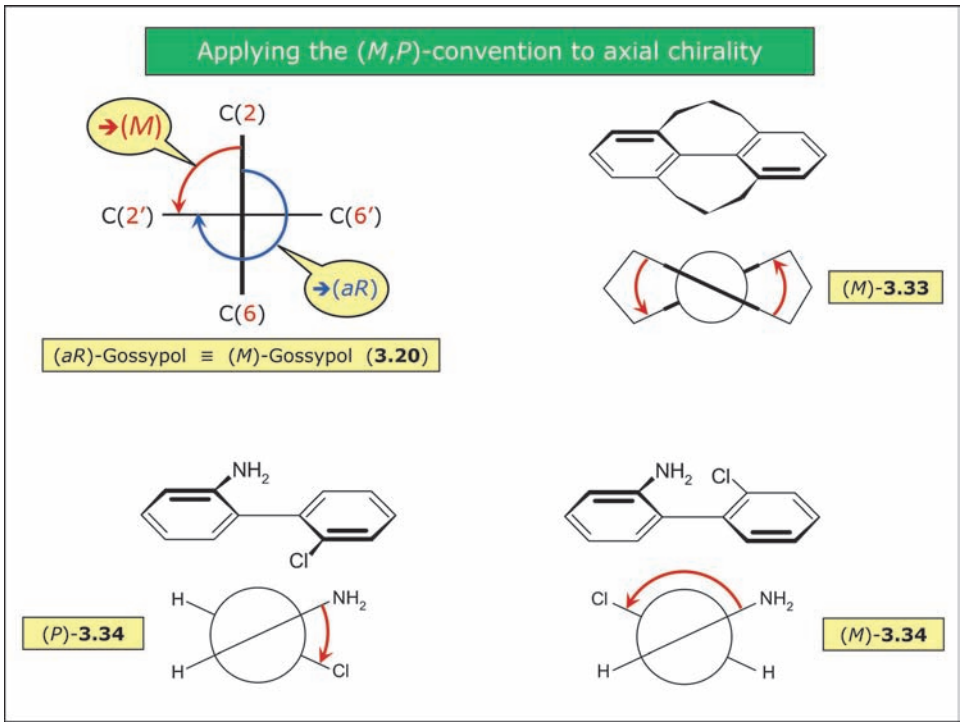

Fig. 3.13. As briefly mentioned in *Fig. 3.7*, the (*M*)- and (*P*)-convention is also applicable and proves quite useful to describe some cases of *axial chirality*; specifically, it was indicated that *(*aR*)-gossypol* (**3.20**) can also be described as (*M*)-gossypol. This assignment is based on the same projection as shown in *Figs. 3.3*, *3.4*, and *3.7*, and repeated here. What now counts as (*M*) or (*P*) is the *direction (counterclockwise or clockwise, resp.) of the shorter rotation* from the senior fiducial group in the front pair to the senior fiducial group in the rear pair. An application is presented with the configurationally stable *doubly bridged 1,1′-biphenyl* **3.33** having D_2 symmetry. Here, the four fiducial groups are equivalent, calling for additional rules in the use of the (*aR*)- and (*aS*)-convention and in arriving at the actual (*aR*)-configuration [1]. In contrast, viewing **3.33** along its axis allows the straightforward application of the helicity nomenclature and the ready assignment of the (*M*)-convention. In fact, as a consequence of their definitions, the (*aR*)-configuration systematically corresponds to the (*M*)-configuration, and (*aS*)- to the (*P*)-configuration.

Interestingly, the application of the helicity convention to axial chirality is possible not only for resolvable atropisomers, but also for *chiral conformers* as illustrated by the unresolvable *2-amino-2′-chlorobiphenyl* (**3.34**). Indeed, it would be inadequate to use the configurational descriptors (*R*) and (*S*) to specify the sense of chirality of the two conformers (*M*)-**3.34** and (*P*)-**3.34** shown.

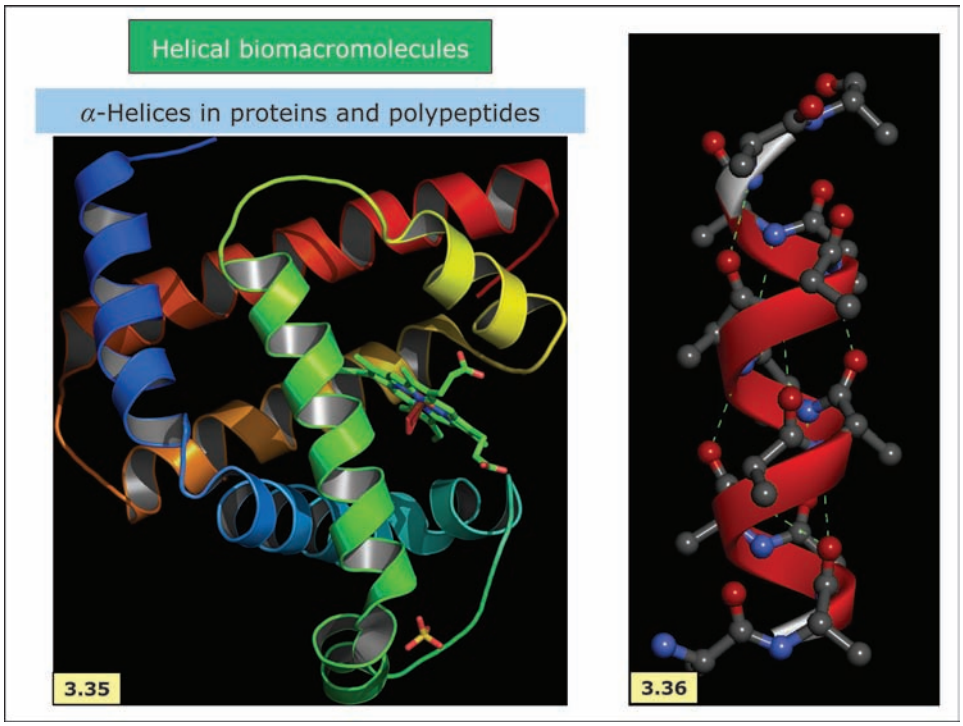

Fig. 3.14. Both natural and synthetic *polypeptides* provide notable examples of conformational helicity. Many proteins have significant portions of their chains stabilized in *α-helix conformations* [40–42]. An example is clearly seen in the 3D-structure of the protein *myoglobin* (**3.35**), which shows colored α-helices all with (*P*)-helicity [43][44]. The O_2-binding site, namely a heme group, is visible at mid-height on the right side of the picture. This protein is of historical interest in that it was the first to have its structure solved by X-ray crystallography.

An example of the intramolecular interactions stabilizing the *α-helical conformation* of polypeptides is illustrated here with a synthetic *poly-alanine* peptide (**3.36**; –NH–CH(CH_3)–CO–NH–CH(CH_3)–CO–) [45][2]). The red helix partly masking the Ala residues emphasizes the helical structure of the backbone of the polypeptide. C-Atoms are in grey, N in blue, and O in red, H-atoms are not shown. The side chains (*i.e.*, the Me groups symbolized by the H-suppressed, terminal C-atoms) are seen pointing outward. The helix itself is stabilized by *intramolecular H-bonds* (some of which are represented as green broken lines) between –NH– and –CO– groups in adjacent turns of the helix.

[2]) Picture courtesy of Prof. *Giulio Vistoli*, University of Milan.

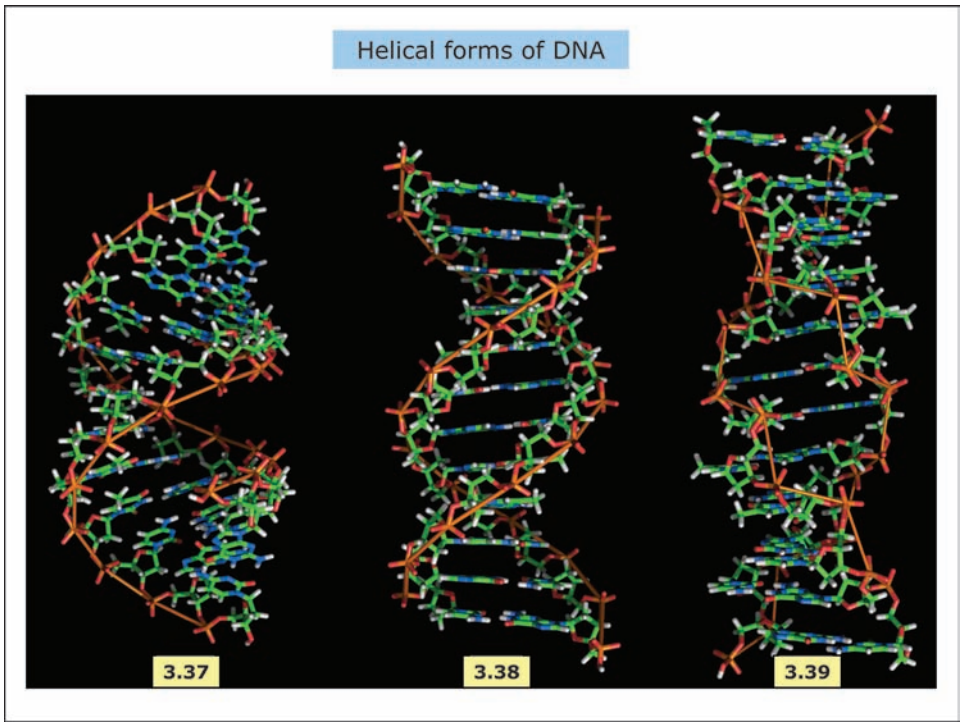

Fig. 3.15. *Deoxyribonucleic acid* (DNA) is an essential biomacromolecule whose functionality is critically dependent on its helical conformation, more precisely on its double-helix structure made of *two antiparallel strands*. The *backbone* of each strand consists of units called *nucleotides* and contains a *phosphate-deoxyribose moiety* to which a *purine or pyrimidine base* is attached. The phosphate-deoxyribose units are joined by ester bonds to form the backbone. The double helix is stabilized by *intermolecular (interstrand) H-bonds* between complementary bases, and by *intramolecular (intrastrand) stacking* of the bases.

Three helical structures are known for doubly stranded DNA, as shown here [46–50]. *B-DNA* (**3.38**) is the *most common form* in aqueous environments and in cells. But rather than being a single conformation, B-DNA has a marked degree of disorder and must, therefore, be seen as a conformational cluster. The minor groove is seen in the center and facing the viewer, while the major groove is seen at the top and bottom of the *Figure*.

A-DNA (**3.37**) dominates in dehydrated samples and resembles the structure of double-stranded RNA and DNA/RNA hybrids. Its minor groove is shallow and wider than in B-DNA, while the major groove is narrower and deeper. Both B-DNA and A-DNA are *right-handed helices*.

Z-DNA (**3.39**) is a rarer structure found in biochemically methylated DNA (of epigenetic significance) and in DNA bound to certain proteins. Interestingly, Z-DNA is a *left-handed helix*, an unusual structure that can be recognized by some specific proteins and may be involved in regulating transcription.

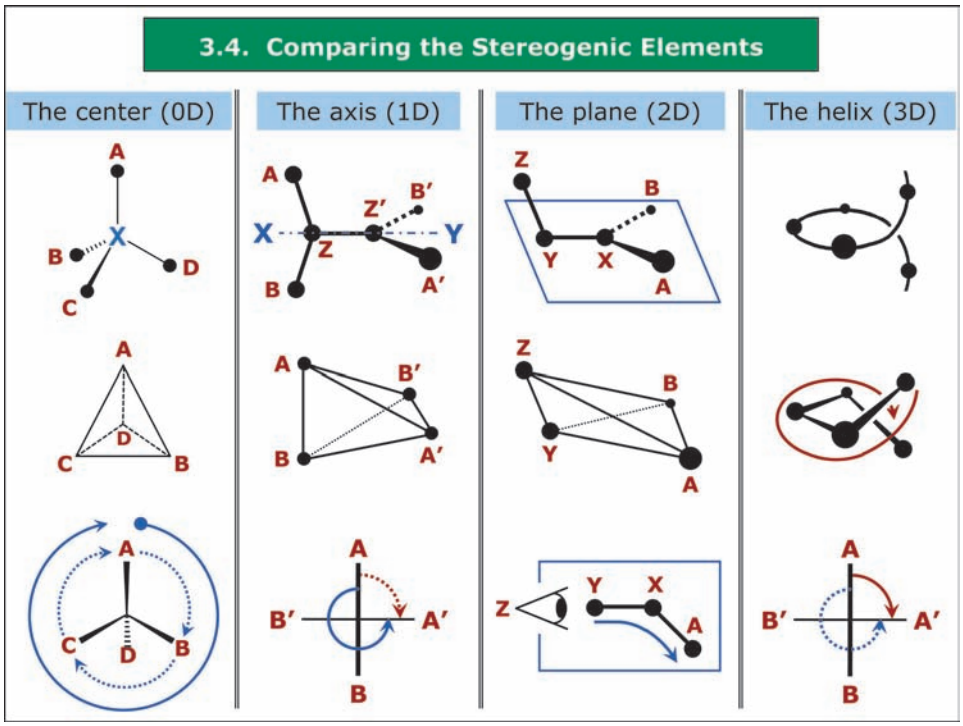

Fig. 3.16. Before moving on, it seems opportune to summarize the *various guises* under which chirality presents itself in chemistry. *Central chirality* involves an atom X at the center (*zero dimensionality*) of an asymmetric environment consisting of four different substituents or groups (A, B, C, and D) occupying the vertices of a virtual *tetrahedron*. The sense of chirality is established by placing the junior substituent D away from the viewer and following the path A > B > C.

Axial chirality can be related to central chirality by stretching the center of chirality X into an axis (*dimensionality 1*) of chirality X – Y. The condition for chirality is now for two atoms, Z and Z′, to lie on the axis and each to carry two different substituents or fiducial groups, A ≠ B and A′ ≠ B′, which occupy the vertices of a virtual *elongated tetrahedron*. Viewing the molecule from either end of the axis, one obtains a projection with the pair A–B perpendicular to A′–B′. The sense of rotation is given by the path (A > B) > (A′ > B′).

In turn, *planar chirality* (*dimensionality 2*) can be related to axial chirality. Five atoms suffice to characterize planar chirality, four of which (A, B, X, and Y) define the plane, while the pilot atom Z is the observer. The sense of rotation is defined by the path Y–X–A.

Helices are intrinsically chiral; their sense of *helicity* (*dimensionality 3*) is defined by the sense of rotation when moving along the helix and away from the viewer. This approach can also be followed in some cases of axial chirality, with (*aS*) corresponding to (*P*).

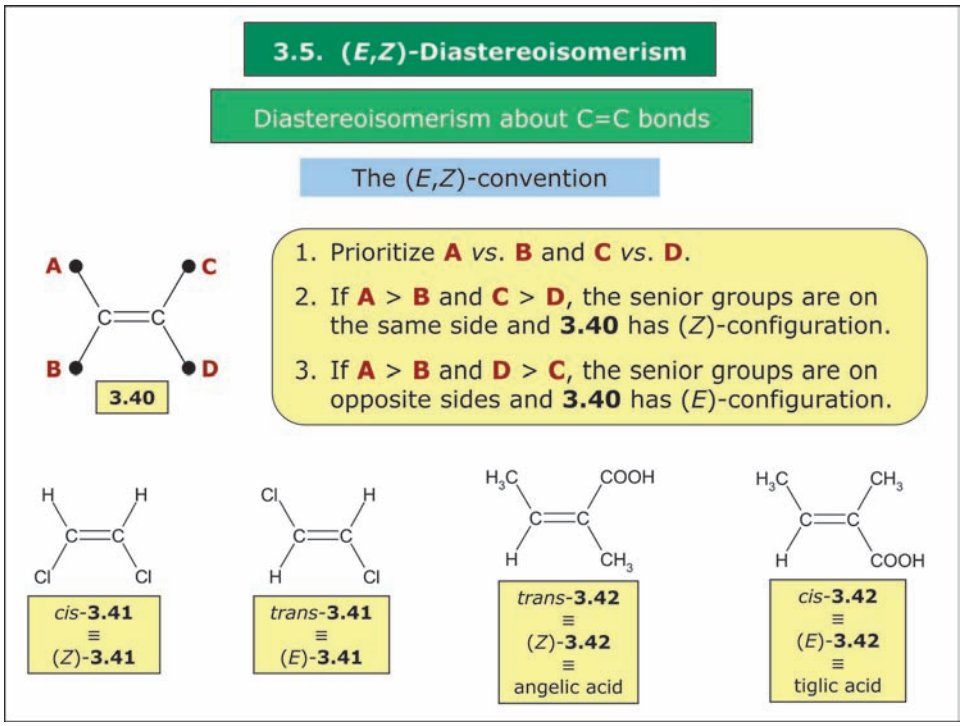

Fig. 3.17. Turning our attention to torsional *diastereoisomerism about double bonds*, we begin with *C=C bonds*, to conclude with C=N and N=N bonds [2–13][17–19]. Geometrically, the two doubly-linked atoms and the four atoms bound to them are coplanar, as illustrated by the *generic structure* **3.40**. The condition for stereoisomerism about double bonds is then for A ≠ B and C ≠ D.

The configurational description of diastereoisomers about double bonds was originally based on the *cis* and *trans* terminology. Assignment using this terminology is easy and unambiguous when B = D = H, as exemplified by *1,2-dichloroethene* (**3.41**) whose *cis*- and *trans*-diastereoisomers are shown. However, confusion occurs when this condition is not met, as illustrated with *2-methylbut-2-enoic acid* (**3.42**). In such a case, it was customary to define a *cis*- and *trans*-configuration based on the relative position of the two identical substituents, here the Me groups, again raising ambiguities. A further problem with the *cis*/*trans* terminology is a possible confusion with *cis*/*trans* isomerism occurring in saturated cyclic systems (see *Part 4*).

The solution came with the *sequence rule*, as outlined in the *Figure*. The (*E*) and (*Z*) stereodescriptors stand for *entgegen* (German opposite) and *zusammen* (together), respectively [51][52]. Note that our examples were chosen to demonstrate that *cis* is not necessarily synonymous with (*Z*), nor *trans* with (*E*) [9–11].

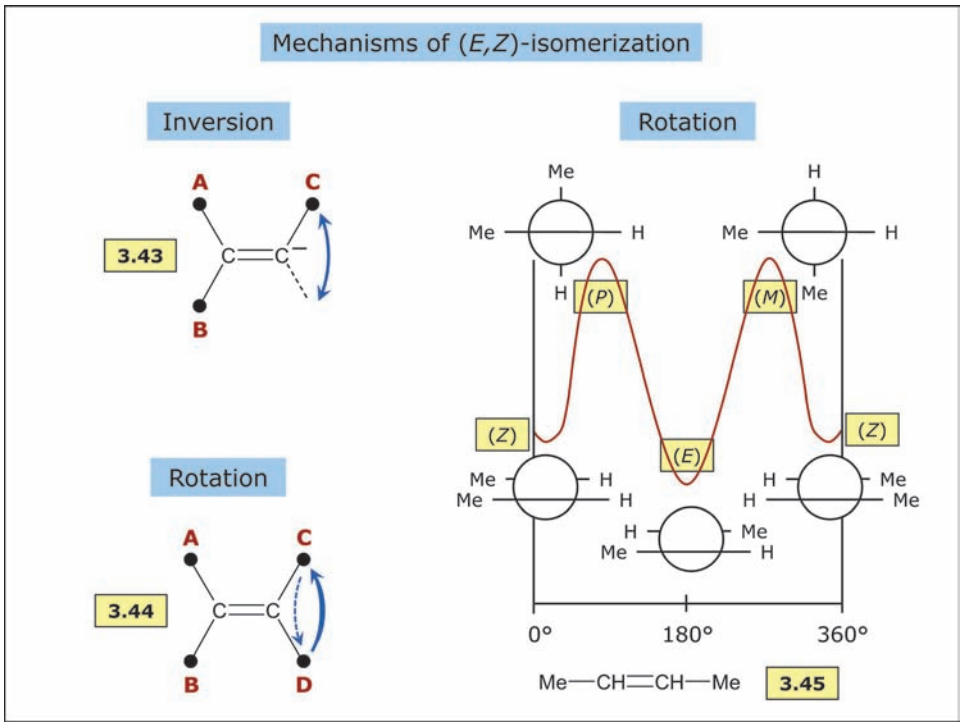

Fig. 3.18. (*E*,*Z*)-Diastereoisomerism resorts to *configurational isomerism*, because the isomers are separated by a high-energy barrier. Furthermore, the (*E*)- and (*Z*)-diastereoisomers do not have the same energy level. We consider first the *mechanisms* of (*E*,*Z*)-isomerization [8][20][53] before briefly comparing the *energy levels* of the diastereoisomers.

The two major mechanisms of stereoisomerization at double bonds are *inversion* and *rotation*. In the case of C=C bonds, *inversion* must be preceded by the *homolytic* or *heterolytic* cleavage of a substituent, followed by the motion of the remaining geminal substituent within the molecular plane as shown in **3.43**. This cleavage is obviously a high-energy process, while the inversion process itself is a markedly lower-energy one. The other main mechanism of isomerization occurs by *rotation about the double bond* as shown in **3.44**. The general curve of torsional strain variation in olefins is illustrated qualitatively for *but-2-ene* (**3.45**). The two *transition states* are chiral (identical energy levels), and have (*P*)- and (*M*)-helicity, respectively. The two *ground states* are the (*Z*)- and (*E*)-diastereoisomers, respectively, the latter being more stable than the former by *ca.* 4 kJ/mol [8][54]. Through-bond and through-space attractive orbital interactions have, however, been found in many cases to stabilize slightly the (*Z*)- over the (*E*)-isomer [54–57].

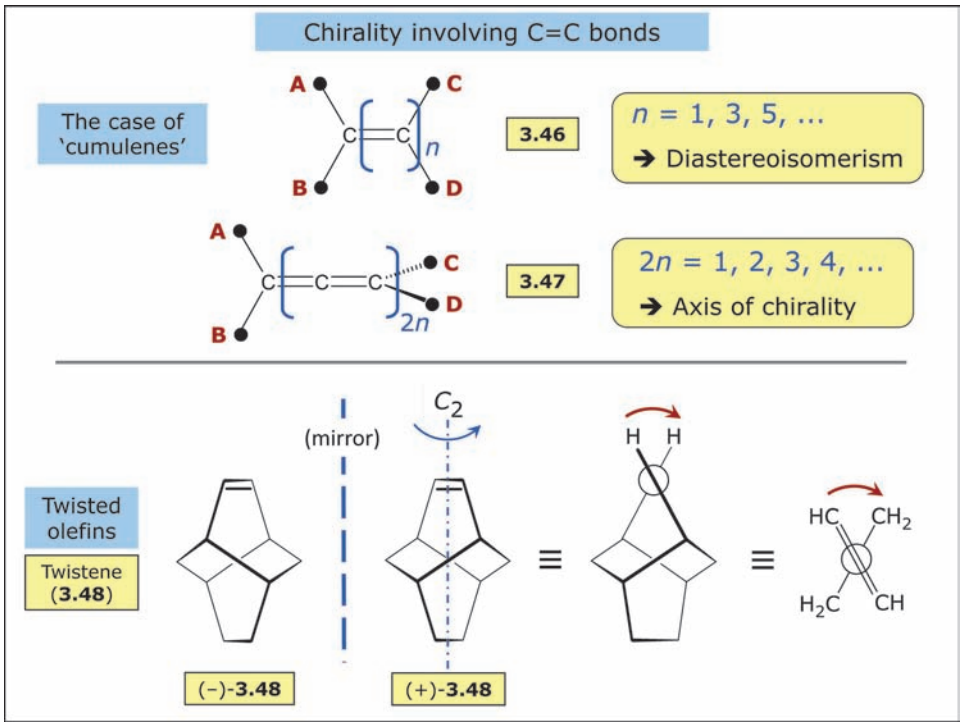

Fig. 3.19. *Figs. 3.17* and *3.18* may leave the impression that C=C bonds have no role to play in chirality. This would be a premature conclusion, however, as already documented in *Fig. 3.4* with *allenes* (**3.6**). Indeed, allenes are a special case of *cumulenes*, namely compounds containing a chain of two or more *cumulative* (consecutive) C=C bonds. Compounds with an *odd number* of cumulative double bonds (*i.e.*, **3.46**; including $n = 1$ which are simply ethenes) occur as (*E*)- and (*Z*)-diastereoisomers when A ≠ B and C ≠ D. In contrast, compounds with an *even number* of cumulative C=C bonds (*i.e.*, **3.47**) have axial chirality when A ≠ B and C ≠ D [55]. Thus, when the condition A ≠ B and C ≠ D is fulfilled, the *axis of stereoisomerism* in cumulenes will be one of *diastereoisomerism* or *enantiomerism* depending on the coplanarity or non-coplanarity of A and B *vs.* C and D.

There is a second possibility for C=C bonds and their substituent atoms to deviate from planarity, which occurs in *strained* or *twisted alkenes* [58–60]. Such compounds are aptly exemplified by *tricyclo[4.4.0.0^{3,8}]dec-4-ene* (*twistene*; **3.48**) [61][62]. The (+)-enantiomer has *(*R*)-configuration* on its four tertiary C-atoms and *(*P*)-helicity* at its twisted C=C bond, as seen and illustrated when viewing the molecule along the axis of the C=C bond and along the C_2 axis. Note that, in such a strained molecule, no stereogenic element can be inverted independently of the others. In other words, there can exist only two stereoisomers, these being enantiomers with opposite configuration in all their stereogenic elements.

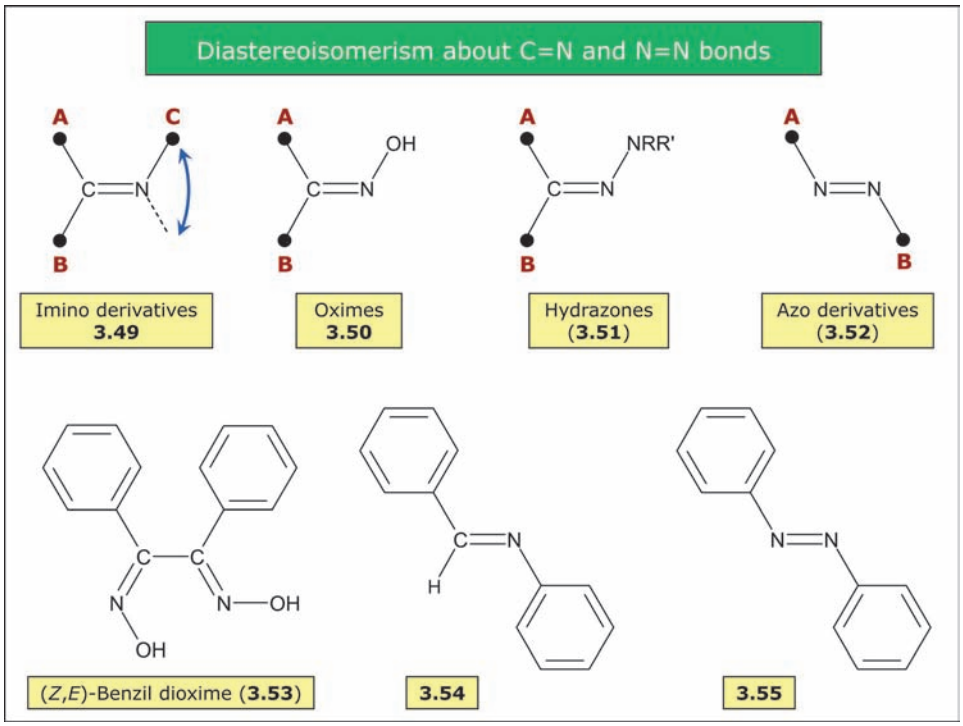

Fig. 3.20. The configuration at stereogenic *C=N and N=N groups*, namely imino and azo derivatives in their broadest sense, was previously described by the prefixes *syn* and *anti*. But, like the *cis* and *trans* terminology, this lacks clarity and has been replaced by the (*E*)- and (*Z*)-convention [11–13]. Thus, *imino derivatives*, **3.49**, will be of (*Z*)-configuration if A > B, as will the subclasses of *oximes*, **3.50**, and *hydrazones*, **3.51**; whereas the *generic azo structure* **3.52** is (*E*)-configured. An interesting application is provided by *benzil dioxime* (**3.53**); its description with the *syn*- and *anti*-terminology would have led to controversy, whereas describing it as (*Z*,*E*) is unambiguous (a subrule states that (*Z*) must be indicated before (*E*)).

Normally, the (*E*)-isomers of *imino and azo derivatives* are thermodynamically preferred over the (*Z*)-isomers, but many factors such as resonance stabilization, steric repulsion, and nonbonded attractive or repulsive interactions play a role. Imino and azo derivatives differ from alkenes in that the inversion process does not require cleavage of a bond. Thus, *methylene imine*, **3.49** (A = B = C = H), has a barrier of rotation of *ca.* 250 kJ/mol and a barrier of inversion approximately twofold lower. Inversion is thus strongly favored over rotation, with a lower barrier of isomerization compared to ethylenes. Nevertheless, the effects of substituents and solvent in the two processes can be markedly different, meaning that there may be a number of exceptions to any attempt at generalization. However, as a general rule it is recognized that, in many *imines*, the barrier to isomerization lies in the range of 80 to 130 kJ/mol [6][7][20][63][64]. Electronegative substituents on the N-atom (*e.g.*, oximes and hydrazones) increase stability toward inversion. Similarly, *azo compounds* are slightly stabilized against inversion compared to the corresponding imino compounds. This was seen with *azobenzene* (**3.55**) compared to the *analogous imine*, **3.54**, which have barriers of isomerization of *ca.* 95 and 75 kJ/mol, respectively.

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