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Stereoisomerism and Conformational Directionality (Prelog Lecture)

Kurt Mislow*

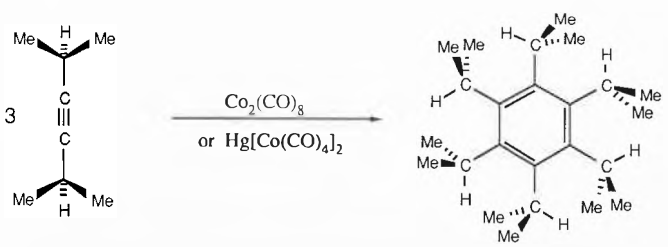
Dedicated to Professor Vladimir Prelog on the occasion of his 80th birthday

The inaugural Prelog Lecture provides me with a unique opportunity to pay tribute to a great scientist, teacher, and friend. As I hope to show, the work of Vladimir Prelog is profoundly relevant to the work that I want to describe today.

Cyclic Directionality

Our work had its inception in the study of a remarkable molecule, hexaisopropylbenzene. According to space-filling models, and as confirmed by single-crystal X-ray analysis[1], the six isopropyl groups are tightly meshed to give a structure with approximate C_{6h} symmetry in which the isopropyl groups are rigidly locked in place. A noteworthy feature of this structure is the directionality imparted to the system by the six gear-locked groups. In the words of *Arnett* and *Bollinger*[2] and of *Hopff* and *Gati*[3], who first reported the synthesis of this compound by trimerization of diisopropylacetylene (Scheme 1), «... because of the requirement that each isopropyl group exactly interlock with its neighbors on either side ... all of the groups are pointed in the same direction, clockwise or counterclockwise, around the perimeter of the ring»[2], and «... Die tertiären Wasserstoffatome sitzen alle in der Ebene des Kerns und sind um diesen so ausgerichtet, dass sie der Molekel eine schaufelradähnliche Form verleihen»[3].

Scheme 1



In hexaisopropylbenzene, the cyclic directionality is conformational in origin. Cyclic directionality is more usually associated with the sequential order of bonded atoms of a ring, i.e., with the constitution of the ring. 2,5-Piperazinedione is an example of a directed ring. This type of cyclic directionality was first described by *Prelog* and *Gerlach* in a paper[4] that appeared in the same year as *Arnett* and *Bollinger*'s paper[2] on hexaisopropylbenzene. It would clearly be useful to have a general definition of directed and undirected cycles that would encompass ring systems as diverse as hexaisopropylbenzene and 2,5-piperazinedione. We therefore propose the following definition[5], which is based on the symmetry of the molecular model:

A *cycle* is defined by three or more noncollinear points in the molecular model. A ring is a special case of a cycle. A cycle is *undirected* if it is bisected by a molecular C_{2n} axis or by a molecular σ plane. Otherwise it is *directed:* this is the necessary and sufficient condition for cyclic directionality.

Several comments are in order. First, this definition applies to nonplanar cycles, such as cyclohexane, as well as to planar ones, and to cycles that are not rings. Second, whether or not a given cycle is directed in a conformationally mobile sys-

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tem may depend on the timescale of observation, since it is the timescale that determines the symmetry of the molecular model. For example, the cyclohexane ring in e,e- or a,a-*trans*-1,2-dimethylcyclohexane is undirected since it is bisected by a C_2 axis on any timescale. However, the cyclohexane ring in a,e-*cis*-1,2-dimethylcyclohexane is undirected only on the timescale of rapid chair inversion, where the molecular model has C_s symmetry and the σ plane bisects the ring: on the timescale of slow inversion, the molecular model has C_1 symmetry and the ring is therefore directed. Third, the same molecule may contain both directed and undirected cycles. For example, the six-membered ring in 1-chlorobicyclo[2.2.1]heptane is undirected because it is bisected by the molecular σ plane, whereas the two enantiotopic five-membered rings are directed.

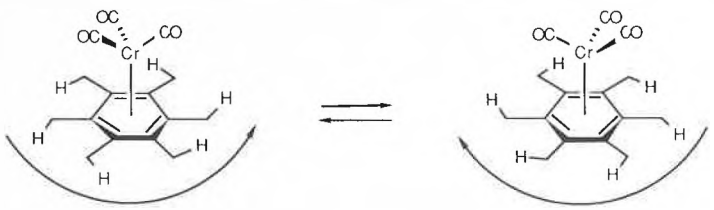


Fig. 1. Schematic representation of the equilibrium between enantiomeric tricarbonylchromium π complexes of hexaisopropylbenzene (hypothetical) or hexakis(dimethylsilyl)-benzene (observed). Enantiomerization, which takes place by internal rotation of the isopropyl or dimethylsilyl side chains, is assumed to be slow compared to rotation of the tricarbonylchromium tripod about the chromium-arene axis. The sense of directionality of the arene ligand is symbolized by the curved arrows and is defined by an arbitrary convention in which priority is given to the orientation of the tertiary hydrogen atoms.

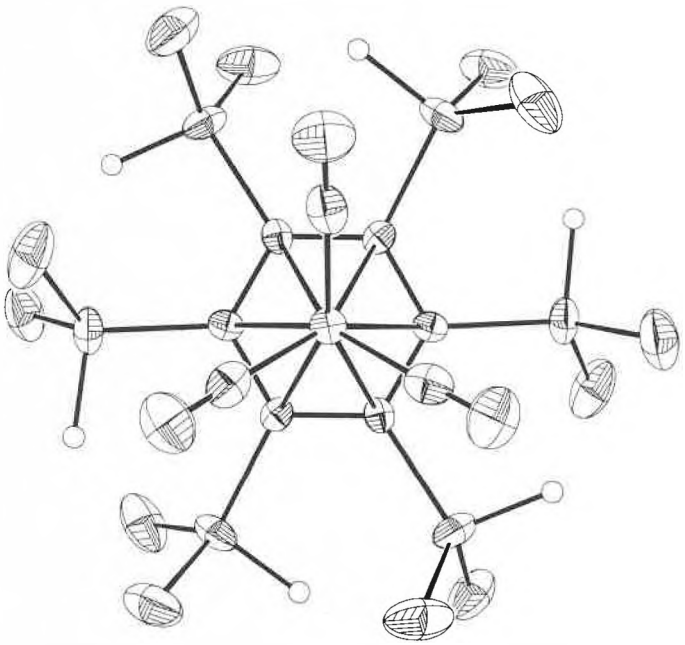


Fig. 2. One enantiomer of tricarbonyl[hexakis(dimethylsilyl)benzene]chromium, viewed along the threefold axis in the crystal. Methyl hydrogens are suppressed for clarity.

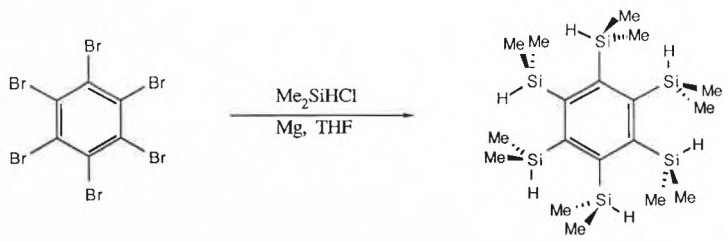
Conformational Enantiomerism in Arene π Complexes

Let us now imagine a hypothetical derivative of hexaisopropylbenzene in which the two faces are rendered nonequivalent by π complexation with tricarbonylchromium (Fig. 1). The effect of such complexation is to destroy plane and center of symmetry, thus yielding a chiral structure and therefore two enantiomers. The *sense* of cyclic directionality is opposite in the ligand ring systems of the two enantiomers, and the directed cycle in the complex thus serves the function of a stereogenic unit. Specification of the sense of cyclic directionality requires a reference point above or below the directed cycle (the «spectator point»): this reference point determines the side or face from which the cycle is being viewed. In the example under discussion, the sense of cyclic directionality in the arene ligand can be defined by use of the chromium atom as the spectator point: in one enantiomer the sense is clockwise, and in the other counterclockwise. Of course what is called «clockwise» and «counterclockwise» depends on some arbitrary convention: if, starting from the methine carbons, priority is given to the methine (tertiary) hydrogens, as in Fig. 1, the direction set is opposite to the one in which priority is given to the methyl groups. It will be immediately obvious that what has just been described is analogous to the specification of *R* and *S* configurations at stereocenters of the type *Cabcd* by the Cahn-Ingold-Prelog rules of stereochemical nomenclature, where the sense of direction (clockwise vs. counterclockwise) of the cycle *abc* is defined by the view from an external point on the side remote from the fourth ligand, *d*[6].

While hexaisopropylbenzene itself resists π complexation, we found that the closely related hexakis(dimethylsilyl)benzene, which is easily prepared (Scheme 2)[7] and which also has a gear-meshed C_{6h} structure[8], is a good deal less congested and therefore readily forms a tricarbonylchromium complex[8]. The variable-temperature ^{1}H-NMR spectrum of this complex provides evidence for a site-exchange process in which the two enantiomers undergo interconversion by internal rotation of the dimethylsilyl side chains, with a concomitant reversal in the sense of cyclic directionality. As might be expected for the less crowded silicon analog, the experimentally determined barrier to rotation, $\Delta G^{\ddagger} = 14.2$ kcal mol^{-1}, is a good deal lower than the calculated (MM2) barrier to rotation of isopropyl groups in hexaisopropylbenzene (ca. 35 kcal mol^{-1})[1].

The π complex crystallizes in the space group $R\bar{3}$, with the enantiomeric molecules stacked along a threefold axis[9]. If the enantiomer in Fig. 2 is viewed along this axis, and if, starting from the silicon atom, priority is given to the attached hydrogens, the sense of cyclic directionality of the arene ring is counterclockwise as seen from the perspective of the chromium atom. It should be noted that the three carbonyl carbons and the three carbonyl oxygens also constitute directed cycles according to our definition. However, the directionality of these cycles is wholly dependent on that

Scheme 2



of the ligated hexakis(dimethylsilyl)benzene: these cycles would be undirected if the ligand were benzene.

The chirotopic[10] tricarbonylchromium fragment in the π complex is stereochemically similar to a chirotopic methyl group located on a threefold axis in a chiral molecule, such as the methyl group in the trisulfoxide of 4-methyl-2,6,7-trithiabicyclo-[2.2.2]octane[11]: in both cases the local C_3 symmetry and chirotopicity of the tricarbonylchromium or methyl rotor is maintained even under conditions of rapid internal rotation about the C_3 axis. In a recent computational study of D_3-ethane, it was shown that although the local symmetry of such chirotopic methyl groups cannot be expressed in the δ distribution of nuclear positions, the local chirality manifests itself in the electron distribution[12]. This effect can be experimentally demonstrated in the tricarbonylchromium π complex of hexakis(dimethylsilyl)benzene: an electron density section through the three carbonyl carbons (Fig. 3) clearly reveals the triskelion character of the contour plots, consistent with the chirality of the electron distribution. The same effect is seen in an electron density section through the chirotopic chromium atom in a plane perpendicular to the threefold axis (Fig. 4).

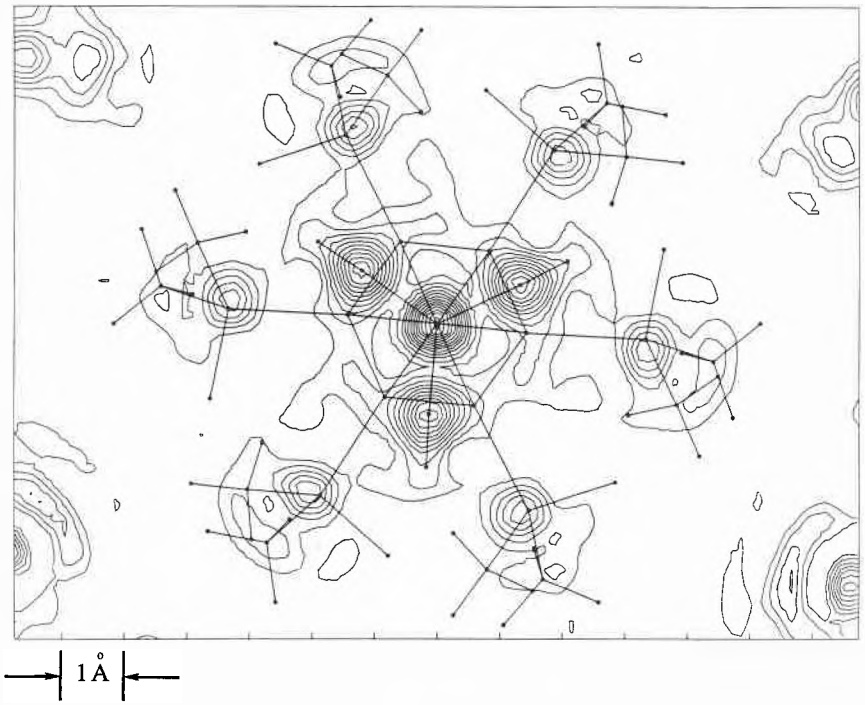


Fig 3. Electron density section through the three carbonyl carbons of tricarbonyl[hexakis-(dimethylsilyl)benzene]chromium, viewed along the threefold axis. The first 15 contours (0.0–7.0 e Å^{-3}) are plotted at 0.5 e Å^{-3} intervals.

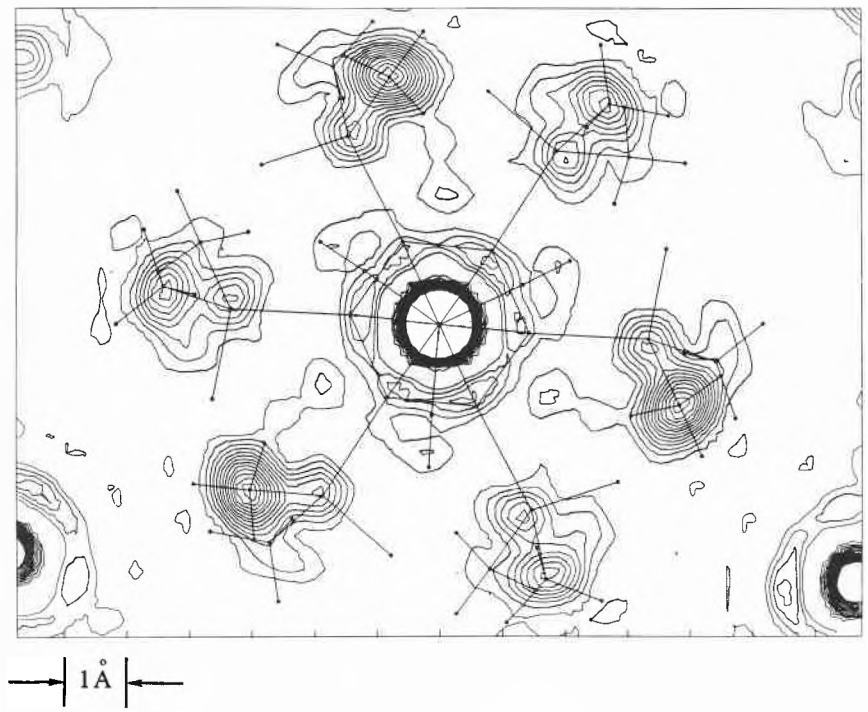


Fig. 4. Electron density section through the chromium atom of tricarbonyl[hexakis(dimethylsilyl)benzene]chromium, viewed along the threefold axis. The first 15 contours (0.0–7.0 e Å^{-3}) are plotted at 0.5 e Å^{-3} intervals. Contours greater than 7.0 e Å^{-3} in the region of the heavy atoms are not shown.

Stereoisomerism in Molecules with Gear-Meshed Dichloromethyl Groups

We now turn to a discussion of cyclic directionality in gear-meshed molecules related to hexaisopropylbenzene in which both of the methyls in the isopropyl groups are replaced by chlorine atoms. Such compounds are synthesized with exceptional ease by photochlorination of the appropriate hydrocarbon precursors. A striking example is hexakis(dichloromethyl)benzene, obtained by photochlorination of hexamethylbenzene (Scheme 3)[13]. The steric requirements of CH_3 and Cl are quite similar[14], so that ground state conformational properties are not significantly affected. This is clearly seen in the isomorphism of hexaisopropylbenzene and hexakis(dichloromethyl)benzene. Both compounds crystallize in the triclinic system, space group $P\bar{1}$, with a single centrosymmetric molecule of approximate C_{6h} symmetry in the unit cell[1,15]. The cell parameters are much the same (Table 1), and even the orientational disorder observed in the two compounds is strikingly similar, with major and minor populations of the rings in a roughly 2:1 ratio (2.075:1 for hexaisopropylbenzene and 1.826:1 for hexakis-(dichloromethyl)benzene).

Scheme 3

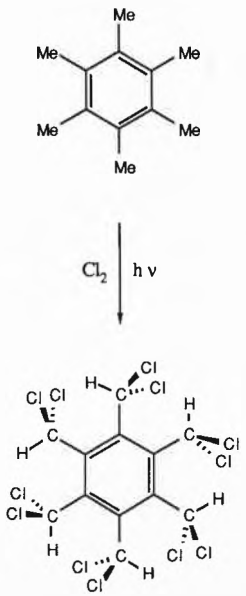


Table 1. Unit cell parameters for two hexasubstituted benzenes (space group $P\bar{1}$, $Z = 1$).

Parameter	Hexaisopropylbenzene[1]	Hexakis(dichloromethyl)benzene[15]
a	6.400(2) Å	6.255(2) Å
b	9.943(3) Å	9.751(4) Å
c	10.223(2) Å	9.773(4) Å
α	117.79(2)°	116.34(3)°
β	94.78(3)°	94.98(3)°
γ	105.58(3)°	108.20(3)°
V	536.7 Å^3	488.4 Å^3

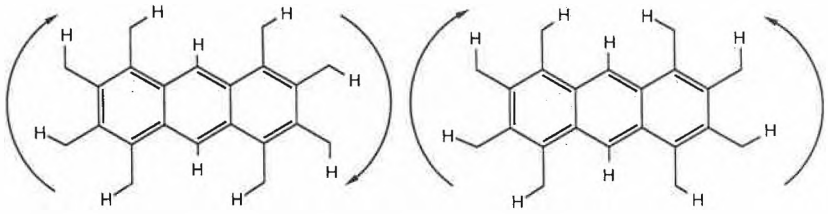


Fig. 5. Two conformational diastereomers of 1,2,3,4,5,6,7,8-octakis(dichloromethyl)-anthracene. Chlorine atoms are suppressed for clarity. – Left: the two sets of four dichloromethyl groups are homodirectional. – Right: the two sets of four dichloromethyl groups are heterodirectional. The curved arrows symbolize sense of directionality according to the convention in Fig. 1.

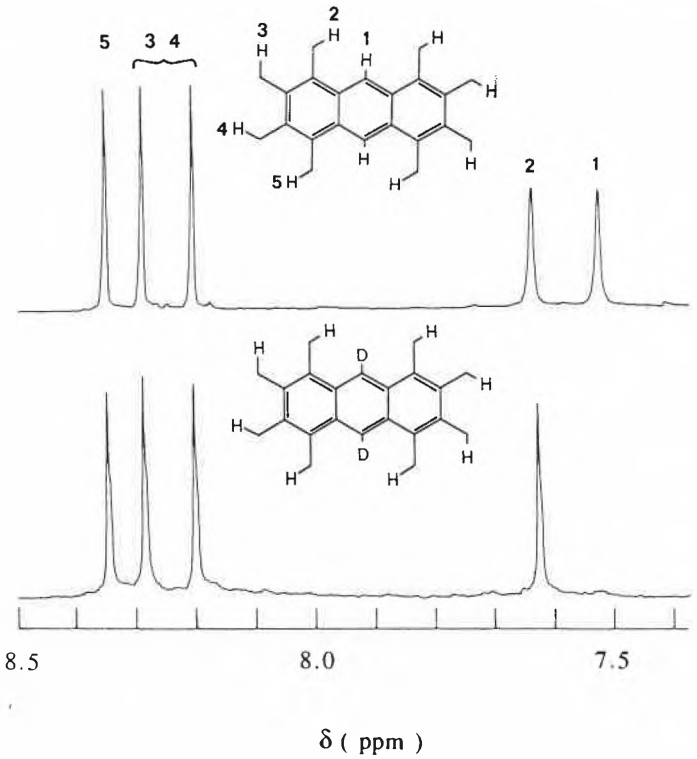


Fig. 6. Top: 250 MHz ^{1}H-NMR spectrum of 1,2,3,4,5,6,7,8-octakis(dichloromethyl)-anthracene in [$^2H_2$]tetrachloroethane at ambient temperature. – Bottom: the corresponding spectrum of the same compound with deuterium atoms in the 9- and 10-positions.

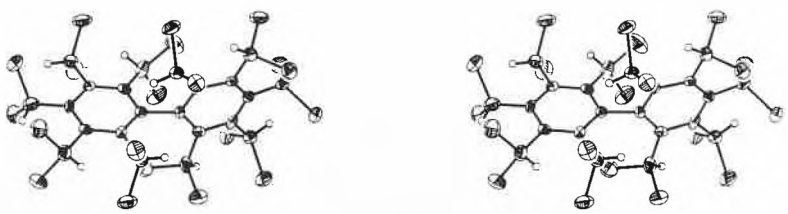


Fig. 7. Stereoview of the X-ray structure of decakis(dichloromethyl)biphenyl.

Photochlorination of 1,2,3,4,5,6,7,8-octamethylanthracene yielded 1,2,3,4,5,6,7,-8-octakis(dichloromethyl)anthracene[15], a molecule that contains two sets of four dichloromethyl groups, one on each of the two terminal rings. Assuming that the two rings are essentially coplanar, a variety of diastereomeric structures are conceivable. Among these are the two shown in Fig. 5, in which the two sets of four gear-meshed dichloromethyl groups are either homodirectional (idealized C_{2h} symmetry) or heterodirectional (idealized C_{2v} symmetry). According to empirical force field calculations (MMP2) the structure with homodirectional groups is more stable by ca. 2 kcal mol^{-1}. The room-temperature ^{1}H-NMR spectrum was found to consist of five singlets in the region between $\delta = 7.5$ and 8.4 (Fig. 6). Barring accidental isochrony, this observation is consistent only with the presence of the homodirectional isomer. The two upfield signals were assigned to H(1) and H(2), the former on the basis of the effect of deuterium substitution at the 9- and 10-positions of the anthracene nucleus on the ^{1}H-NMR spectrum (Fig. 6) and the latter on the basis of its chemical shift – it is the only one of the four dichloromethyl protons which is not situated in a strongly deshielding region – and of an NOE difference spectrum. The three remaining protons are deshielded because they are tucked into the cleft formed by the two chlorines in the neighboring dichloromethyl groups. Application of the saturation spin transfer method permitted the assignment of the signal corresponding to H(5), the proton with which H(2) is involved in dynamic mutual exchange, and also yielded a barrier for topomerization, $\Delta G^{\neq} = 22$ kcal mol^{-1} at 391 K.

Photochlorination of decamethylbiphenyl afforded decakis(dichloromethyl)-biphenyl[16], in which each of the two rings carries a set of five gear-meshed dichloromethyl groups. The compound crystallizes in the monoclinic system, space group $P2_1/n$; the planes of the two rings are essentially perpendicular to one another, and the molecule has approximate C_2 symmetry (Fig. 7). When the rings in the idealized C_2 structure are viewed from any point along the C_2 axis, the two sets within each enantiomer are seen to be homodirectional by internal (intramolecular) comparison, whereas the enantiomeric sets are seen to be heterodirectional by external (intermolecular) comparison (Fig. 8). The room-temperature ^{1}H-NMR spectrum featured the expected five signals (Fig. 8). The most upfield signal was assigned to the unique proton which, unlike the other four, experiences the shielding effect of a neighboring benzene ring instead of the deshielding effect of a dichloromethyl gear notch (Fig. 7). It is interesting to note that interconversion of the enantiomeric decakis(dichloromethyl)biphenyls may in principle proceed by either one of two independent mechanisms: by rotation about the central biphenyl bond or by rotation about the

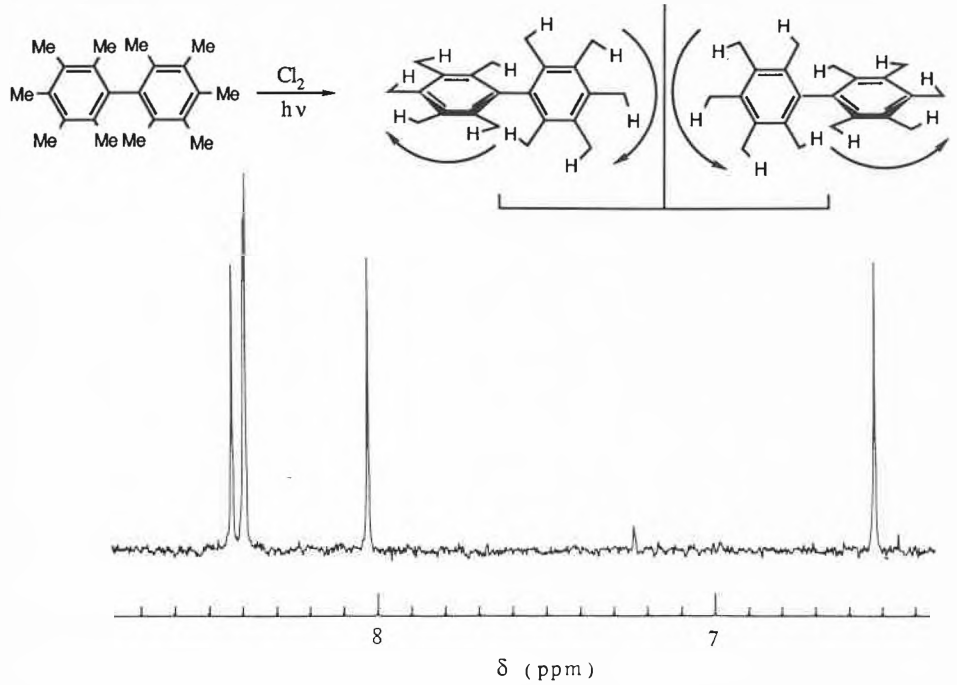


Fig. 8. Top: photochlorination of decamethylbiphenyl to decakis(dichloromethyl)biphenyl. The enantiomers are related by the vertical mirror line, and the sense of directionality of the rings is symbolized by curved arrows according to the convention in Fig. 1. – Bottom: 250 MHz ^{1}H-NMR spectrum of the racemic mixture in tetrachloromethane at ambient temperature.

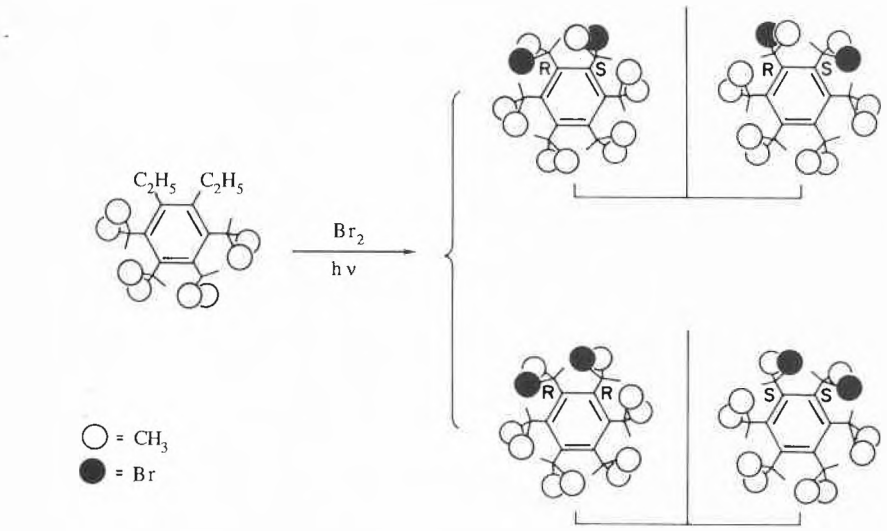


Fig. 9. Photobromination of 1,2-diethyl-3,4,5,6-tetraisopropylbenzene to a diastereomeric mixture of 1,2-bis(1′-bromoethyl)-3,4,5,6-tetraisopropylbenzene. Filled and open circles represent bromine atoms and methyl groups, respectively. The tertiary hydrogens are indicated by short lines. Enantiomers are related by vertical mirror lines. – Top: the (1′S,2′R)- and (1′R,2′S)-enantiomer. – Bottom: the (1′R,2′R)- and (1′S,2′S)-enantiomer.

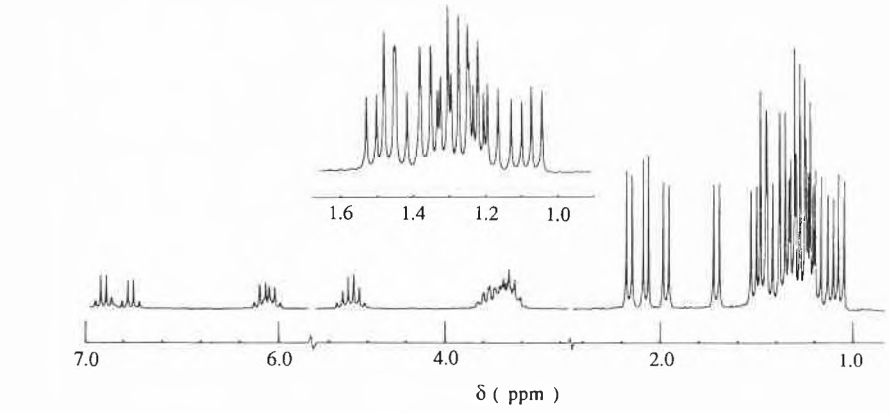


Fig. 10. 250 MHz ^{1}H-NMR spectrum of the photobromination product (Fig. 9) in [$^2H_6$]benzene at ambient temperature.

benzene-dichloromethyl bonds in one of the rings. The sense of directionality of the rings is reversed by either one of these two conformational processes.

Conformational Cycloenantiomerism

1,2-Bis(1′-bromoethyl)-3,4,5,6-tetraisopropylbenzene, prepared by photobromination of 1,2-diethyl-3,4,5,6-tetraisopropylbenzene, is a gear-meshed molecule in which one methyl group in each of two neighboring isopropyls in hexaisopropylbenzene is replaced by a bromine atom (Fig. 9)[5]. Each of the two α-bromoethyl groups contains a stereocenter, and two diastereomers are therefore expected. One of these (Fig. 9, top) consists of a pair of enantiomers which owe their existence to the conformational rigidity of the system and which are in principle interconvertible by rotation about the benzene–(α-bromoethyl) and benzene–isopropyl bonds. That is, under conditions of rapid internal rotation this diastereomer is a *meso*-compound. The other pair (Fig. 9, bottom) does not depend for its existence on conformational factors: each enantiomer retains its configurational identity even under conditions of rapid internal rotation. The product of bromination consists of an approximately equimolar mixture of the two diastereomers, as judged by the relative intensities of the four methyl signals in the α-bromoethyl region (δ = 1.7–2.2) of the ^{1}H-NMR spectrum (Fig. 10).

The diastereomer that gives rise to the two downfield doublets at δ = 2.06 and 2.15 was isolated from the mixture and identified as the one shown at the top of Fig. 9 on the basis of aromatic solvent-induced shifts. This diastereomer possesses a structural feature that we have not commented on so far: when models of the two enantiomers are reflected through a mirror plane perpendicular to the planes of the benzene rings, the sense of cyclic directionality of the aromatic ring, arbitrarily defined by the orientation of the methine hydrogens, is reversed, while the cyclic pattern of configurational descriptors (*R* and *S*) of the stereocenters remains unaffected. This property is not confined to this particular pair of enantiomers but is shared by the six enantiomeric pairs whose substitution patterns are shown in Fig. 11. Of particular interest is the observation that the relationship between the enantiomers of the pair with six stereocenters (Fig. 11, pair **f**) bears a striking resemblance to the relationship between the enantiomers of cyclohexaalanyl (Fig. 12): here too, reflection through a mirror plane perpendicular to the average ring planes reverses the sense of ring directionality, as defined by the amide bond vectors, while the cyclic pattern of configurational descriptors is left undisturbed. By analogy to the cyclohexaalanyls, which were classified as «cycloenantiomers» by *Prelog* and *Gerlach*[4], it seems appropriate to designate the enantiomers of pair **f** as «conformational cycloenantiomers»[5,17]. The same description

may be attached to the other five pairs in Fig. 11, including the one (pair **a**) that has been experimentally realized.

An obvious distinction between conformational cycloenantiomers and cycloenantiomers of the type exemplified by cyclohexaalanyl is that the former are in principle interconvertible by internal rotation, whereas bonds must be broken to interconvert the latter.

It is instructive to look at the enantiomers of pair **f** in a different light. Imagine three slices through the molecule, one in the plane of the ring and the other two above and below the middle slice, with the outer two slices containing representative portions of the CH_3 or Br substituents. If the sense of cyclic directionality of the arene ring is defined as before, and if the sense of cyclic directionality of the two substituent patterns is also defined by some arbitrary convention, then the three-tiered cyclic directionality can be represented schematically by a triplet of curved arrows (Fig. 13). Precisely the same analysis is applicable to conventional molecules of the type exemplified by the enantiomeric 2,3,4-trihydroxyglutaric acids, even though they bear no obvious chemical resemblance to pair **f** (Fig. 14). Here, too, three-tiered cyclic directionality obtains, with one cycle each for the three molecular fragments containing C(2), C(3), and C(4). In both systems the two outer cycles are diastereotopic.

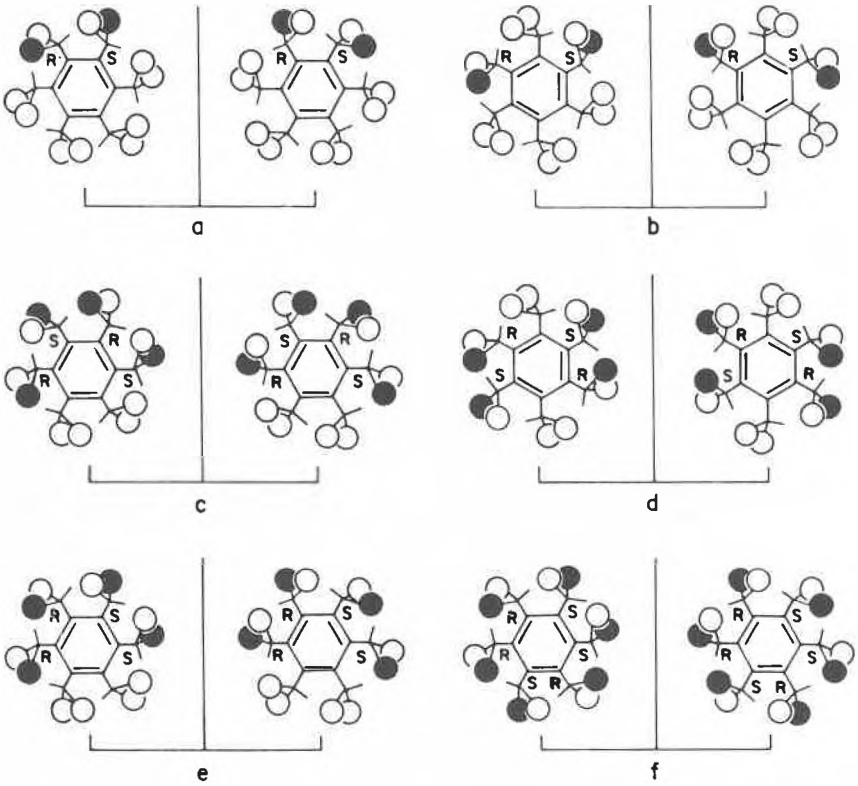


Fig. 11. Six racemic pairs of compounds derived from hexaisopropylbenzene in which two, four, or six methyl groups (open circles) are replaced by halogen atoms (filled circles) and in which the cyclic pattern of configurational descriptors (R and S) of the stereocenters remains unchanged upon reflection through a mirror plane (vertical line) at right angles to the benzene plane.

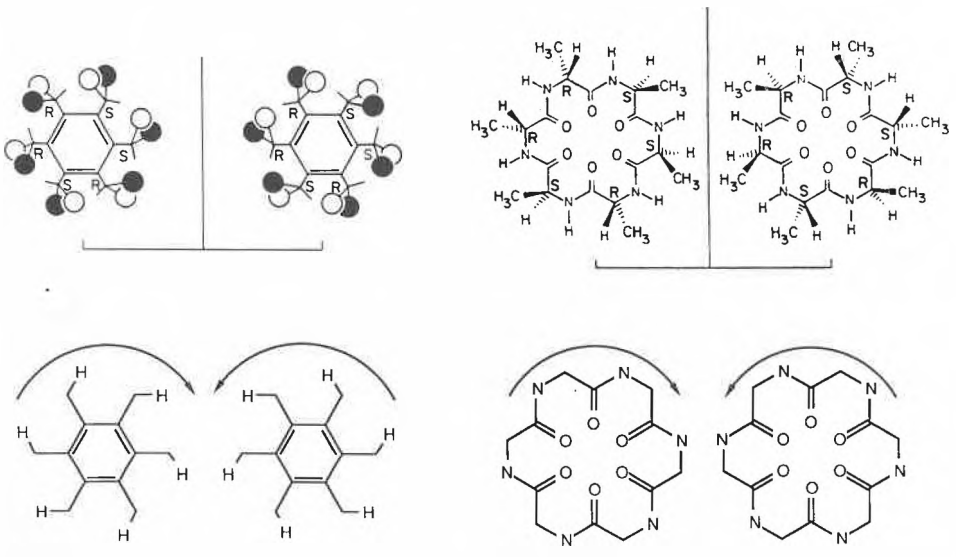


*Fig. 12. Left: a pair of conformational cycloenantiomers (pair **f** in Fig. 11) and the corresponding sense of cyclic directionality (bottom) according to the convention in Fig. 1. – Right: cycloenantiomeric cyclohexaalanyls (top) and the corresponding sense of cyclic directionality (bottom) according to the normal convention in peptide chemistry.*

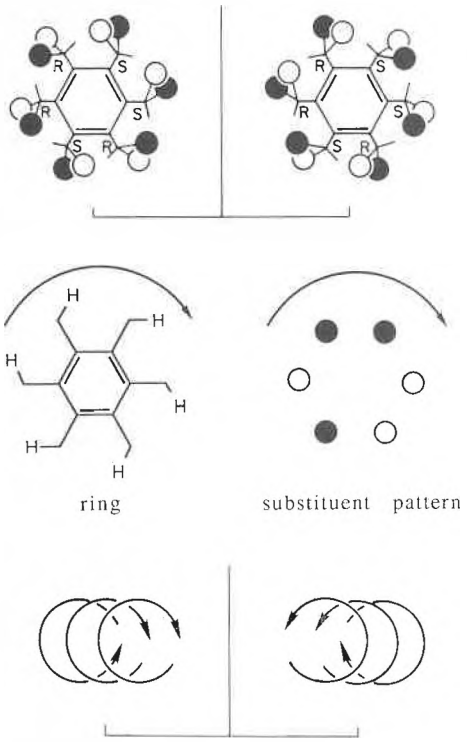


*Fig. 13. Top: a pair of conformational cycloenantiomers (pair **f** in Fig. 11). – Middle: arbitrary conventions adopted to assign sense of directionality to the ring (left) and to the substituent pattern (right). – Bottom: triplets of arrows that symbolize the three-tiered directionality in the enantiomers shown at the top.*

In chiral trihydroxyglutaric acid, a switch of the hydrogen atom and hydroxy group at C(3) converts each enantiomer into its topomer. This switch is symbolically represented by a reversal in the direction of the middle arrow in Fig. 14, which leaves the triplet of arrows unchanged except for orientation in space. Thus the middle one of the three directed cycles in chiral trihydroxyglutaric acid is not stereogenic; that is, C(3) is not a stereocenter. Now imagine a hypothetical process, analogous to the transposition of hydrogen and hydroxy at C(3), in which the methine hydrogens in pair **f** are detached from their carbon atoms and then reattached to the other side, with concomitant inversion of configuration at all six stereocenters (Fig. 15). Each enantiomer is thus converted into its topomer, and it follows that the middle one of the three directed cycles in pair **f** is also not stereogenic.

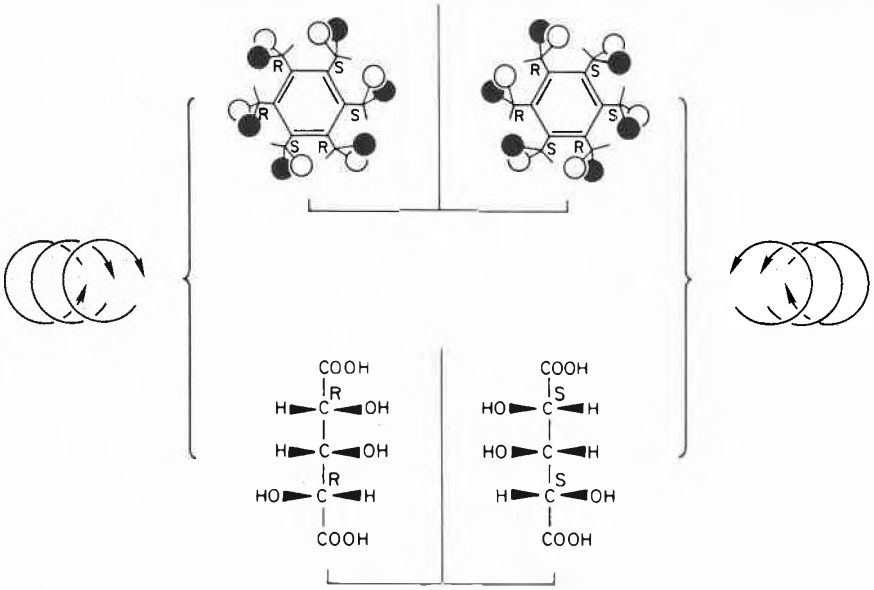


Fig. 14. Triplets of arrows symbolize three-tiered directionality in a pair of conformational cycloenantiomers (top) as well as in the enantiomers of chiral 2,3,4-trihydroxyglutaric acid (bottom). Because the directionality conventions are arbitrary, no one-to-one relationship exists between the individual structures at the top and those at the bottom. For example, the enantiomers at the top could be transposed without affecting the crucial correlation between top and bottom pairs that is symbolized by the triplets of arrows.

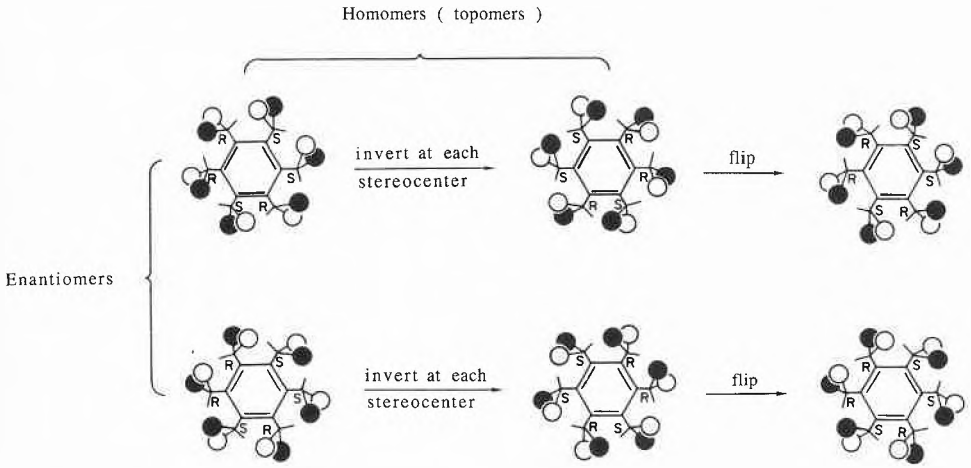


Fig. 15. A hypothetical process in which the tertiary hydrogen atoms in a pair of conformational cycloenantiomers are detached from their carbon atoms and then reattached to the other side. In this process the configuration at each stereocenter is inverted, but each enantiomer yields a topomer of itself rather than the other enantiomer.

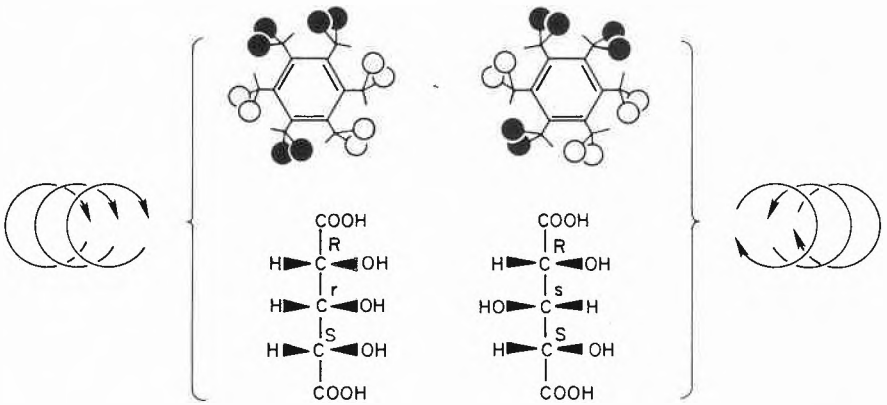


Fig. 17. Triplets of arrows symbolize three-tiered directionality in the pair of conformational diastereomers described in Fig. 16 (top) as well as in the diastereomers of achiral 2,3,4-trihydroxyglutaric acid (bottom). No one-to-one relationship exists between the individual structures at the top and those at the bottom, as explained in Fig. 14.

The preceding analysis is valid not only for pair **f** but is applicable to all types of conformational cycloenantiomers (Fig. 11), as well as to cyclohexaalanyl and to the related cycloenantiomers discussed by *Prelog* and *Gerlach* [4]. In all of these structures, the two outer cycles are related by a C_2 operation if the middle cycle is undirected, as is easily seen if we substitute a hydrogen atom for the hydroxy group in chiral trihydroxyglutaric acid or if we excise the six NHCO groups in the cycloenantiomeric cyclohexaalanyls [5]. Symbolically, absence of directionality in the middle cycle may be represented by excision of the middle arrow. It follows that in none of the discussed cases is cyclic directionality responsible for enantiomerism.

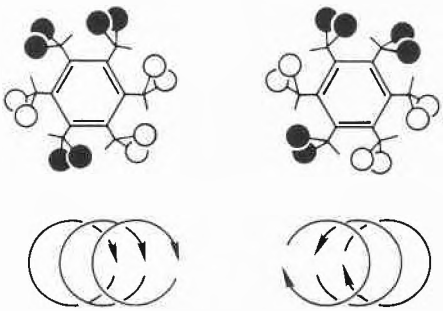


Fig. 16. Top: conformational diastereomers of 1,2,4-triisopropyl-3,5,6-tris(dibromomethyl)benzene. Filled and open circles represent bromine atoms and methyl groups, respectively. – Bottom: the corresponding triplets of arrows, using the convention in Fig. 13.

Let us next imagine an isomer of pair **f**, the hypothetical compound 1,2,4-triisopropyl-3,5,6-tris(dibromomethyl)benzene, which shows the same substituent pattern on each side of the ring as pair **f**, except that now the two patterns are related by a plane of symmetry that contains the plane of the benzene ring (Fig. 16). Thus the molecule is achiral and contains no stereocenters. We are again dealing with three-tiered cyclic directionality, only now the two outer cycles are enantiotopic, and the molecule exists in two diastereomeric forms that differ only in the sense of directionality of the middle cycle, i.e., in the sense of ring directionality. In this case, the appropriate analogy is to the diastereomers of achiral 2,3,4-trihydroxyglutaric acid, in which C(3) is a stereocenter (Fig. 17). The two diastereomers can be interconverted, in the case of trihydroxyglutaric acid by transposition of hydrogen atom and hydroxy group at C(3), and in the case of the hexabromo compound by detachment of the methine hydrogens from their carbon atoms and reattachment on the other side, or by internal rotation of the side chains (Fig. 18). The stereogenicity of the middle cycle is thus demonstrated in both cases.

Note that the projection of each C_s structure in Fig. 17 onto the mirror plane

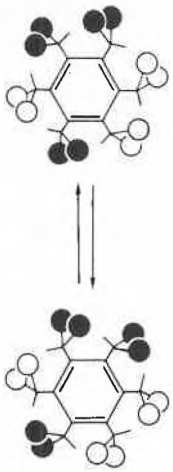


Fig. 18. The hypothetical process described in Fig. 15 now interconverts diastereomers. The same result is obtained by rotation of the dibromomethyl and isopropyl groups about the bonds to the benzene ring.

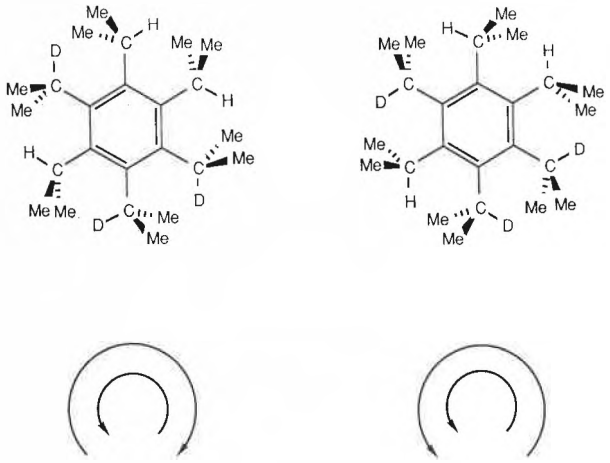


Fig. 19. Top: Conformational diastereomers of a hexaisopropylbenzene isotopomer in which three deuterium atoms are attached to the tertiary carbons at positions 1, 2, and 4 of the ring. – Bottom: in the two pairs of arrows that characterize the two diastereomers, the inner and outer arrows symbolize the sense of cyclic directionality of the substituent pattern and of the ring, respectively, according to arbitrary conventions similar to those shown in Fig. 13.

gives a two-dimensional image which may be characterized by a set of *two* arrows in the plane: one arrow symbolizes the sense of directionality of the two outer cycles, which are now combined, while the other symbolizes the sense of directionality of the middle cycle. The two sets of arrows, one homodirectional and the other heterodirectional, serve the same function as the triplets of arrows in Fig. 17. Where the cyclic array of substituents lies in the plane of the ring, this mode of representation may be more convenient (Fig. 19).

No stereoisomers of the novel type illustrated by the examples in Fig. 16 and Fig. 19 have as yet been reported, and the synthesis of these or analogous compounds thus remains a challenge for the future.

Conclusion

In this Lecture I have attempted to show that the concept of cyclic directionality has inspired the synthesis of compounds with novel stereochemical features; some of these, for example decakis(dichloromethyl)biphenyl and 1,2-bis(1′-bromoethyl)-3,4,5,6-tetraisopropylbenzene, have been experimentally realized while others, such as 1,2,4-triisopropyl-3,5,6-tris(dibromomethyl)benzene, are still on the drawing board. More significantly, we saw that a commonality of cyclic directionality patterns has allowed us to recognize heretofore unsuspected stereochemical similarities among molecules with utterly disparate structures, such as those exemplified in Fig. 14 and Fig. 17. At the very least, this concept therefore serves the purpose of providing novel insights into the stereochemical relationships among molecules.

It is a pleasure to acknowledge the help of my coworkers, whose names are given in the citations to our work. Without their enthusiasm, dedication, experimental skill, and intellectual contributions, this work could not have been accomplished. I also thank the National Science Foundation for its unstinting support of our research. Finally, I want to express my indebtedness to Vladimir Prelog, whose seminal contributions to stereochemistry have been a source of inspiration to me over the years. This Lecture is dedicated to him as a token of my enduring respect and admiration.

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