Stereoisomerism and Local Chirality†

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Abstract: The traditional linkage between stereoisomerism and local chirality that is expressed in terms such as "asymmetric carbon atom" or "element of chirality" represents a source of conceptual confusion in modern stereochemistry. Molecular segments must be viewed from two separate and distinct aspects: their character as stereogenic units and their local symmetry. The first is dependent on bonding connectivity (constitution) and is rooted in graph and permutation group theory, whereas the second is independent of constitution and is rooted in the theory of symmetry groups. Although these two aspects are in principle distinct and serve different purposes, they happen to overlap in the case of the regular tetrahedral permutation center. It is for this reason that the concepts of chirality and stereogenicity are most closely associated in organic stereochemistry where this center plays a dominant role. The present analysis clarifies stereochemical concepts, sheds new light on the meaning of stereochemical terminology, and ipso facto disposes of a number of notions introduced into stereochemistry since van 't Hoff's day. To complete our analysis of stereochemical theory, a new treatment of prochirality is proposed. A theoretical framework is constructed that assigns membership in one of three classes of prochirality to any achiral molecular model according to symmetry.

According to van 't Hoff,1 a carbon atom that is combined with four different univalent groups and whose "affinities" are directed toward the vertices (or, equivalently, faces) of a tetrahedron is "asymmetric."2 This term refers to the environment of the carbon atom at the center of the tetrahedron, rather than to the atom itself.3 However, "asymmetric" could obviously just as well refer to the environment of the ligands that are attached to the carbon atom. Why then should this term be reserved for the ligating center? To resolve this question, we must first address the more general problem of symmetry and chirality at the local level.

Local Symmetry

We recently discussed the dissection of geometric objects into isometric segments, with emphasis on objects that represent rigid models of molecules.4 It was shown that when such an object is partitioned into an ensemble of segments by a cut, the relationship among the segments is dictated by the symmetry of the ensemble, i.e., the object, the cut, and the segments in situ. Intrinsic to this analysis is the restriction that no segment may contain a symmetry element that does not also belong to the molecular model. Two important corollaries from this are that all segments of a chiral model are chiral, and that the segments of an achiral model may be achiral or chiral. Thus, if G and H are the point groups of the model and of any one of its segments, respectively, then H, the local symmetry group, must be a subgroup of G. This condition expresses the fact that every segment must

† Dedicated to the memory of George W. Wheland.

to be symmetry-adapted to \( G \), regardless of the nature of the molecular model.7

Local symmetry is a general concept, and refers to every point and segment of the molecular model, whether such space is occupied by an atom or not. Where local symmetry is used with reference to a single atom, it is customary to speak of \( H \) as the site symmetry group, which may be defined as the subgroup of \( G \), that is composed of all symmetry operations that leave the nucleus unmovd. Note that molecular models built from atom sets properly represent molecular symmetry but generally induce incorrect assessment of local or site symmetry. For example, the symmetry of hydrogen atoms in such sets \( C_{\text{H}} \) corresponds to the local symmetry of \( H \) in \( H_2 \) and \( HCl \), but not to that of \( H \) in \( H_2O \) \( (C_{\text{v}}) \), \( H \) in \( CH_4 \) \( (C_{\text{h}}) \), or \( H \) in \( CHBrClIF \) \( (C_{\text{3v}}) \). Of course, a given type of atom may exhibit more than one local symmetry in certain molecules; for example, the carbon atoms in \( D_{2d} \) tetramethylallene \( (1) \) have \( D_{2d} \), \( C_{\text{3v}} \), and \( C_2 \) site symmetries.5

(6) In this sense, a segment has no identity outside of its identity as a part of the molecular model. That is, the symmetry of such a segment is inseparable from that of its environment. An analogy might here be drawn to the concept of “atom-in-molecule”: the properties of such a bonded atom (a “segment”) are distinct from those of the corresponding atom in the unbound state (a “fragment”). From the perspective of symmetry, what a segment is therefore depends on where it is.7

The general model of the molecule is a linear combination of the distribution functions of the three elementary particles (the electron, the proton, the neutron). The nuclear point model retains only the 6 nuclear distribution. Degenerate permutations in the general model require the symmetry equivalence of the permitted parts, whereas degenerate permutations in the point model are based on nuclear labels and do not require symmetry equivalence of the permuted parts. A further approximation idealizes the nuclear positions to the vertices of regular coordination polyhedra or permutation frames. This model allows all the permutations of the first two models as well as permutations yielding enantiomorphous structures; such permutations are insensible on the first two models without the addition of an inversion operation. Along with this polyhedral model come stronger restrictions on the systems to which the model is applicable. While the model may correctly account for possible stereoisomers it may incorrectly or ambiguously predict the internal or external symmetry relations. To exemplify the relation among these three models, consider the results of permutations on \( CH_3CH_2CH\overline{C}l \) with respect to each model. The exchange of Br and Cl distributions in general and point models yields a new structure that is not symmetry-related to the parent structure. The polyhedral model, however, yields the mirror image from the same permutation. On the other hand, while transposition of the two hydrogens in the ethylene group is a degenerate permutation in the polyhedral as well as in the point model, it creates a new structure in the general model.8

Flurry, R. L., Jr., J. Am. Chem. Soc., 1981, 103, 2901 and references therein. The term “site symmetry” is also used in solid-state chemistry with reference to the location of an atom or group of atoms in the crystal.

(9) In \( 1 \), the three carbon atoms that differ in site symmetry also happen to differ in connectivity, but there is no essential connection between these two characteristics. For example, in \( C_{1} \) 1,1-dichloroallene the three carbon atoms differ in connectivity but have the same site symmetry \( C_{\text{3}} \), whereas in the \( C_{2d} \) conformations of methanol the three methyl hydrogens are constitutionally equivalent but differ in site symmetry \( C_{\text{2d}} \), whereas in the \( C_{2} \) site symmetry \( C_{\text{3d}} \). (10) This is an expression of Curie’s principle of superposition of symmetry groups: in a composite system, only those symmetry elements remain that are common to the component subsystems.11

The site symmetries of atoms in molecules fall into two classes, chiral and achiral.12 It would be useful to have terms to denote membership in these two classes. Such terms should have no connotations of bonding type or connectivity, because chirality and achirality are purely geometric attributes that are in no way dependent on models of bonding.13 In the words of Cahn, Ingold, and Prelog:14 “Thus, the main framework for the classification of chirality has to be geometrical. To introduce theories of chemical bonding, or structural energetics, at this fundamental level would create great difficulties.”

In a natural extension of previous and generally accepted terminology,15 we therefore propose to characterize as chirotopic any atom, and, by extension, any point or segment of the molecular model, whether occupied by an atomic nucleus or not, that resides within a chiral environment, and as achirotopic any one that does not. We may speak of chirotopic and achirotopic centers, atoms, groups, faces, etc. and collectively of chirotopic and achirotopic units or segments. Thus, for example, a chirotopic atom is one with chiral site symmetry, a chirotopic set of atoms is one with chiral local symmetry, and so forth.

Chirotopic and Achirotopic Segments. Chirotopic atoms may occupy sites of \( C_{\text{3v}}, D_{2d}, T, O, \) or \( I \) symmetry. An atom with cyclic site symmetry \( (C_{\text{v}}) \) may be located in a molecule whose point symmetry is not \( C_{\text{v}} \). A chirotopic atom whose site symmetry is higher than \( C_{\text{v}} \) must be located at the center of a molecule with the same point symmetry.16 An atom with \( C_{1} \) site symmetry occupies a general position in the model. The above applies with equal force to any chirotopic segment in the model.

All segments of a chiral model are chirotopic, for “It [i.e., chirality] is an all-pervasive property, as it affects all parts of a chiral structure.”17 While it is possible to segment an achiral model into exclusively chirotopic atoms, there will necessarily always be at least one point in such a model that is achirotopic, even though it may not correspond to a site occupied by a nucleus. More generally, all points in a model that remain invariant under a rotation-reflection operation are achirotopic. For example, in \( meso-1,2\)-dichloro-1,2-dibromoethane, there are two achiral conformations, with \( C_{2} \) and \( C_{1} \) symmetry. In the former (2), the only chirotopic point is the center of symmetry, whereas in the latter (3), the achirotopic points constitute the plane of symmetry. In both conformations, all atoms are chirotopic.

Chirotopic atoms located in chiral molecules are enantiotopic by external comparison between enantiomers. Chirotopic atoms located in achiral molecules are enantiotopic by internal and


(13) Where the local symmetry refers to sets of atoms whose relative position in space remains invariant under the given conditions, there is no need for recourse to the directed valence bond model. For example, for the purpose of describing its local symmetry, \( CH_3 \) is treated as a set of four atoms, distributed tetrahedrally in space, whose neighborhood relationships remain fixed, and without reference to the question of which atom is bonded to which.


Stereoisomerism and Local Chirality


The essential feature of interest is the chiral environment of the atom, and the present discussion fully applies to all chirotopic stereocenters. This includes the central carbon atom in the vespertilionis, whose site symmetry is $D_2$. The site symmetry of "asymmetric carbon atoms" must by definition be $C$:  

(26) Whether a stereocenter is chirotopic or not may depend on the distribution of ligands, as, for example, in P$_2$N$_2$C.  


It follows that among chiral assemblies constructed from achiral permutation frames and achiral ligands, the regular tetrahedron is the only skeleton in which every transposition of ligands is equivalent to a reversal in the sense of chirality of the ligated assembly. Even so, this relation obtains only under special conditions.

We are therefore faced with a remarkable coincidence. First, the building block of organic chemistry, the tetravalent carbon atom, is also representative as a regular tetrahedral ligating center. Second, when such a center is appropriately complemented with four different achiral ligands, chirotopicity and stereogenicity are uniquely linked. It is this coincidence that accounts for the enormous practical success of the concept of the "asymmetric carbon atom".

The preceding discussion demonstrates the need to maintain a strict distinction between chirotopicity and stereogenicity in the treatment of stereochemical problems. The next two sections illustrate the way in which this distinction serves to throw new light on some notions that are prevalent in stereochemistry.

On "Chiral Methyl Groups". From the beginning, the designation of a methyl group as "chiral" or "asymmetric" has been exclusively restricted to CHDT. However, the biochemical significance of this isotopic labeling (as in "chiral acetic acid" (CHDTCOOH) lies primarily in the transformation of CH₃ into a stereogenic center; local chirality, i.e., chirotopicity, plays at most a secondary role. Indeed, methyl groups that are chirotopic without being stereogenic are ubiquitous in chemistry and in biochemistry; thus all CH₃ groups in chiral molecules are ipso facto chirotopic. We provide two particularly instructive examples.

In 1,2,3,4-tetrachloro-5,8,9-trimethyltriptocene (9), three chemical shifts are observable for the 9-methyl protons at -90 °C. Under these conditions the three hydrogen atoms are clearly distinguishable (diastereotopic) and the 9-methyl group is chirotopic, but obviously it is not stereogenic. Although at room temperature this distinguishability is lost due to rapid site exchange on the NMR time scale, the CH₃ group remains chirotopic. Similarly, CH₃'s in the 5- and 8-positions are also chirotopic. These groups remain chirotopic under all conceivable time scales of observation.

The local symmetry of the CH₃ group in is C₃ on any time scale, barring inversion at sulfur or bond-breaking processes. The hydrogen atoms are therefore always indistinguishable (homotopic) even though the CH₃ group must remain chirotopic.

On "Pseudoasymmetric Carbon Atoms". The central carbon atom (C-3) in the two achiral diastereomers (11, 12) of 2,3,4-

A are related by a mirror element. C₆ and C₈ can be brought into coincidence by rotation of α and β about A and B, respectively. All three points (A, B, C₈, A) are now pairwise related through mirrors, and the figure in E₁ is therefore an equilateral triangle (ii). Similarly, the step from E₁ to E₂ is accomplished by passing mirror planes through the edges of the equilateral triangle. Three new points are created. Rotation of the mirror elements, this time about the edges, brings the three new points into coincidence. As before, all points are pairwise related through mirrors. The new figure is the regular tetrahedron. Because all symmetry operations can be expressed as permutations, it follows that all transpositions (pairwise relations) have the same effect as reflection for two points in E₁, the vertices of the equilateral triangle in E₁, and the vertices of the regular tetrahedron in E₁.

(31) This special feature of the regular tetrahedron may be demonstrated by construction. Choose two points (A, B) in one dimension (E¹). Each is mirror-related to the other through the midpoint between them. (There are no figures in E² of more than two points such that each point is mirror-related to all others.) Together, the analogue in E², mirror lines α and β are passed through A and B. Two new points are created, C₆ by reflection of A through β and C₈ by reflection of B through α (see i); neither C₆ and B nor C₈ and

(32) This equivalence relation, unqualified, is valid only in the simplest cases, e.g., with ligands such as H, the halogens, CN, etc. In general, it also requires that there be no restriction on the freedom of orientation of the ligands relative to the ligating center and that the internal motion be uncorrelated as well as unrestricted.

(33) In bis(9-triptycyl)methane the 9-triptycyl groups undergo unrestricted rotation, but this motion is tightly coupled (gear effect) and the isomer count is consequently restricted to CHDT. However, the biochemical significance of this isotopic labeling (as in "chiral acetic acid" (CHDTCOOH) lies primarily in the transformation of CH₃ into a stereogenic center; local chirality, i.e., chirotopicity, plays at most a secondary role. Indeed, methyl groups that are chirotopic without being stereogenic are ubiquitous in chemistry and in biochemistry; thus all CH₃ groups in chiral molecules are ipso facto chirotopic. We provide two particularly instructive examples.

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trihydroxyglutaric acid has been dubbed "pseudoasymmetric". This atom is attached to four ligands that differ in structure, and although C-3 is therefore "according to definition, undoubtedly an "asymmetric" carbon atom", a plane of symmetry passes through C-3 in the model. The designation of C-3 as "asymmetric" therefore seems to be inappropriate, if not actually contradictory. Small wonder that "this molecule was troublesome to van 't Hoff.
Fischer, Landolt, Mohr, and Pope, and has been a source of contention ever since.2,4,6

However, it is easily shown that the difficulty stems from the same unwarranted linkage of stereoisomerism and chirality that we have already discussed for the traditional "asymmetric carbon atom". In compounds such as CHBrClF the carbon atom is stereogenic and chirotopic, whereas the chiral stereoisomers of 2,3,4-trihydroxyglutaric acid (13, 14) contain a tetrahedral coordination center (C-3) that is nonstereogenic and achirotopic. According to Jaeger,21 the latter fails to qualify as an "asymmetric carbon atom"—a striking illustration of our contention that the classical chemical purposes served by this concept are those that express its character as a stereocenter independent of local symmetry.45

The relationship between the central carbon atoms in compounds exemplified by CHBrClF, 11, and 13 can now be meaningfully analyzed under the separate and distinct aspects of ligand permutability (relating to stereoisomerism) and symmetry. With respect to permutability, C11BrCIF resembles 11 since transposition of two ligands yields a new structure. With respect to symmetry, CHBrClF resembles 13 since both molecules are asymmetric and the four ligated groups are all nonequivalent (the two CHOOCOOH groups in 13 or 14 are diastereotopic and are expected to differ spectroscopically and in reactivity).46

With respect to stereogenicity, the central carbon atom in achiral molecules of type 11 thus differs in no way from that in a molecule like CHBrClF, even though the latter is asymmetric. With respect to local and molecular symmetry, molecules of type 11 differ in no way from molecules like meso-2,4-dihydroxyglutaric acid or 2-propanol, even though the central carbon atom in the last two molecules is nonstereogenic: in their most symmetric conformation, all three molecules have C₃ symmetry, with two enantiotopic groups (CHOOCOOH or CH₃) attached to the central carbon atom. The stereochemical description of molecules of type 11 thus presents no difficulties so long as the traditional linkage between stereogenicity and local symmetry is broken.

The term "pseudoasymmetric" therefore lacks any meaningful reference to symmetry and geometry. It is seen to be an artifact of an unwarranted superposition of stereogenicity onto local chirality. Nothing illustrates more strikingly the historical confusion engendered by the enforced linkage between stereoisomerism and chirality than this infelicitous term. The same applies, of course, to derived and allied terminology, such as "pseudoasymmetric" center, etc.

Stereochemistry without Stereoisomerism

Since the days of van't Hoff and Le Bel, stereochemistry has been firmly wedded to the concept of a molecule as an assembly of atoms connected by localized valence bonds. From this arise all classification schemes and theoretical constructs that deal with the question of stereoisomerism. Indeed, the very concept "stereoisomer" owes its existence to a classification scheme that assigns first priority to bonding connectivity (constitution) and that defines as "stereoisomers" those molecular states that have the same constitution but that differ with respect to certain measurable properties because of differences in the spatial arrangements of the constituent atoms. That has been the meaning and content of "stereochemistry" ever since the term was first employed in 1890 by Victor Meyer.2

It is well to remember, however, that stereochemistry had its beginnings before the advent of structural theory: Pasteur's recognition that the optical activity of tartaric acid is a manifestation of molecular dissymmetry (i.e., chirality) owed nothing to that theory.2,4,6 Thus, an analysis of molecular models that gives primacy to symmetry and chirality instead of constitution follows in the tradition of Pasteur, the "founder of stereochemistry",27 even though it represents a radical departure from traditional stereochemistry practiced since van't Hoff. As we have seen, "stereogenicity" and "local symmetry" are conceptually distinct. The former is grounded in the theory of graphs and permutation groups, whereas the latter is based on the theory of symmetry groups; the former refers to a model that requires specification of constitution, of permutation frames, and of structural energetics, whereas the latter requires no specification other than a distribution of atoms that is consonant with the time scale of observation.39 This section, whose seemingly paradoxical title is meant to serve as a reminder of our disassociation from the traditional meaning of stereochemistry as a subject solely concerned with stereoisomerism,48 deals with some aspects of the chirality/achirality dichotomy apart from stereochemistry and with the problem of chiral descriptors.

Chirotopicity and Optical Activity. Chirotopicity is appropriate to the analysis of physical or chemical properties that depend on chirality. In this section we discuss one such property, optical activity.

Thus, although the molecule as a whole acts as the chrophore in any chiroptical measurement (as is obviously the case in, say, hexahelicene), it is often found convenient to dissect the model into a local, "achiral" chrophore and a chirotopic perturbation environment. Sector rules (e.g., the octant rule for the carbonyl chromophore) can then be developed that relate the sign and amplitude of the Cotton effect to the spatial distribution of the perturbing atoms about the chrophore, regardless of constitution.49 All that matters is the chiral distribution of atoms among the sectors. However, although the sectors are formally constructed on the basis of local achirality in the chrophore, the actual site symmetry of the chrophomeric atoms in the achiral molecule must be chiral. For example, the octant rule is based on local C₂ symmetry of the unperturbed carbonyl chrophore in, say, formaldehyde, but the same group in, say, (+)-3-methylcyclohexanone has local C₃ symmetry, and the carbonyl group is therefore chirotopic.49

By the same token, chirotopic CH₃ groups should be capable of acting as optically active chrophores. This is indeed what is experimentally observed by Raman circular intensity differential spectroscopy.50 Methyl groups can thus be used as probes of molecular chirality in molecules such as (+)-α-phenylethylamine. Similarly, optical activity of octahedral transition-metal (Werner) complexes of the type Co(en),41 arises from chiral perturbation of d-d or charge-transfer transitions on the metal atom or on the metal plus its ligating atoms.51 This chrophore

(45) Thus, for example, (3R,5S)-3-dimethylthephan-4-ol should function like R,R,R,C(OH) in an asymmetric arylaldehyde synthesis, even though C₄ is not an "asymmetric carbon atom". For a related reaction, see: Mislow, K.; Prelog, V.; Schererrer, H. Helv. Chim. Acta 1958, 41, 1410.

Figure 1. Flow chart for the classification of topic relationships. The decisions in response to questions are given by heavy (yes) and light (no) lines. The questions are as follows: (1) Are the atoms related by a symmetry operation of the molecule? (2) Are they related by a symmetry operation of the first kind (proper rotation)? (3) Do they have the same bonding connectivity (constitution)?

is also formally considered achiral, but since the site symmetry is \( D_2 \), the metal atom is chirotopic.

Enantiotopic chromophores have an equal but opposite effect on optical activity. For example, since the \( \text{CH}_3 \) groups in 2-chloropropane are enantiotopic, their effect on Raman optical activity is nullified through mutual cancellation in the \( C_2 \) conformation.

Symmetry and Spectral Anisochrony. We recently proposed a classification of pairwise relations between isometric structures based primarily on symmetry and only secondarily (if at all) on constitution. We argued that in many ways such an approach is preferable to the traditional one, which is based primarily on constitution. This new classification was also applied to topic relationships, i.e., to the description of segments in relation to others within the model. Let us define atoms or sets of atoms that are related by a symmetry operation in \( G \) as symmetry equivalent and those that are not as symmetry nonequivalent. All topic relationships may then be classified as shown in Figure 1. Bonding connectivity plays no role in analyses based solely on considerations of symmetry, and such analyses are therefore blind to the distinction between diastereotopic and constitutionally isomers or between diastereotropic and constitutionally heterotopic atoms: all that needs to concern us in such a case is that the models are symmetry nonequivalent.

When no distinction is made between "diastereomer" and "constitutional isomer", there is no need for the term "stereoisomer", since the relationship between enantiomers (object and nonsuperposable mirror image) does not require any knowledge of constitution or structural energetics: the geometric attribute of chirality alone requires the existence of two mirror-image-related stereoisomers. "Stereoisomerism" and "stereoheterotropism" thus fall by the wayside under the novel classification, since these terms have no meaning unless constitution is specified.

The new classification of topic relationships is especially well suited for the analysis of problems in spectroscopy: resonances due to symmetry equivalent and nonequivalent atoms are isochronous and anisochronous, respectively. These distinctions are particularly significant in NMR spectroscopy. Differences in screening constants between diastereotropic and constitutionally heterotopic groups are dealt with by precisely the same theory, i.e., the anisochronies observed in both cases stem from a single source: the symmetry nonequivalence of nuclei.

Specification of Chirality and Chirotopicity. Models of enantiomers have the opposite handedness; i.e., they differ in their sense of chirality. Since chirality is a geometric property that is independent of constitution, it should be possible to specify sense of chirality without having to resort to schemes based on the permutational approach or requiring prior specification of chemical bonding, i.e., schemes tied to the concept of stereoisomerism.

For example, the center of mass in a chiral molecule might be taken as the origin of a coordinate system. Three mutually perpendicular vectors intersecting at that origin will then define the handedness of the coordinate system and thus serve to specify molecular chirality. The three vectors could be chosen by some algorithm based on the distribution of electrons and/or nuclei in the molecule and independent of connectivity, but because the choice of this algorithm is entirely arbitrary, it follows that the same enantiomer could be "right-handed" or "left-handed", depending on the choice. That is, sense of chirality is not absolute.

Furthermore, a set of vectors in a given chiral structure is enantiomorphously related only to the corresponding set in the enantiomer, and not to that in any other structure. Accordingly there must be as many distinct chiral descriptors as there are symmetry-unrelated chiral structures, since each set of descriptors is limited to one particular structure and its enantiomer.

Similarly, it is possible in principle to assign symmetry-adapted descriptors to all chirotopic segments in a molecular model. Such descriptors must be different for all symmetry-nonequivalent segments. An infinity of such descriptors is required because chirality is sampled continuously, and where there is one chirotopic point in a model there is an infinite number. Where, for chemical reasons, the analysis is limited to a finite number of chirotopic segments, each segment requires a separate descriptor. For example, each of the five atoms in CHBrClF must be given its own chirotopic descriptor, one that indexes the sense of chirality defined by the environment of that atom (e.g., \( \alpha \) for \( H \), \( \beta \) for \( C \), \( \gamma \) for \( F \), etc.). In the enantiomer, the corresponding descriptors indicate the opposite handedness for the corresponding environments (e.g., \( \alpha \) for \( H \), \( \beta \) for \( C \), \( \gamma \) for \( F \), etc.). Because there are only two symmetry-related molecular environments, i.e., those of the two enantiomers, and because the chiral environments (and hence the chirotopic descriptors) of the individual atoms are interdependent, it follows that each descriptor (e.g., \( \alpha \)) can only be used in conjunction with others from the same molecular environment (e.g., \( \beta \), not \( \beta \)). It further follows that enantiomeric relationships may be expressed by reference to any chirotopic point in the model; in the example above, \( \alpha \) and \( \beta \) fully express the relationships between the enantiomers of CHBrClF, even though reference is made to the environment of a nonstereogenic atom (\( H \)) rather than to that of a stereogenic one (\( C \)).

Chirality Descriptors and the Labeling of Stereoisomers and Stereogenic Elements. The chirotopic descriptors discussed in the preceding section are obviously unsuitable for the purpose of establishing a systematic nomenclature for stereoisomers. On the other hand, because such systems of nomenclature must deal with molecules that are not related by symmetry (e.g., diastereomers), their unquestioned usefulness in the enumeration and description of
of individual stereoisomers demands as a price the loss of relevance to the symmetry relationships among molecules and their segments. For example, in all such systems of nomenclature two descriptors suffice to label all enantiomers: one for the "right-handed" and one for the "left-handed" molecule. This is the basis for the familiar dichotomy of symbols such as D/L, R/S, Δ/Λ, etc. However, the sense of chirality of nonenantiomeric molecules cannot be properly compared, and the use of such symbols with reference to the chirality of two nonenantiomeric structures (e.g., d-glucose and L-mannose, or (R)-alanine and (S)-leucine) therefore clearly indicates that such symbols are incompatible with the symmetry relationships among models of these structures. In fact, except in the case of enantiomers, chirality labels attached to stereoisomers or stereogenic units are not, and cannot be, symmetry-adapted. They are not generally compatible with the sense of molecular or local chirality because they serve a different purpose altogether: the identification and naming of stereoisomers. Typically, labels for stereoisomers refer to a construct, intended as a model for stereoisomerism, that consists of a permutation frame (the skeleton) ligating a unit and one or a set of ligands that are permutable among the sites of the skeleton. The labels are meant to describe the orientation of the ligands on the skeleton, and are assigned by a set of arbitrary rules, e.g., the sequence and conversion rules of the CIP system.\(^{(62)}\) They solely serve to identify stereoisomers and have no bearing whatever on symmetry relationships among or within molecular models.\(^{(63)}\) It is therefore inappropriate to refer to them as "chiral descriptors".

That the labels attached to stereogenic atoms are incompatible with the local chirality of these atoms may be illustrated by two examples. According to CIP rules, the configurations at C-3 in 11 and 12 are specified by "chiral descriptors" \((r\) and \(s\)), even though the atoms in question are achiriotropic. The labels used to provide a distinction between 11 and 12 are therefore seen to be merely nomenclatural devices that bear no relation to the local symmetry of the atoms to which they refer. As a second example, consider the compound formed by esterification of the hydroxyl group at C-3 in 11 with \((S)\)-lactic acid. According to CIP rules, the configuration at C-3 in this ester is \(R\). According to the same rules, the configuration at C-3 in the mirror image of this ester is \(S\), even though the atoms in the two esters are enantiomeric. Once again, we see that such labels bear no relation to the local sense of chirality.

We conclude this section with a general commentary on the CIP system of factorization. In their original paper on the specification of asymmetric configurations,\(^{(65)}\) Cahn, Ingold, and Prelog stated that "three-dimensional space can in principle be divided into two heterochiral classes (in the sense of chirality)."\(^{(66)}\) Prelog and Helmchen stated that "stereoisomers with chirality planes and chirality axes are in fact atropisomeric conformers."\(^{(67)}\) Paradoxically, the selection of "elements of chirality" in a sense of chirality.

The concept of "axial chirality" was introduced as "axial asymmetry" in the 1956 paper by Cahn, Ingold, and Prelog\(^{(68)}\) and illustrated with four classes of structures: alenes, alkylidenecycloalkanes, spirans, and biaryls. In their 1956 paper\(^{(69)}\) a fifth class was added, the adamantoids, and biaryl as a class was said to be "conformational" while the other four classes were "clearly configurational". In the most recent (1982) revision of the CIP system\(^{(70)}\) Prelog and Helmchen stated that "stereoisomers with chirality planes and chirality axes are in fact atropisomeric conformers." Spirans, alkylidenecycloalkanes, and adamantoids thus no longer qualify for "axial chirality". However, chiral biaryls and alenes seem to have survived the vicissitudes of this definition.

(61) According to Ruch,\(^{(71)}\) chiral ligated assemblies composed of an achiral skeleton and achiral ligands can be divided into two heterochiral classes (in the sense of "chirality") only if the skeleton belongs to class \(r\) (e.g., the regular tetrahedron). However, as also pointed out by Ruch,\(^{(72)}\) even so the manner of "chirality labels" (e.g., "planes of chirality", "elements of chirality") cannot be properly compared, and the use of such symbols with reference to the chirality of two nonenantiomeric structures (e.g., \(d\)-glucose and \(L\)-mannose, or \((R)\)-alanine and \((S)\)-leucine) therefore clearly indicates that such symbols are incompatible with the symmetry relationships among models of these structures.

(62) A chiral group is defined as a "chirality center" only if the skeleton belongs to class \(r\) (e.g., the regular tetrahedron). However, as also pointed out by Ruch,\(^{(72)}\) even so this division cannot be accomplished unless the ligands differ by no more than one distance (the shortest distance parameter likened to the diameter of a sphere)\(^{(73)}\). (63) A chiral center is defined as a "chirality center" only if the skeleton belongs to class \(r\) (e.g., the regular tetrahedron). However, as also pointed out by Ruch,\(^{(72)}\) even so this division cannot be accomplished unless the ligands differ by no more than one distance (the shortest distance parameter likened to the diameter of a sphere)\(^{(73)}\).
molecule: neither chirotopicity nor optical activity are exclusively attributable to individual atoms in such a molecule.

For all of these reasons it is advisable to abandon expressions such as “center of chirality”, “axial chirality”, and the like.

**Prochirality**

In connection with the preceding analysis, we were led to reexamine the concept of “prochirality”.70 This term was introduced by Hanson in 196671 and has received wide currency, especially in biochemistry.72 Defined as “the property of an achiral assembly of point ligands that becomes chiral if one of its point ligands is replaced by a new one”, “elements of prochirality” were intended to match the “elements of chirality” that had been introduced in the CIP scheme.14 In all of its applications, “prochirality” has been restricted to systems in which replacement of a single ligand leads to a stereogenic center. By logical extension, a “pro-prochiral center” is exemplified by the methyl group in CH3COH, and a “pro-pro-prochiral center” by CH3.35 “Elements of prochirality” are therefore prostereogenic in the same sense that “elements of chirality” are stereogenic.

“Prochirality” as presently defined refers exclusively to atoms or sets of atoms (i.e., the skeleton and its ligands) in the molecule. While admitting to the possibility of describing certain achiral molecules as “prochiral”, Hanson advised that “this course will not be followed since it would serve no practical purpose.”71 Despite this admonition, there are numerous references in the literature to “prochiral molecules” or “prochiral substrates”, a practice that is virtually unavoidable in light of the close association with “chiral”. Indeed, it seems hard to understand why the model of a molecule such as meso-tartaric acid should not be called “prochiral”, since substitution of one of the two enantiotopic hydrogens on C-2 or C-3 by, say, deuterium breaks a degeneracy and produces a chiral molecule; this is precisely what happens when a similar replacement takes place on the “prochiral center” of CH3Cl.35 Evidently, the practical purpose of “elements of prochirality” is expressed solely by their character as prochiraltopic units. That C-3 in glyceraldehyde is chirotopic and yet is given the label “prochiral”, a term explicitly defined for an “achiral (pro)chirotopic center” in spite of the apparent lack of correspondence to local symmetry characteristics such as “center of chirality”, “axial chirality”, and the like.

We thus recognize that “elements of prochirality” suffer from the same lack of correspondence to local symmetry characteristics as “elements of chirality”. This problem can be easily avoided if the usage of “prochirality” with reference to prostereoisomerism is altogether abandoned, and such a course of action seems at least worthy of consideration.74

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**Table I. (Pro)p-chirotopicity and (Pro)p-chirotopicity as Attributes of Models of Molecules and Their Segments**

<table>
<thead>
<tr>
<th>desymmetrization index p</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>description of molecule (segment)</td>
<td>chiral (chirotopic)</td>
<td>(pro)p-chiral (pro)chirotopic</td>
<td>(pro)p-chiral (pro)chirotopic</td>
<td>(pro)p-chiral (pro)chirotopic</td>
</tr>
<tr>
<td>molecular or local symmetry</td>
<td>Cn, Dn, T, O, I</td>
<td>Cn, C1, S, Sn</td>
<td>Cn, Cnh</td>
<td>Dnd, Dnh, Td, T, C1, C2, K, Kp</td>
</tr>
<tr>
<td>invariant achirotopic subspace</td>
<td>none</td>
<td>a plane or the central point</td>
<td>an axis or the central point</td>
<td>the central point</td>
</tr>
</tbody>
</table>

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A Classification of Achiral Symmetries. If prochirality is to be properly matched to chirality, the former, like the latter, must express a purely geometric attribute, and the term must be applicable to all objects, including models of molecules, without regard to constitution. This condition is not satisfied by the present definition71 or by current usage.70 However, it is possible to construct a theoretical framework that achieves the desired end while retaining chemical relevance.

The symmetry equivalence of molecular subunits is concisely expressed in Neumann’s principle that “the physical properties of a system are invariant to its symmetry operations”.75 The applications of this observation are laid out in Curie’s inference that phenomena are created by a reduction in symmetry.11 It is in this spirit that we approach our treatment of prochirality.

Our concern is with the desymmetrization of achiral objects, which, by definition, contain one or more symmetry elements of the second kind76 (σ, i, or S). Such symmetry elements may be destroyed through replacement of a point in the object by a differently labeled one, provided that the point to be replaced is not invariant under the symmetry operations that are associated with those elements.77 We content ourselves with two examples.

Replacement of a point in an object that belongs to C2m destroys i if the point lies off center but on the mirror plane and destroys both i and σ if the point lies off the mirror plane. A chemical analogy might be the replacement in trans-1,2-dichloroethylene of one Cl by a Br and the addition of Br⁻ to the σ-bond to form a chiral bromonium ion, respectively. Note that in this example it is not possible to destroy σ without destroying i as well. In general, if σ and Sα (e.g., Sα = i) coexist in an object, desymmetrization leading to the destruction of σ will always destroy Sα whereas the converse does not hold.

As a second example, consider an object with D3d symmetry. Replacement of a point that lies off center on the Sα axis, i.e., along the intersection of the three mirror planes, destroys the improper axis but none of the planes. Replacement of a point that lies off the Sα axis but on a mirror plane destroys all symmetry elements of the second kind except for that plane. Finally, replacement of a point that lies off center on a C2 axis or in a general position destroys all symmetry elements of the second kind (i.e., converts all achirotopic subspaces into chirotopic ones) and leads to a chiral object.

These examples demonstrate that achiral objects, including models of molecules, may be desymmetrized in a well-defined manner by destruction of symmetry elements of the second kind to yield either chiral objects or achiral objects of lower symmetry. Our concept of prochirality is based on the principle that replacement of a point with site symmetry Hh by 2-differently labeled points yields an object whose symmetry is H. As such, it matches

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chirality as an attribute related purely to symmetry.

We define as (pro)-chiral (p > 0) any finite, achiral object that can be desymmetrized into a chiral object by at most p stepwise replacements of a point by a differently labeled one and as (pro)-chirality the corresponding property of an achiral object. All such objects contain subspaces (points, lines, or planes) that remain invariant under every improper rotation (rotation-refection) of the point group, and the aforementioned replacements are restricted to points lying outside these achirotopic subspaces. (Pro)-chirotopicity is defined in parallel for segments of achiral objects. Use of the term "desymmetrization" will hereafter be restricted to the point-replacement scheme described in the above definitions.

We now list the characteristics of the (pro)-chiral classes (Table 1) and illustrate each with chemical examples. Models with p = 3 may belong to D3h, C3v, C3, and C1 for p = 3, 2, 1, and 0, respectively. M represents a π-bonded ligand, e.g., a transition-metal π-complex.

Figure 2. Partial desymmetrization lattice for triptycene (17). The index p is shown on the right for each row of (pro)-chiral structures. Symmetries are D3h, C3v, C3, and C1 for p = 3, 2, 1, and 0, respectively. M represents a π-bonded ligand, e.g., a transition-metal π-complex.

Figure 3. Desymmetrization lattice for (pro)-chiral objects. See text for additional comments.

of (pro)-chiral H on C-1 yields (pro)-chiral 19. Replacements are not necessarily restricted to ligand substitutions; thus π-complexation of 17 (corresponding to replacement of a point on the σ plane) yields (pro)-chiral 20, a known compound for M = Cr(CO)3. By the same token, σ-complexation of 17 by addition of D to C-1 (corresponding to replacement of a point in a general position) yields chiral 21.

Models with p = 2 may belong to C3v or C3 and are (pro)-chiral. As before, desymmetrization need not occur in a stepwise manner. For example, replacement of (pro)-chiral H on C-1 in 18 (Figure 2) by Y yields (pro)-chiral 22, whereas replacement of a chirotopic point by π-complexation yields chiral 23.

Models with p = 1 may belong to S2v, C1, or C1 and are (pro)-chiral. Under the operation of S2v or i, a single point in the model remains invariant, and under the operation of i or σ only all the points in the plane. These are the achirotopic points. All other points in the model are chirotopic and fall into enantiotopic pairs related by S2v, i, or σ. Only a one-step desymmetrization to a chiral object is possible, e.g., 22 to 24, and 19 or 20 to 25 (Figure 2).

Models with p = 0 lack symmetry elements of the second kind. Therefore, by definition, (pro)-chiral = chiral. There are no


(81) Desymmetrization of achiral objects to chiral ones by the point-replacement procedure can only lead to objects with C3v symmetry. The other chiral symmetries (D3, T, O, I) are listed in Table 1 for completeness.

archirotopic points in such a model. With the definition of this class, all possibilities for (pro)-chirality in E1 are exhausted.

A desymmetrization lattice for achiral objects is displayed in Figure 3. As shown by transformations such as $D_{2h} \rightarrow C_2$ and $C_{ab} \rightarrow C_{nv}$ and as also illustrated by the examples in Figure 2, desymmetrization need not occur in a stepwise manner, i.e., from (pro)$^2$-chiral to (pro)$^4$-chiral: replacement of any (pro)$^4$-chirotopic point will necessarily yield a (pro)$^2$-chiral object. Thus, all (pro)$^4$-chiral objects except those with spherical ($K_2$) symmetry may be rendered (pro)$^2$-chiral ($C_2$) by replacement of a point that lies on a mirror plane but off an axis, and all achiral objects except those with $K_a$, $D_{ab}$, or $C_{av}$ symmetry may be rendered asymmetric by replacement of a point in a general position.22,83

We close this discussion on a historical note. According to our scheme, desymmetrization of an object with $T_d$ symmetry yields an object that can belong to only one of four subsymmetries ($C_{3v}$, $C_{2v}$, $C_2$, or $C_1$). Van 't Hoff, on the basis of a very different approach to desymmetrization, arrived at the same conclusion for the subsymmetries of substituted methane.19

Acknowledgment. We are deeply grateful to numerous members of the stereochemical community for stimulating discussions and correspondence over a period of years. We also thank the National Science Foundation (CHE-8009670) for support of this work.

Study of Proline Peptide Bond Conformation and Ring Dynamics in Crystalline Cyclic Peptides Using $^{13}$C MAS NMR

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Abstract: We have studied three cyclic peptides, cyclo(Val-Pro-Gly)$_2$, cyclo(Phe-Pro-D-Ala)$_2$, and cyclo(Gly-Pro-D-Ala)$_2$, in the crystalline powder form by using $^{13}$C MAS NMR. A comparison of chemical shift differences ($\Delta$) between the $\beta$- and $\gamma$-carbons of the proline ring suggests that the Val-Pro and Phe-Pro peptide bonds are cis and that the Gly-Pro bonds are trans. These results for crystalline samples agree with those obtained in solution and are verified by crystal structures of cyclo(Phe-Pro-D-Ala)$_2$ and cyclo(Gly-Pro-D-Ala)$_2$. Solid-state relaxation data show that the disorder reported at one proline ring in the crystal structure of the latter peptide results from ring motion. A ring correlation time of 1.2 X 10$^{-10}$ is obtained when the relaxation data are analyzed by using the two-site exchange model suggested by the crystal structure.

In recent years high-resolution $^{13}$C NMR spectra of powders have been obtained by using cross-polarization and magic-angle sample spinning.1-3 This technique has been applied to study crystalline peptides where measurement of solid-state and solution chemical shifts permit comparison of peptide conformation in solution and the solid state.4 In this regard cyclic heptapeptides of the type cyclo(Xxx-Pro-D-Yyy)$_2$ or cyclo(Xxx-Pro-Gly)$_2$ (where Xxx and Yyy are any other amino acid residues) are particularly attractive because certain aspects of their solution conformation are well-defined by their chemical shifts.5-10 For instance, the spectrum immediately shows if the peptide conformations have average $C_2$ symmetry on the NMR time scale. In addition, since the barrier to cis-trans-isomerization of a peptide bond (e.g., Xxxx-Pro) is about 15-20 kcal/mol,11 lifetimes of the isomers are large on the NMR time scale and distinct signals are observed for the cis and trans isomers. Therefore, chemical shift measurements have established that these heptapeptides exist in solution in two forms of average $C_2$ symmetry on the NMR time scale, one with all the peptide bonds as trans,10 and the other with two Xxx-Pro bonds as cis. The chemical shift difference between the $\beta$- and $\gamma$-carbon resonances ($\Delta$) is used to assign the cis and trans isomers. For a cis Xxx-Pro bond $\Delta$ is ca. 8-12 ppm whereas this difference is smaller, 2-6 ppm, for the trans case.12

(82) Spherical symmetry ($K_2$) provides a unique model for desymmetrization, in that all points outside the center are (pro)$^2$-chirotopic. Replacement of such a point yields a (pro)$^2$-chiral object ($C_2$). In the latter, all points outside of the rotation axis are (pro)$^2$-chirotopic, and replacement of such a point yields a (pro)$^2$-chiral object ($C_2$). In turn, all points in the last object outside the mirror plane are chirotopic, and replacement of such a point yields a chiral object ($C_2$). It is thus seen that in a spherical object, stepwise desymmetrization is unavoidable, and that $p_{min} = 3$ in $E^3$.

(83) If replacements are restricted to ligands on a permutation frame, it may not be possible to desymmetrize the model in other than a stepwise manner. Such is the case, for example, in (pro)$^4$-chiral CH$_4$ ($T_d$) and (pro)$^4$-chiral PF$_5$, ($D_{3h}$). However, this constraint, which is imposed by giving primacy to constitution over symmetry, is lifted under our treatment of (pro)$^2$-chirality. For example, addition of H$^+$ to CH$_4$ yields (pro)$^2$-chiral CH$_3^+$ ($C_{3v}$) directly, without the intervention of a (pro)$^2$-chiral intermediate.

(84) According to ab initio calculations, the ground-state symmetry of CH$_3^+$ is $C_1(C_2H_2)$, $C_1(H_2)$ in Pople's framework group notation as modified by Flurry. See: Raghavachari, K., Whiteside, R. A., Pople, J. A., Schleyer, P. v. R. J. Am. Chem. Soc. 1981, 103, 5649.