nor POPC undergo a phase transition, since there are no discontinuities in ln k vs. pressure plots.[16] Pressure, however, does compress the host lipid matrix (POPC), and in part the positive $\Delta V^{\ddagger}$ of transfer reflects the work necessary to overcome this effect. Finally, MPNPC is an amphiphilic molecule and changes in volume can arise from electrostriction effects near the charged choline moiety or by hydrophobic hydration of the fatty acid chains. The transfer rates of pyrene conjugated hydrocarbons[4] (uncharged and nonpolar molecules) indicate a $\Delta V^{\ddagger}$ similar to that for MPNPC, correcting for differences in molecular weight (W. W. Mantulin, unpublished data). Therefore, by comparison it appears that the zwitterionic polar head group of MPNPC is not as important a factor as the aliphatic region in establishing the size and magnitude of $\Delta V^{\ddagger}$ for transfer.[17] Since transfer of amphiphiles is governed by "hydrophobic interactions",[14] we postulate a change in the packing of water around MPNPC (hydration density) in the activated state. Future studies to test this hypothesis will focus on the use of neutral salts in a lyotropic series, in conjunction with high-pressure perturbation, to vary lipophile hydration.[18]

Acknowledgment. We acknowledge stimulating discussions with Drs. G. Weber and D. Jameson. The authors are indebted to Dottie Tullos for preparing the manuscript, Susan Kelly for providing the line drawing, and F. W. C. Fu for technical assistance. This research was supported by the Specialized Center of Research in Atherosclerosis HL-27341 (H.J.P. & W.W.M.) and Grant HL-27104 (W.W.M.) and a grant from the Robert A. Welch Foundation, Q906 (H.J.P.).

Registry No. POPC, 6753-55-5; MPNPC, 79821-58-2.

(16) Heremans, K.; DeSmedt, H.; Wuytack, F. *Biophys. J.* **1982**, *37*, 74–75.
(17) Massey, J. B.; Gotto, A. M., Jr.; Pownall, H. J. *J. Biol. Chem.* **1982**, *257*, 5444–5448.
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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.[5] 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.

(1) van 't Hoff, J. H. "Voorstel tot uitbreiding der tegenwoordig in de scheikunde gebruikte structuur-formules in de ruimte; benevens een daarmee samenhangende opmerking omtrent het verband tusschen optisch actief vermogen en chemische constitutie van organische verbindingen"; J. Greven: Utrecht, 1874. van 't Hoff, J. H. *Arch. Néerl. Sci. Exactes Nat.* **1874**, *9*, 445. van 't Hoff, J. H., "A Suggestion Looking to the Extension into Space of the Structural Formulas at Present Used in Chemistry and a Note upon the Relation between the Optical Activity and the Chemical Constitution of Organic Compounds"; Benfey, O. T., Ed.; Dover Publications: NY, 1963; Classics of Science (Classics in the Theory of Chemical Combinations), Vol. 1. See also: van 't Hoff, J. H. *Bull. Soc. Chim. Fr.* **1875**, *23* (2), 295.
(2) For a historical overview, see: (a) Riddell, F. G.; Robinson, M. J. T. *Tetrahedron* **1974**, *30*, 2001. (b) Mason, S. F. *Top. Stereochem.* **1976**, *9*, 1. (c) Ramsay, O. B., Ed. "van 't Hoff – Le Bel Centennial"; American Chemical Society: Washington, DC, 1975; ACS Symp. Ser. No. 12. (d) Ramsay, O. B. "Stereochemistry"; Heyden: London, 1981.
(3) "Wir bezeichnen deshalb ein solches Kohlenstoffatom als ein asymmetrisches, wobei in Erinnerung gebracht werden möge, dass diese Bezeichnung sich nicht auf die Gestalt des Kohlenstoffatoms, sondern auf dessen räumliche Lage im Molekül bezieht".[4]
(4) van 't Hoff, J. H. "Die Lagerung der Atome im Raume"; Herrmann, F., Transl. and Ed.; F. Vieweg und Sohn: Braunschweig, 1877.
(5) Anet, F. A. L.; Miura, S. S.; Siegel, J.; Mislow, K. *J. Am. Chem. Soc.* **1983**, *105*, 1419. It must be emphasized that this segmentation is an abstract and purely geometric operation and not a chemical fragmentation.

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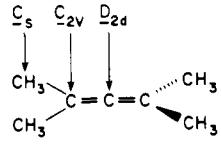
be symmetry-adapted to G,[6] regardless of the nature of the molecular model.[7]

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,[8] which may be defined as the subgroup of G that is composed of all symmetry operations that leave the nucleus unmoved. 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 ($C_{\infty v}$) corresponds to the local symmetry of H in H_2 and HCl, but not to that of H in H_2O (C_s), H in CH_4 (C_{3v}), or H in CHBrClF (C_1). 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_{2v}, and C_s site symmetries.[9]



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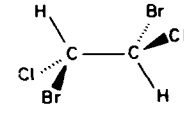
In discussing the local symmetry in a molecular model, account must also be taken of the molecular environment. For most chemical purposes, the symmetry of the model in isolation approximates the symmetry of the system, and this approximation will be adopted in all subsequent discussion. We note, however, that under certain circumstances (e.g., interactions among molecules in the solid state, solute–solvent interactions, gas-phase aggregations) the intersection of the symmetry of the model in isolation with the symmetry of the molecular environment may result in desymmetrization.[10]

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_n, D_n, T, O, or I symmetry. An atom with cyclic site symmetry (C_n) may be located in a molecule whose point symmetry is not C_n. A chirotopic atom whose site symmetry is higher than C_n 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 also 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_i and C_s symmetry. In the former (**2**), the



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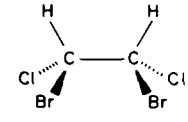

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only achirotopic point is the center of symmetry, whereas in the latter (**3**), the achirotopic points constitute the plane of symmetry. In both conformations, all atoms are chirotopic.

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

(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 δ nuclear distribution. Degenerate permutations in the general model require the symmetry equivalence of the permuted 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 infeasible 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 their internal or external symmetry relations. To exemplify the relation among these three models, consider the results of permutations on $CH_3CH_2CHBrCl$ 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 methylene 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_{2v}-1,1-dichloroallene the three carbon atoms differ in connectivity but have the same site symmetry (C_{2v}), whereas in the C_s conformations of methanol the three methyl hydrogens are constitutionally equivalent but differ in site symmetry (C_s and C_1).

(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]

(11) Curie, P. *J. Phys.* (*Paris*) **1894**, *3*, 393. See also: Shubnikov, A. V.; Koptsik, V. A. "Symmetry in Science and Art"; Plenum Press: New York, 1974; pp 328–336.

(12) The site symmetry of molecules in crystals has been similarly classified. See: Zorkii, P. M.; Razumaeva, A. E.; Belsky, V. K. *Acta Crystallogr., Sect. A* **1977**, *A33*, 1001.

(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.

(14) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.

(15) Mislow, K.; Raban, M. *Top. Stereochem.* **1967**, *1*, 1. See also: Kaloustian, S. A.; Kaloustian, M. K. *J. Chem. Educ.* **1975**, *52*, 56. Eliel, E. L. *Ibid.* **1980**, *57*, 52.

(16) For a survey of high-symmetry chiral molecules, see: Farina, M.; Morandi, C. *Tetrahedron* **1974**, *30*, 1819. Nakazaki, M. *Top. Stereochem.* **1984**, *15*, 199.

(17) Hirschmann, H.; Hanson, K. R. *Top. Stereochem.*, **1983**, *14*, 183.

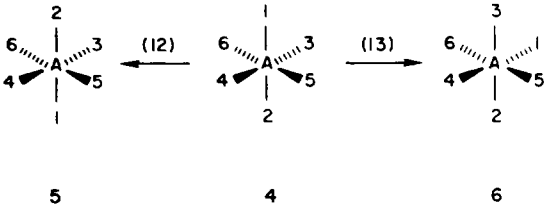
therefore also by external comparison, since internal heterotopism is a sufficient condition for external heterotopism, but not the other way around.[18] Conversely, all enantiotopic atoms are chirotopic.

On the Nature of the "Asymmetric Carbon Atom"

In the model conceived by van 't Hoff, the differences among the ligands attached to a tetravalent carbon atom may be expressed by appropriate labeling (e.g., numerical indexing or color coding) of the vertices or faces of a regular tetrahedron. The symmetry of the labeled tetrahedron is a subgroup of T_d. Accordingly, the regular tetrahedron functions as a permutation center or skeleton with four equivalent sites, and models of stereoisomers are generated by permutation of the ligands among these sites.[19] In this formulation, stereoisomers are recognized as prototypes of permutational isomers,[23] and the "asymmetric carbon atom" as the prototype of a *stereogenic atom*.[24] Indeed, the classical chemical purposes served by the concept of the "asymmetric carbon atom", i.e., enumeration, classification, and description of stereoisomers, are those that express its character as a stereogenic element. This identity as a stereocenter depends on models of bonding since, by definition, stereoisomers have the same bonding connectivity (constitution). The character of such an atom as a chirotopic entity is, however, separate and distinct from its character as a stereocenter, as evidenced by the fact that the ligands in, for example, CHBrClF are also chirotopic but are obviously not stereogenic. Thus, returning to the question raised at the beginning of this paper, there is no reason whatsoever to reserve the term "asymmetric" or "chiral"[26] for the ligating center in such a molecule.

The crux of the matter is that *chirotopicity and stereogenicity are conceptually distinct*; consider, for example, the halogen atoms in CHBrClF (chirotopic but nonstereogenic) and the carbon atoms in the CHCl groups of 1,2-dichloroethene (achirotopic but stereogenic). Nevertheless, stereogenicity and local chirality appear to be inseparably linked in the practice of organic chemistry, as epitomized by the very expression "asymmetric carbon atom". An explanation of this linkage requires a more general discussion of the relation between ligand permutations and symmetry operations.

If a permutation is to effect the same changes as a geometric symmetry operation, all unpermuted points must be invariant under this operation. It follows that in order to convert a chiral assembly constructed from an achiral skeleton and achiral ligands into the enantiomorph by a single ligand transposition, the sites on the skeleton that are occupied by the transposed ligands must be related by a mirror plane in the skeleton and all the remaining sites must be located on the same mirror plane.[29] If all the mirror planes in a skeleton share this property, the skeleton is said to belong to class a; otherwise it belongs to class b.[29] All skeletons belonging to class b allow for at least one ligand transposition that is not equivalent to a reflection. As an example, consider ligand transpositions in a chiral hexacoordinate complex with a regular octahedral skeleton (O_h). Here, although all sites are pairwise related by mirror planes of the skeleton, only transposition of ligands in the trans sites leads to the enantiomorph, because these sites are related by one of three mirror planes (σ_h) that contain the remaining four sites (e.g., **4** → **5**); transposition of one pair of ligands between cis sites does not necessarily afford the enantiomorph because these sites are related by one of six mirror planes (σ_d) that contain only two sites (e.g., **4** → **6**).



Membership in class a is not, however, sufficient to establish equivalence between ligand transposition and formation of the enantiomorph. For example, in a regular trigonal-bipyramidal skeleton (D_{3h}), apical and equatorial sites are not related by a mirror plane, and transposition of a pair of ligands between these positions in a chiral complex will not lead to the enantiomorph but to an anisometric[30] structure (e.g., **7** → **8**). Indeed, for any skeleton except the regular tetrahedron, there exists at least one transposition of ligands that does not lead to the enantiomorph.

(18) Reisse, J.; Ottinger, R.; Bickart, P.; Mislow, K. *J. Am. Chem. Soc.* **1978**, *100*, 911.

(19) As van 't Hoff recognized,[20] and as further discussed in Herrmann's rendition of van 't Hoff's work[4] and in later editions,[21] there exists an alternative mode of modeling the desymmetrization of a regular tetrahedron. In this mode, the differences among the ligands are expressed in the shape of the tetrahedron itself ("La forme du têtaèdre [sic] même indique l'espèce de la combination"[20a]) in such a way that the lowered symmetry of the tetrahedron conforms to the substitution pattern. Thus, only CH_4 and the like may be represented by a regular tetrahedron in this mode, and the asymmetric atom must be represented by an irregular tetrahedron.[22] This mode of representation was regarded by van 't Hoff as the physically more realistic of the two, since the interplay of forces among the ligand atoms was expected to have an effect on the shape of the tetrahedron.[4,20,21] However, if the angles subtended by the central ligating atom are constrained to remain tetrahedral so that changes in the shape of the tetrahedron are solely the result of changes in bond lengths, the two modes of representation become equivalent in the sense that only five point symmetries (T_d, C_{3v}, C_{2v}, C_s, and C_1) are representable by either mode. In what is to follow, all references are to the permutational mode. We note in this connection that the conditions entailed in a reversal in sense of chirality depend not only on the model of the molecule but also on the nature of the parameters chosen to define that sense. For example, if the "asymmetric carbon atom" is represented by an array of four differently labeled points located at the vertices of a regular tetrahedron, any deformation of the model that leads to a reversal in sense of chirality requires the intermediacy of an array in which all four vertices are constrained to lie in a single plane. On the other hand, if the "asymmetric carbon atom" is modeled by an irregular tetrahedron, deformation of the model through an achiral but nonplanar shape (e.g., C_{2v} or C_{3v}) into its mirror image suffices to effect a reversal in sense of chirality.

(20) (a) van 't Hoff, J. H. "La Chimie dans l'Espace"; P. M. Bazendijk: Rotterdam, 1875. (b) van 't Hoff, J. H. "Dix Années dans l'Histoire d'une Theorie"; P. M. Bazendijk: Rotterdam, 1887. Marsh, J. E., Transl. and Ed. "Chemistry in Space"; Clarendon Press: Oxford, 1891.

(21) van 't Hoff, J. H. "Die Lagerung der Atome in Raume"; F. Vieweg und Sohn: Braunschweig, 1894, 1908. van 't Hoff, J. H. "The Arrangement of Atoms in Space"; Eiloart, A., Transl. and Ed.; Longmans, Green and Co.: London, 1898. See also: van 't Hoff, J. H.; Meyerhoffer, W. "Stereochemie"; F. Deuticke: Leipzig and Vienna, 1892.

(22) Detailed directions for the construction of tetrahedra of symmetry lower than T_d are given in the Appendix (pp 46–53) of ref 4.

(23) Ugi, I.; Marquarding, D.; Klusacek, H.; Gokel, G.; Gillespie, P. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 703. See also: Dugundji, J.; Kopp, R.; Marquarding, D.; Ugi, I. "Perspectives in Theoretical Stereochemistry – a Computer Oriented Representation of the Logical Structure of Stereochemistry"; Lecture Note Series; Springer Verlag: Heidelberg, in press.

(24) McCasland, G. E. "A New General System for the Naming of Stereoisomers"; Chemical Abstracts: Columbus, OH, 1953; p 2. The term was defined as "(a) An atom (usually carbon) of such nature and bearing groups of such nature that it can have two non-equivalent configurations. (b) An atom bearing several groups of such nature that an interchange of any two groups will produce an isomer (stereoisomer)". Although definition b refers to maximally labeled permutation centers, e.g., C in Cabcd and P in Pabcde, we believe that the usefulness of the term can be expanded (in the spirit of definition a) by deletion of the conditional "any". Submaximally labeled permutation centers then also qualify as stereogenic atoms, e.g., P in trigonally bipyramidal Pa_4b.[25] By extension, any mono- or polyatomic permutation center or skeleton may be referred to as a *stereogenic element* or *unit*, or as a *stereocenter*, if ligand permutation produces stereoisomers. Note, however, that these terms are not necessarily limited to permutational isomers.

(25) It is worth noting that the apical isomer of Pa_4b is a representative of a frequently overlooked class of nonplanar stereoisomers: models of molecules in this class do not contain any chiral arrangements of four distinguishable points (atoms).

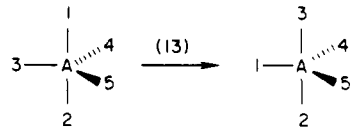
(26) The essential feature of interest is the chiral environment of the atom, and the present discussion fully applies to all chirotopic stereocenters.[27] This includes the central carbon atom in the vespirenes,[28] whose site symmetry is D_2. The site symmetry of "asymmetric carbon atoms" must by definition be C_1.

(27) Whether a stereocenter is chirotopic or not may depend on the distribution of ligands, as, for example, in Pa_2b_2c.

(28) Haas, G.; Prelog, V. *Helv. Chim. Acta* **1969**, *52*, 1202. See also: Haas, G.; Hulbert, P. B.; Klyne, W.; Prelog, V.; Snatzke, G. *Ibid.* **1971**, *54*, 491. Mills, O. S., et al., unpublished results cited in: Prelog, V.; Bedekovič, D. *Ibid.* **1979**, *62*, 2285.

(29) (a) Ruch, E. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 65; (b) *Theor. Chim. Acta (Berlin)* **1968**, *11*, 183. (c) Ruch, E.; Schönhofer, A. *Ibid.* **1968**, *10*, 91. See also: Ruch, E. *Acc. Chem. Res.* **1972**, *5*, 49.

(30) Mislow, K. *Bull. Soc. Chim. Belg.* **1977**, *86*, 595.



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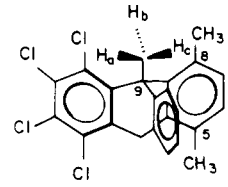
It follows that among chiral assemblies constructed from achiral permutation frames and achiral ligands, *the regular tetrahedron is the only skeleton in which every transposition of ligands is equivalent to a reversal in the sense of chirality of the ligated assembly.*[31] Even so, this relation obtains only under special conditions.[32]

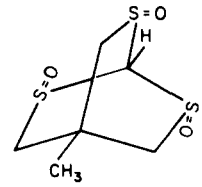
We are therefore faced with a remarkable coincidence. First, the building block of organic chemistry, the tetravalent carbon atom, is also representable as a regular tetrahedral ligating center. Second, when such a center is appropriately complemented with four different achiral ligands, chirotopicity and stereogenicity are uniquely linked.[32] 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,[34] the designation of a methyl group as "chiral" or "asymmetric" has been exclusively restricted to CHDT.[35,36] However, the biochemical significance of this isotopic labeling (as in "chiral acetic acid" (CHDTCOOH)[34,35]) lies primarily in the transformation of CH_3 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 CH_3 groups in chiral molecules are ipso facto chirotopic.[37] We provide two particularly instructive examples.

In 1,2,3,4-tetrachloro-5,8,9-trimethyltriptycene (**9**), three chemical shifts are observable for the 9-methyl protons at −90 °C.[38] Under these conditions the three hydrogen atoms are clearly





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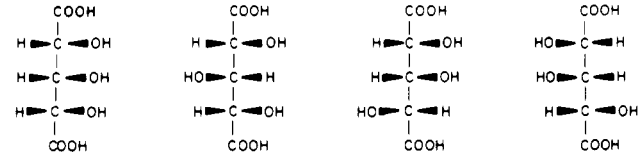
distinguishable (diastereotopic) and the 9-methyl group is chirotopic, but obviously it is not stereogenic. Although at room temperature this distinguishability is lost due to rapid site exchange on the NMR time scale, the CH_3 group remains chirotopic. Similarly, CH_3's in the 5- and 8-positions are also chirotopic. These groups remain chirotopic under all conceivable time scales of observation.[39]

The local symmetry of the CH_3 group in **10**[41] is C_3 on *any* time scale, barring inversion at sulfur or bond-breaking processes. The hydrogen atoms are therefore always indistinguishable (homotopic) even though the CH_3 group must remain chirotopic.[42]

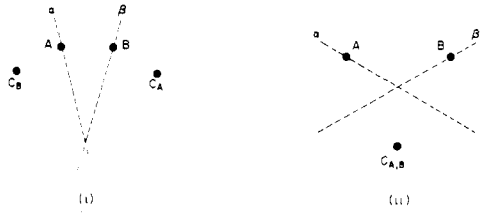
On "Pseudoasymmetric Carbon Atoms". The central carbon atom (C-3) in the two achiral diastereomers (**11**, **12**) of 2,3,4-



11 12 13 14

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",[43] 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,

(31) This special feature of the regular tetrahedron may be demonstrated by construction. Choose two points (A,B) in one dimension (E^1). Each is mirror-related to the other through the midpoint between them. (There are no figures in E^1 of more than two points such that each point is mirror-related to all others.) To generate the analogue in E^2, mirror lines α and β are passed through A and B. Two new points are created, C_A by reflection of A through β and C_B by reflection of B through α (see i); neither C_A and B nor C_B and



A are related by a mirror element. C_A and C_B can be brought into coincidence by rotation of α and β about A and B, respectively. All three points (A, B, $C_{A,B}$) are now pairwise related through mirrors, and the figure in E^2 is therefore an equilateral triangle (ii). Similarly, the step from E^2 to E^3 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 E^1, the vertices of the equilateral triangle in E^2, and the vertices of the regular tetrahedron in E^3.

(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]

(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 in appropriately substituted derivatives is therefore higher than would be the case in the absence of correlated rotation. See: Guenzi, A.; Johnson, C. A.; Cozzi, F.; Mislow, K. *J. Am. Chem. Soc.* **1983**, *105*, 1438. Thus, derivatives with substitution pattern 16 (Table I, loc. cit.) form three racemic pairs which are not interconverted in the absence of gear slippage; in two of these, transposition of the substituents a and b on the central carbon atom does not yield the enantiomeric form. Similarly, transposition of H and OH on the central carbon atom in bis(2,3-dimethyl-9-triptycyl)carbinol (substitution pattern 12) does not interconvert D and L isomers (cf. Figure 5, loc. cit.).

(34) Cornforth, J. W.; Redmond, J. W.; Eggerer, H.; Buckel, W.; Gutschow, C. *Nature (London)* **1969**, *221*, 1212. Lüthy, J.; Rétey, J.; Arigoni, D. *Ibid.* **1969**, *221*, 1213.

(35) Floss, H. G.; Tsai, M.-D. *Adv. Enzymol.* **1979**, *50*, 243. Floss, H. G.; Tsai, M.-D.; Woodard, R. W. *Top. Stereochem.* **1984**, *15*, 253.

(36) Similarly, by "chiral phospho group" is meant $P^{16}O^{17}O^{18}O$. See: Knowles, J. R. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1982**, *41*, 2424 and references therein. Lowe, G. *Acc. Chem. Res.* **1983**, *16*, 244 and references therein.

(37) Of course, the presence of chirotopic methyl groups need not be restricted to chiral molecules. For example, the CH_3's in achiral 2-chloropropane are chirotopic.

(38) Nakamura, M.; Ōki, M.; Nakanishi, H.; Yamamoto, O. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2415. Similar observations have been made for chirotopic CF_3 groups: Khan, M. A.; Tavares, D. F.; Rauk, A. *Can. J. Chem.* **1982**, *60*, 2451 and references therein.

(39) Chirality and achirality are properties of the model and must be appropriate to the time scale of observation.[40]

(40) Mislow, K.; Bickart, P. *Isr. J. Chem.* **1976/1977**, *15*, 1.

(41) Franzen, G. R.; Binsch, G. *J. Am. Chem. Soc.* **1973**, *95*, 175.

(42) The C_3 symmetry of such a CH_3 group cannot be represented by the δ distribution of the four nuclei[7] but is clearly shown by the electron distribution (Gutiérrez, A.; Jackson, J. E.; Mislow, K., unpublished results).

(43) Jaeger, F. M. "Spatial Arrangements of Atomic Systems and Optical Activity"; McGraw-Hill: New York, 1930; pp 41–42.

Fischer, Landolt, Mohr, and Pope, and has been a source of contention ever since".[44]

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, but there is no reason to exclude structural types with elements in which stereogenicity is unaccompanied by chirotopicity or vice versa. Compounds such as **11** and **12** contain a tetrahedral coordination center (C-3) that is stereogenic and achirotopic, whereas the chiral stereoisomers of 2,3,4-trihydroxyglutaric acid (**13**, **14**) contain a tetrahedral coordination center (C-3) that is nonstereogenic and chirotopic. According to Jaeger,[43] 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, CHBrClF 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 CHOHCOOH groups in **13** or **14** are diastereotopic and are expected to differ spectroscopically and in reactivity).

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 C_s symmetry, with two enantiotopic groups (CHOHCOOH or CH_3) 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 "propseudoasymmetric" 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.[2,46] 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",[47] even though it represents a radical departure from traditional stereochemistry as 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 stereoisomerism 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.

Though the molecule as a whole acts as the chromophore 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" chromophore and a chirally perturbing environment. Sector rules (e.g., the octant rule for the carbonyl $n \rightarrow \pi^*$ transition) can then be developed that relate the sign and amplitude of the Cotton effects to the spatial distribution of the perturbing atoms about the chromophore, *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 chromophore, the actual site symmetry of the chromophoric atoms in the achiral molecule must be chiral. For example, the octant rule is based on local C_{2v} symmetry of the unperturbed carbonyl chromophore in, say, formaldehyde, but the same group in, say, (+)-3-methylcyclohexanone has local C_1 symmetry, and the carbonyl group is therefore chirotopic.

By the same token, chirotopic CH_3 groups should be capable of acting as optically active chromophores. 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 $Co(en)_3^{3+}$ 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 chromophore

(44) O'Loane, J. K. *Chem. Rev.* **1980**, *80*, 41.

(45) Thus, for example, (3*R*,5*R*)-3,5-dimethylheptan-4-ol should function like $R_1R_2R_3COH$ in an asymmetric atrolactic acid synthesis, even though C-4 is not an "asymmetric carbon atom". For a related reaction, see: Mislow, K.; Prelog, V.; Scherrer, H. *Helv. Chim. Acta* **1958**, *41*, 1410.

(46) "Are the atoms of the right [tartaric] acid grouped on the spirals of a dextrogyrate helix, or placed at the summits of an irregular tetrahedron, or disposed according to some particular asymmetric grouping or other? We cannot answer these questions. But it cannot be a subject of doubt that there exists an arrangement of the atoms in an asymmetric order, having a nonsuperposable image. It is not less certain that the atoms of the left acid realize precisely the asymmetric grouping which is the inverse of this" [Pasteur, L. "Researches on Molecular Asymmetry of Natural Organic Products"; Alembic Club Reprint No. 14, Livingstone: Edinburgh, 1964]. Pasteur's "dissymétrie" and "dissymétrique" were mistranslated as "asymmetry" and "asymmetric".[44] See ref 20b, pp 29–30, for the original version.

(47) Robinson, R. *Tetrahedron* **1974**, *30*, 1477.

(48) This is in the spirit of Jaeger's exhortation: "Retournons à Pasteur!" See: Jaeger, F. M. *Bull. Soc. Chim. Fr.* **1923**, *33*, 853.

(49) See, for example: Crabbé, P. "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry"; Holden-Day: San Francisco, 1965. Caldwell, D. J.; Eyring, H. "The Theory of Optical Activity"; Wiley-Interscience: New York, 1971. Charney, E. "The Molecular Basis of Optical Activity"; Wiley-Interscience: New York, 1979. Barron, L. D. "Molecular Light Scattering and Optical Activity"; Cambridge University Press: Cambridge, 1982. Mason, S. F. "Molecular Optical Activity and the Chiral Discriminations"; Cambridge University Press: Cambridge, 1982.

(50) Barron, D. *Nature (London)* **1975**, *255*, 458. Hug, W.; Kint, S.; Bailey, G. F.; Scherer, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 5589.

(51) Schipper, P. E. In "Stereochemistry of Optically Active Transition Metal Compounds"; Douglas, B. E., Saito, Y., Eds.; American Chemical Society: Washington, DC, 1980; ACS Symp. Ser. 119, pp 73–90. Saito, Y. "Inorganic Molecular Dissymmetry"; Springer-Verlag: New York, 1979; Chapter 6.

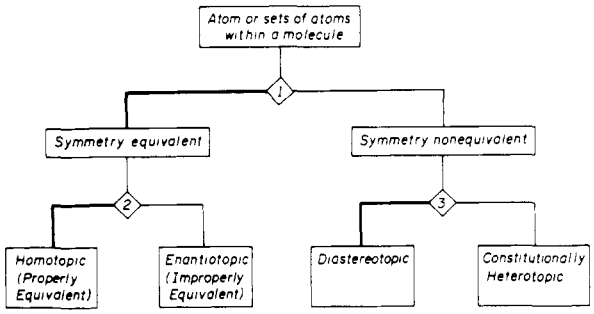


Figure 1. Flow chart for the classification of topic relationships. The decisions in response to questions are given by heavy (yes) and light (no) lines. The questions are as follows: (1) Are the atoms related by a symmetry operation of the molecule? (2) Are they related by a symmetry operation of the 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_3, the metal atom is chirotopic.

Enantiotopic chromophores have an equal but opposite effect on optical activity. For example, since the CH_3 groups in 2-chloropropane are enantiotopic, their effect on Raman optical activity is nullified through mutual cancellation in the C_s conformation.

Symmetry and Spectral Anisochrony. We recently proposed[30] a classification of pairwise relations between isomeric 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,[15] 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.[52]

Bonding connectivity plays no role in analyses based solely on considerations of symmetry, and such analyses are therefore blind to the distinction between diastereomers and constitutional isomers or between diastereotopic and constitutionally heterotopic atoms: all that needs to concern us in such a case is that the models are symmetry nonequivalent.[53] 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 structures. "Stereoisomerism" and "stereoheterotopism"[54] 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 diastereotopic 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.[18]

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[23,29] or requiring prior specification of chemical bonding,[14,17,55,56] 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.[57] 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,[58] 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.[59] 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., α for H, β for C, γ for F, etc.).[60] In the enantiomer, the corresponding descriptors indicate the opposite handedness for the corresponding environments (e.g., $\bar{\alpha}$ for H, $\bar{\beta}$ for C, $\bar{\gamma}$ for F, etc.).[60] Because there are only two symmetry-relatable 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,[6] it follows that each descriptor (e.g., α) can only be used in conjunction with others from the same molecular environment (e.g., β, *not* $\bar{\beta}$). It further follows that enantiomeric relationships may be expressed by reference to *any* chirotopic point in the model; in the example above, α and $\bar{\alpha}$ 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

(52) The terms "properly and improperly equivalent" (Figure 1) were suggested by R. A. Davidson (private communication).

(53) It is well to remember that diastereomers may differ more in physical or even in chemical properties than constitutional isomers. A classic example[21] is the conversion of maleic, but not fumaric, acid to a cyclic anhydride.

(54) Hirschmann, H.; Hanson, K. R. *Eur. J. Biochem.* **1971**, *22*, 301.

(55) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Experientia* **1956**, *12*, 81.

(56) Prelog, V.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 567. See also: Prelog, V.; Helmchen, G. *Helv. Chim. Acta* **1972**, *55*, 2581.

(57) The center of mass in chiral molecules with D_n or higher symmetry coincides with the unique point whose site symmetry is equal to the molecular symmetry. In molecules with C_n symmetry the site symmetry of the center of mass is also C_n, but its position is not uniquely defined by that symmetry.

(58) In principle an arbitrary algorithm based on through-space (*not* through-bond) distances could be formalized to index a chiral molecule without reference to bonds. Taking the center of mass (1) as the point of first priority, three more points (2, 3, 4) are chosen in order of descending priority. Point 2 is the point furthest from 1. Point 3 is the point of greatest perpendicular distance from the line 12. Finally, point 4 is the point of greatest normal distance from the plane 123. The descriptor, say (+) or (−), would then be given by the sense of the helix 1234. Where two or more points share the characteristic of greatest distance, additional characteristics (e.g., greatest slope or curvature) of these points would have to be considered. The above is intended only as an example of a possible algorithm and not as the basis for a nomenclatural scheme.

(59) This statement should not be construed to negate the meaning of "absolute configuration", since that term is defined with respect to a given, say right-handed, coordinate system.

(60) The chirotopic descriptors (α, β, γ, etc.) could be established, for example, by an algorithm similar to that developed for the center of mass.[58] We are not, however, proposing a new system of nomenclature.

of individual stereoisomers demands as a price the loss of relevance to the symmetry relationships among molecules and their segments.

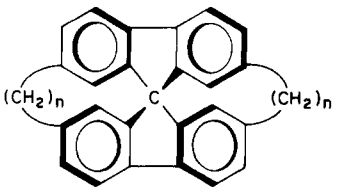
For example, in all such systems of nomenclature two descriptors suffice to label all enantiomers: one for the "right-handed" and one for the "left-handed" molecule. This is the basis for the familiar dichotomy of symbols such as D/L, *R*/*S*, Δ/Λ, etc. However, the sense of chirality of nonenantiomeric 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) representing the ligating unit and of 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.[14,55] They solely serve to identify stereoisomers and have no bearing whatever on symmetry relationships among or within molecular models.[61] It is therefore inappropriate to refer to them as "chiral descriptors".

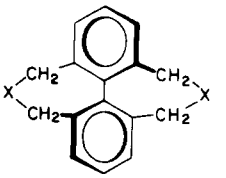
That the labels attached to stereogenic atoms are incompatible with the local chirality of these atoms may be illustrated by two examples. According to CIP rules, the configurations at C-3 in **11** and **12** are specified by "chiral descriptors" (*r* and *s*), even though the atoms in question are achirotopic. 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 *also R*, even though the atoms in the two esters are enantiotopic. 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,[55] Cahn, Ingold, and Prelog stated that "three-dimensional space can in principle be occupied asymmetrically about the zero-, one-, or two-dimensional elements of symmetry, that is, the point (or centre), the line (or axis), and the plane". This notion was embodied in the CIP system for the specification of molecular chirality as "centers", "axes", and "planes of chirality" (collectively referred to as "elements of chirality").[14,62] More recently, Prelog and Helmchen have identified these elements as stereogenic units.[56,63]

Paradoxically, the selection of "elements of chirality" in a molecule does not depend on local or molecular chirality. Consider, for example, two classes of molecules with D_2 symmetry, the vespirenes (**15**, n = 6–8)[28] and the doubly bridged biphenyls (**16**, X = O, S, CO, CH_2).[64] In both **15** and **16** the center of mass



15



16

is the unique point with D_2 site symmetry.[57] This point coincides with the central carbon atom in **15**, which is also a stereocenter, and with the center of the biphenyl bond in **16**. Yet it is only the vespirenes that are considered to possess a "center of chirality",[28] while the biphenyls are said to possess "axial chirality"[28,65] even though, according to CIP convention, "centers of chirality" need not coincide with atomic centers.[14,56,62,66] This example makes it abundantly clear that local or molecular chirality is not at issue and that "elements of chirality" are related purely to stereogenicity. Similarly, the central atom in molecules with *T* symmetry (e.g., tetra-*tert*-butylphosphonium ion[67] and tetrakis(trimethylsilyl)silane[68]) is located at the unique point with *T* site symmetry, yet, because it is not a stereocenter, that atom does not qualify as a "center of chirality" under the CIP system.[14] Conversely, in molecules with C_n symmetry there is no unique point whose symmetry identifies it as the molecular center,[57] yet it is only the stereogenic units in such molecules that are described as "elements of chirality" under the CIP system.

"Elements of chirality" are not related to observable quantities. They cannot be identified or characterized by any physical or chemical measurements; for example, it is impossible to identify "elements of chirality" by chiroptical or spectroscopic (e.g., NMR) observations.[69] It cannot be emphasized too strongly that the purely stereogenic character of "elements of chirality" in a molecule must not be confused with the chirality properties of that molecule. For example, a stereospecific rearrangement of a chiral educt with a single stereocenter M to a chiral product with a single stereocenter N is commonly referred to as a "transfer of chirality from M to N" (i.e., from "center of chirality" M to "center of chirality" N). In fact, however, what is transferred in this process are stereocenters (M → N): chirality is retained throughout, not transferred. It is equally misleading to speak of a molecule as being "chiral (or optically active) at M", where the intent is to express M's property as a stereocenter in a chiral

(61) According to Ruch,[29] chiral ligated assemblies composed of an achiral skeleton and achiral ligands can be divided into two heterochiral classes (in the manner of shoes or screws) only if the skeleton belongs to class a (e.g., the regular tetrahedron). However, as also pointed out by Ruch,[29a] even so this division cannot be accomplished unless the ligands differ by no more than *one* continuously varying parameter (likened to the diameter of a sphere).

(62) (a) Cahn, R. S. *J. Chem. Educ.* **1964**, *41*, 116. (b) Prelog, V. *Proc. K. Ned. Akad. Wet., Ser. B: Phys. Sci.* **1968**, *71*, 108. (c) *Chem. Br.* **1968**, *4*, 382. (d) Helmchen, G.; Haas, G.; Prelog, V. *Helv. Chim. Acta* **1973**, *56*, 2255. (e) Prelog, V. *Science (Washington, D.C.)* **1976**, *193*, 17.

(63) Hirschmann and Hanson[17] have advanced an alternative factorization scheme based on "elements of stereoisomerism"; in their scheme, primacy is explicitly given to stereogenicity.

(64) Mislow, K.; Glass, M. A. W.; Hopps, H. B.; Simon, E.; Wahl, G. H., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 1710.

(65) The concept of "axial chirality" was introduced as "axial asymmetry" in the 1956 paper by Cahn, Ingold, and Prelog[55] and illustrated with four classes of structures: allenes, alkylidenecycloalkanes, spirans, and biaryls. In their 1966 paper[14] a fifth class was added, the adamantoids, and biaryls as a class were said to be "conformational" while the other four classes were "clearly configurational". In the most recent (1982) revision of the CIP system[56] 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 allenes seem to have survived the vicissitudes of this definition.

(66) Tetrasubstituted adamantanes (formula 62 in ref 14) exemplify "centers of chirality" that do not coincide with atomic centers.

(67) Schmidbaur, H.; Blaschke, G.; Zimmer-Gasser, B.; Schubert, U. *Chem. Ber.* **1980**, *113*, 1612.

(68) Bartell, L. S.; Clippart, F. B., Jr.; Boates, T. L. *Inorg. Chem.* **1970**, *9*, 2436. See also: Iroff, L. D.; Mislow, K. *J. Am. Chem. Soc.* **1978**, *100*, 2121.

(69) Identification of a stereogenic element (e.g., a "chirality element") requires prior definition of the molecular bonding graph, which is based on the localized valence bond model. This poses few difficulties in the case of most conventionally structured, i.e., covalently bonded, molecules (e.g., organic compounds) but may lead to problems in the domain of inorganic or organometallic chemistry, where bonding relationships are more complex. For example, in 1-fluoro-2-chloroferrocene, which are the stereogenic elements: the C_5H_3FCl ring, whose faces represent enantiotopic coordination sites, or the carbon atoms in the ring, which, if viewed as formally bonded to Fe, function as tetracoordinate stereocenters? Such questions defy solutions based on observations and must be settled arbitrarily (from the point of view of bonding theory) on grounds of perceived convenience in stereochemical nomenclature.

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

desymmetrization index p	0	1	2	3
description of molecule (segment)	chiral (chirotopic)	(pro)^1-chiral ((pro)^1-chirotopic)	(pro)^2-chiral ((pro)^2-chirotopic)	(pro)^3-chiral ((pro)^3-chirotopic)
molecular or local symmetry	C_n, D_n, T, O, I	C_s, C_i, S_{2n}	C_{nv}, C_{nh}	D_{nd}, D_{nh}, T_d, T_h, O_h, I_h, K_h
invariant achirotopic subspace[a]	none	a plane or the central point	an axis or the central point	the central point

[a] A set of points that remain stationary under every improper rotation of the point group.

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 1966[71] and has received wide currency, especially in biochemistry.[72] Defined[73] 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 CH_3COOH, and a "pro-pro-prochiral center" by CH_4.[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 CH_2FCl. Evidently, the practical purpose of "elements of prochirality" is expressed solely by their character as prostereogenic units. Thus, C-3 in glyceraldehyde is chirotopic and yet is given the label "prochiral", a term explicitly defined for an "achiral assembly". That C-3 persists as a "prochiral center" in spite of this apparent paradox indicates that the label "prochiral" corresponds to the stereocenter that would be generated upon substitution of one of the diastereotopic hydrogens by, say, deuterium. Similarly, all the chirotopic methyl groups in, say, cholesterol are regarded as "pro-prochiral".

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 altoghether abandoned, and such a course of action seems at least worthy of consideration.[74]

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 definition[71] 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 kind[76] (σ, i, or S_n). 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 C_{2h} 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-dichloroethene of one Cl by a Br and the addition of Br^+ to the π-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 S_n (e.g., $S_2 \equiv i$) coexist in an object, desymmetrization leading to the destruction of σ will always destroy S_n, whereas the converse does not hold.

As a second example, consider an object with D_{3d} symmetry. Replacement of a point that lies off center on the S_6 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 S_6 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 C_2 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 H by a differently labeled point yields an object whose symmetry is H.[78] As such, it matches

(70) For a recent review, see: Eliel, E. L. *Top. Curr. Chem.* **1982**, *105*, 1.

(71) Hanson, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 2731.

(72) "Thus, there are now two major areas of interest, chirality and prochirality" (Bentley, R. In "New Comprehensive Biochemistry, Vol. 3: Stereochemistry"; Neuberger, A., van Deenen, L. L. M., Tamm, Ch., Eds.; Elsevier Biomedical Press: Amsterdam, 1982). See also: Bentley, R. "Molecular Asymmetry in Biology"; Academic Press: New York, 1969; Vol. 1. Alworth, W. L. "Stereochemistry and Its Application in Biochemistry"; Wiley-Interscience: New York, 1972.

(73) Hirschmann, H. *Trans. N.Y. Acad. Sci., Ser. II* **1983**, *41*, 61.

(74) "Prostereoisomerism" and "prostereogenic element" are terms that not only speak directly to the issue but that also, unlike "prochiral", embrace the potential for stereoisomerism in situations where "elements of chirality" are not involved. For example, the phosphorus atom in trigonal bipyramidal Pa_5 is prostereogenic because the b can be apical or equatorial in Pa_4b. Similarly, the central atom M in the octahedral complex Ma_5b and the tetragonal (planar) complex Ma_3b is prostereogenic because the b's can be either cis or trans in Ma_4b_2 and Ma_2b_2.

(75) Donaldson, J. D.; Ross, S. D. "Symmetry and Stereochemistry"; Halsted Press Div., Wiley: New York, 1972; p 132.

(76) Jaeger, F. M. "Lectures on the Principle of Symmetry and Its Applications in All Natural Sciences"; Elsevier: Amsterdam, 1917; Chapter 2.

(77) These restrictions ensure that each replacement results in a desymmetrization.

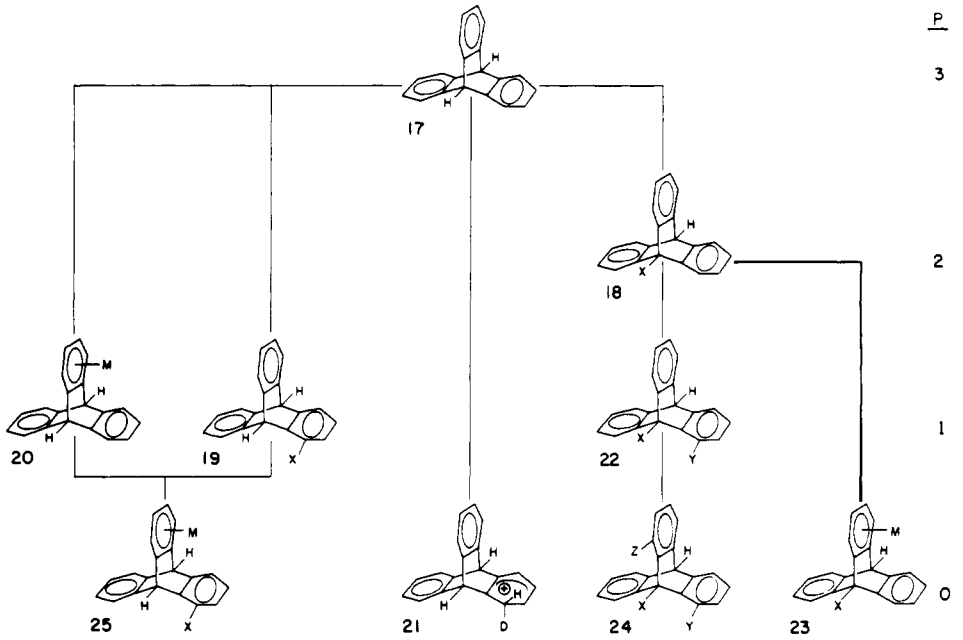


Figure 2. Partial desymmetrization lattice for triptycene (**17**). The index p is shown on the right for each row of (pro)^p-chiral structures. Symmetries are D_{3h}, C_{3v}, C_s, and C_1 for p = 3, 2, 1, and 0, respectively. M represents a π-bonded ligand, e.g., a transition-metal η^6-complex.

chirality as an attribute related purely to symmetry.

We define as *(pro)^p-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)^p-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–reflection) of the point group, and the aforementioned replacements are restricted to points lying outside these achirotopic subspaces. *(Pro)^n-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)^p-chiral classes (Table I) and illustrate each with chemical examples.[79]

Models with p = 3 may belong to D_{nd}, D_{nh}, one of the achiral cubic groups, I_h, or K_h and are (pro)^3-chiral. Because of their high symmetry, members of this class serve as good examples for the desymmetrization procedure. Consider a model of (pro)^3-chiral triptycene (**17**, Figure 2). The achirotopic points in **17** are distributed among the following subspaces: central point (D_{3h} site symmetry), rotation axes (C_{3v} or C_{2v} site symmetry), and mirror planes (C_s site symmetry). The points in these three categories are (pro)^p-chirotopic, with p = 3, 2, and 1, respectively. All other points lie in general positions and are chirotopic (p = 0). In Figure 2 are shown various ways in which replacement of points in the model yields structures with lower symmetry and p indices. Replacement of (pro)^2-chirotopic H on C-9 or C-10 in **17** by another atom (X) yields (pro)^2-chiral **18**, whereas replacement

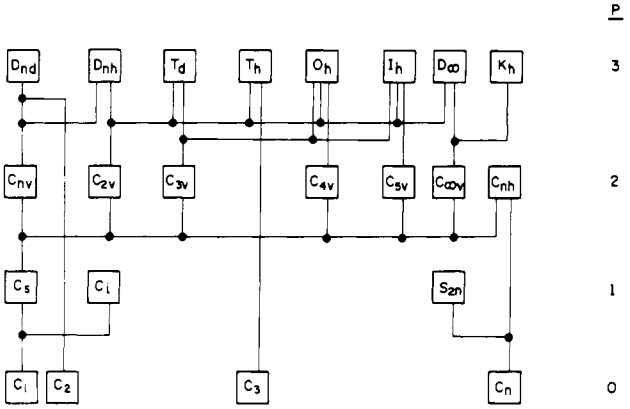


Figure 3. Desymmetrization lattice for (pro)^p-chiral objects. See text for additional comments.

of (pro)^1-chirotopic H on C-1 yields (pro)^1-chiral **19**. Replacements are not necessarily restricted to ligand substitutions; thus π-complexation of **17** (corresponding to replacement of a point on the σ_h plane) yields (pro)^1-chiral **20**, a known compound for M = $Cr(CO)_3$.[80] 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 C_{nv} or C_{nh} and are (pro)^2-chiral. As before, desymmetrization need not occur in a stepwise manner. For example, replacement of (pro)^1-chirotopic H on C-1 in **18** (Figure 2) by Y yields (pro)^1-chiral **22**, whereas replacement of a chirotopic point by π-complexation yields chiral **23**.

Models with p = 1 may belong to S_{2n}, C_i, or C_s and are (pro)^1-chiral. Under the operation of S_{2n} or i, a single point in the model remains invariant, and under the operation of σ so do 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 S_{2n}, 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)^0-chiral ≡ chiral.[81] There are no

(78) Where the replacing point is not new to the model, the symmetry of the object becomes the local symmetry of the ensemble of points that are similar to the replacing point. Thus, in the replacement of H on C-3 of (*E*)-2-chloro-2-butene by Cl, the H has C_s site symmetry but the symmetry of the product ((*Z*)-2,3-dichloro-2-butene) is the same as the local symmetry of the ensemble of Cl's, i.e., C_{2v}. Similarly, the symmetries of the five possible products obtained upon replacement of H in chlorododecahedrane (C_{3v}) by Cl are D_{3d}, C_{2v}, C_{2v}, C_s, and C_2, corresponding to the local symmetries of the two Cl's, and not C_{3v}, C_s, C_s, C_1, and C_1, corresponding to the site symmetries of the replaced H's.

(79) The construct of (pro)^p-chirality is based on the desymmetrization of achiral symmetry groups. As such, the index p may appear to bear some resemblance to the chirality index n discussed by Ruch.[29c] However, the index p, as we define it, accounts for the desymmetrization of the entire object, and not merely of the permutation frame (skeleton). As a consequence, in our scheme there is no class of objects that cannot be desymmetrized to chiral ones. That is, we do not recognize intrinsically achiral objects; for example, n = 0 but p = 3 for benzene (D_{6h}).

(80) Pohl, R. L.; Willeford, B. R. *J. Organomet. Chem.* **1970**, *23*, C45.

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

achirotopic points in such a model. With the definition of this class, all possibilities for $(pro)^p$-chirality in E^3 are exhausted.

A desymmetrization lattice for achiral objects is displayed in Figure 3. As shown by transformations such as $D_{2d} \rightarrow C_2$ and $C_{nh} \rightarrow C_n$, and as also illustrated by the examples in Figure 2, desymmetrization need not occur in a stepwise manner, i.e., from $(pro)^p$-chiral to $(pro)^{p-1}$-chiral: replacement of any $(pro)^p$-chirotopic point will necessarily yield a $(pro)^p$-chiral object. Thus, all $(pro)^3$-chiral objects except those with spherical (K_h) symmetry may be rendered $(pro)^1$-chiral (C_s) by replacement of a point that lies on a mirror plane but off an axis, and all achiral objects except those with K_h, $D_{\infty h}$, or $C_{\infty v}$ symmetry may be rendered asymmetric by replacement of a point in a general position.[82,83]

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_s, 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 methanes.[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.

(82) Spherical symmetry (K_h) 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 ($C_{\infty v}$). In the latter, all points outside of the rotation axis are $(pro)^1$-chirotopic, and replacement of such a point yield a $(pro)^1$-chiral object (C_s). 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_1). It is thus seen that in a spherical object, stepwise desymmetrization is unavoidable, and that $p_{max} = 3$ 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 $(pro)^3$-chiral CH_4 (T_d) and $(pro)^3$-chiral PF_5 (D_{3h}). However, this constraint, which is imposed by giving primacy to constitution over symmetry, is lifted under our treatment of $(pro)^p$-chirality. For example, addition of H^+ to CH_4 yields $(pro)^1$-chiral CH_5^+ (C_s)[84] directly, without the intervention of a $(pro)^2$-chiral intermediate.

(84) According to ab initio calculations, the ground-state symmetry of CH_5^+ is $C_s[C_s(CH_3), C_1(H_2)]$ in Pople's framework group notation as modified by Flurry.[8] See: Raghavachari, K.; Whiteside, R. A., Pople, J. A., Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5649.

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 ($\Delta\delta_{B\gamma}$) between the β- and γ-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 1.2×10^{-11} s 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 hexapeptides 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., Xxx–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 hexapeptides exist in solution in two forms of average C_2 symmetry on the NMR time scale, one with all the peptide bonds as trans[9,10] and the other with two Xxx–Pro bonds as cis.[5-8] The chemical shift difference between the β- and γ-carbon resonances ($\Delta\delta_{\beta\gamma}$) is used to assign the cis and trans isomers. For a cis Xxx-Pro bond $\Delta\delta_{\beta\gamma}$ is ca. 8–12 ppm whereas this difference is smaller, 2–6 ppm, for the trans case.[12]

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[§] National Bureau of Standards.

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