n-Butyllithium was purchased from Foote Mineral Co.[16] in 1.6 *M* hexane solution.

trans-2-Hexenoic and *trans*-3-hexenoic acids were obtained commercially, the former recrystallized and the latter distilled to 99+% purity. *cis*-2-Hexenoic acid was prepared by the method of Rappe and Adeström.[17] *cis*-3-Hexenoic acid was prepared by the rearrangement of *trans*-2-hexenoic acid using lithium diisopropylamide (see below).

Equipment.—All nmr spectra were recorded on a JEOLCO C-60 spectrometer in CCl_4. All shifts are reported relative to tetramethylsilane. Ir spectra were recorded on a Perkin-Elmer IR-457 spectrometer.

Anionic Rearrangement of Hexenoic Acids.—Anhydrous THF (20 ml) and diisopropylamine (1.7 g, 0.0174 mol) were added to a dry, nitrogen-flushed flask and maintained under a nitrogen atmosphere throughout the reaction. *n*-Butyllithium in hexane (8.45 ml of 1.6 *M*, 0.0176 mol) was added to the magnetically stirred solution followed by addition of hexenoic acid (1.0 g, 0.00875 mol), each added at a controlled rate for maintaining the temperature below 0°. The solution was stirred for 30 min at room temperature, quenched with 10% HCl, and extracted with petroleum ether (bp 30–60°). The extracts were dried, the solvent was evaporated, and the mixtures of acids were converted to methyl esters with ethereal diazomethane. The products were analyzed by glpc (4-ft column, 10% $AgNO_3$–ethylene glycol) at 65° column temperature. The four methyl hexenoate isomers were readily separated at their indicated retention times: methyl *cis*-2-hexenoate (3.5 min), methyl *trans*-2-hexenoate (4 min), methyl *trans*-3-hexenoate (16 min), and methyl *cis*-3-hexenoate (32 min). These esters were subsequently trapped for their complete spectral analysis and comparison with authentic samples.

The hexenoic anion solutions prepared as above were quenched with D_2O (20 ml) and acidified with dilute HCl. The acids were extracted and the solutions dried and evaporated. The extent of deuterium incorporation in the 2 position was determined by nmr and the total deuterium content confirmed by mass spectral analysis.

Alkylations of Anions with Methyl Iodide.—Alkylation was carried out by the addition of methyl iodide (1.5 mol per mole of acid). The alkylations were complete within 90 min. Washings and isolation of products were the same as described above. The acids were converted to methyl esters with diazomethane and analyzed by glpc (4-ft column, $AgNO_3$–ethylene glycol). These esters were trapped and fully characterized with the exception of the isomeric methyl 2,2-dimethyl-3-hexenoates (cis and trans).

Spectral Data.—Spectral data for *trans*-2-, *trans*-3-, *cis*-2-, and *cis*-3-hexenoic acids and methyl esters have been documented.[17,18]

Methyl *cis*-2-methyl-3-hexenoate: nmr (CCl_4) δ 5.30 (m, 2, olefinic), 3.55 (s, 3, OCH_3), 3.22 (d, 1, α CH), 2.02 (m, 2, allylic CH_2), 1.15 (d, 3, CH_3), 0.95 (t, 3, CH_3); ir (CCl_4) 1740 cm^{-1} (C=O), no bands in 970-cm^{-1} region; mass spectrum (70 eV) *m/e* 142.

Methyl *trans*-2-methyl-3-hexenoate: nmr (CCl_4) δ 5.40 (m, 2, olefinic), 3.59 (s, 3, OCH_3), 2.95 (m, 1, α CH), 2.05 (m, 2, allylic CH_2), 1.15 (d, 3, CH_3), 0.98 (t, 3, CH_3); ir (CCl_4) 1740 (C=O), 968 cm^{-1} (trans double bond); mass spectrum (70 eV) *m/e* 142.

Isomeric mixture (cis and trans) of methyl 2,2-dimethyl-3-hexenoate: nmr (CCl_4) δ 5.4 (m, 2, olefinic), 3.55 (s, 3, OCH_3), 2.05 (m, 2, allylic CH_2), 1.2 (s, 6, CH_3), 1.0 (t, 3, CH_3); ir (CCl_4) 1740 (C=O), 968 cm^{-1} (trans double bond); mass spectrum (70 eV) *m/e* 156.

Registry No.—Methyl *cis*-2-methyl-3-hexenoate, 31599-11-8; methyl *trans*-2-methyl-3-hexenoate, 31599-12-9; methyl *cis*-2,2-dimethyl-3-hexenoate, 31599-13-0; methyl *trans*-2,2-dimethyl-3-hexenoate, 31599-14-1; *cis*-2-hexenoate dianion, 31599-17-4; *trans*-2-hexenoate dianion, 31599-18-5; *cis*-3-hexenoate dianion, 31599-15-2; *trans*-3-hexenoate dianion, 31599-16-3.

Acknowledgment.—The authors are grateful to Thomas F. Kumosinski for the ultracentrifuge determination of the dianion aggregates and to C. J. Dooley for the mass spectral analyses.

(16) Reference to a particular manufactured product does not constitute a recommendation by the U. S. Department of Agriculture over similar products not mentioned.

(17) C. Rappe and R. Adeström, *Acta Chem. Scand.*, **19**, 383 (1965).

(18) A. F. Mabrouk, H. J. Dutton, and J. C. Cowan, *J. Amer. Oil Chem. Soc.*, **41**, 153 (1964); (b) E. N. Frankel, E. Selke, and C. A. Glass, *J. Amer. Chem. Soc.*, **90**, 2446, (1968).

Elements of Stereoisomerism and Prostereoisomerism[1]

H. HIRSCHMANN*

Department of Medicine, Case Western Reserve University, Cleveland, Ohio 44106

KENNETH R. HANSON*

Department of Biochemistry, The Connecticut Agricultural Experiment Station, New Haven, Connecticut 06504

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The elements of stereoisomerism, such as centers of stereoisomerism, which are used to specify the differences between stereoisomers can be tested for chirality by two reflection tests. These tests allow one to determine (a) whether the description of the configuration of an element requires reference to a chiral object, and (b) whether the element can or cannot contribute to the chirality of a molecular model. Definitions of the various chiral (*e.g.*, chiral centers) and achiral elements are proposed which are based on both reflection tests. Additional steric elements must be defined if all atoms and groups within a molecule that can be distinguished by chemical or physical tests are also to be distinguished in chemical discourse. These are named elements of prostereoisomerism and are defined by relating them to the corresponding elements of stereoisomerism. Prochiral centers constitute an important class of such elements. The prochirality concept is also applied to achiral configurations.

In developing the sequence rule procedure for specifying molecular chirality, Cahn, Ingold, and Prelog used as their steric elements the center, axis, and plane and on occasion the conformational helix.[2] They considered two types of the center, axis, and plane (the chiral and the pseudoasymmetric) but did not provide an explicit definition of these categories. Following this approach one of us[3] introduced the concept of prochiral elements and defined these by relating them to the cor-

(1) (a) Supported in part by Grants AM 9105 and K6-AM-14367 from the National Institutes of Health (H. H.), and GB 12428 from the National Science Foundation (K. R. H.). (b) The study was undertaken as a result of discussions by the Panel on Stereonomenclature of the Office of Biochemical Nomenclature, National Academy of Sciences–National Research Council (current panel membership: S. Englard, K. R. Hanson, H. Hirschmann, S. J. Kiehl, and G. J. Schroepfer, Jr.; corresponding members: D. Arigoni and W. Klyne) and its predecessor, the NAS–NRC Subcommittee on Biochemical Nomenclature. Our preliminary conclusions were presented at a IUPAC–IUB meeting at the Ciba Foundation in London (1968) and in greater detail at a Table Ronde Roussel in Paris (1970).

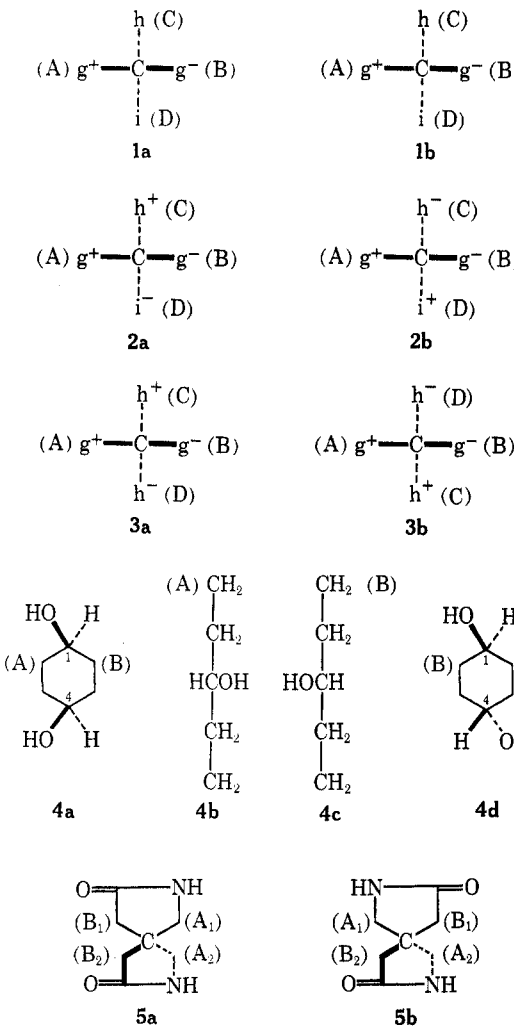
(2) R. S. Cahn, C. K. Ingold and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385, 511 (1966).

(3) K. R. Hanson, *J. Amer. Chem. Soc.*, **88**, 2731 (1966).

responding chiral and pseudoasymmetric elements. The necessity for revising the definition of prochirality became clear when it was recognized that two fundamentally different approaches to factorizing a molecule into its steric elements had been employed. Cahn, *et al.*,[2] emphasized that the factorization step is prior to and independent of the use of the sequence rule. On the other hand, Hanson[3] made the sequence rule the final arbiter in deciding when two ligands at a center were alike or distinct. Although in the vast majority of cases the proper classification of a steric element is quite obvious, enough ambiguous cases were encountered to prompt us to search for precise definitions that would be independent of any specific system of nomenclature.

Some of the problems may be illustrated by quoting a passage from van't Hoff's "Chemistry in Space."[4] "In the first place, with regard to asymmetry, of course no carbon atom situated in a closed chain can be combined with four different groups, but if it does not possess a plane of symmetry it will still be asymmetric." If a carbon atom is to be regarded as asymmetric if it is joined to four different groups or if it does not lie in a plane of symmetry, we need to know which criterion governs when there is a conflict between these definitions. This is the case if two of the ligands form an enantiomeric pair as in Cg^+g^-hi (**1a**).[5] Those who stressed the difference between the four ligands have called the central carbon atom asymmetric;[6,7a] Werner[8] spoke of pseudoasymmetry to distinguish this case from those having "wirklich asymmetrische Kohlenstoffatome," *i.e.*, those with four ligands that were either materially or constitutionally distinct; Wittig[9a] called attention to the plane of symmetry and found that such a carbon atom is neither asymmetric nor "vorgetäuscht asymmetrisch." If we replace one or both of the achiral ligands (h, i) of **1** by chiral ones (as, *e.g.*, in **2a**) we lose the plane of symmetry. The recently published IUPAC rules[10] classify the central carbon atom of $Cg^+g^-h^+i$ as pseudoasymmetric, whereas Eliel[11] stated that it could be asymmetric. Werner called attention to case **3a** and, consistent with his definition, classified it as pseudoasymmetric. The IUPAC document also comments on this case, points out that the *molecule* is chiral, but the definitions given do not allow one to classify the central carbon as either asymmetric or pseudoasymmetric.

Both Werner[8] and the IUPAC[10] rules base their distinction between asymmetric and pseudoasymmetric carbon atoms on the nature of the difference between ligands. In order to decide whether two ligands are equivalent, enantiomeric, or otherwise distinct we must



have a clear understanding of what is meant by ligand. As the quotation from van't Hoff indicates, the meaning of ligand is not obvious if it is joined to the ligating atom by more than one bond. Wittig[9b] suggested that the bidentate ligand of an asymmetric carbon atom that is located in a ring could be split into two different halves, but used larger fragments on other occasions.[9c] The size of ligands attached to a chiral carbon atom also varies when they are compared for purposes of determining their sequence rule priorities:[2] exploration of a ligand stops when a difference has been found, but this process may require a return to the chiral atom whose ligands are being examined. Also no fixed terminus of a ligand was set when, for the purpose of determining asymmetric carbon atoms, the term group was defined[10] as "the series of atoms attached to one bond."

A definition of the asymmetric carbon atom with wider scope than the traditional ones was given by Mislow[7b] when he described it as an atom to which four substituents are attached which differ in the sense that an exchange of any two gives a new stereoisomer. According to this definition the carbinol carbons of 1,4-cyclohexanediol (**4a**) and the central carbon atoms of **5a–7a**[12] are asymmetric. Clearly this use of the term is unrelated to the way the space around these carbon atoms is occupied, as C-1 of cyclohexanediol lies in a plane of symmetry and the central atoms of

(4) J. H. van't Hoff, "Chemistry in Space," J. E. Marsh, Ed., Clarendon Press, Oxford, 1891, p 115.

(5) Throughout this paper simple lower case letters (g, h, ...) are used if the ligands have a plane of symmetry, and the symbols g^+ and g^-, etc., for a pair of enantiometric ligands. Capital letters (A, B, ...) signify proximal atoms as defined in [3] and the statement that follows [3].

(6) G. W. Wheland, "Advanced Organic Chemistry," 2nd ed, Wiley, New York, N. Y., 1949, p 192.

(7) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, New York, N. Y., 1966: (a) p 91; (b) p 25; (c) p 50; (d) p 116.

(8) A. Werner, "Lehrbuch der Stereochemie," G. Fischer, Jena, 1904, p 28.

(9) G. Wittig, "Stereochemie," Akademische Verlagsgesellschaft, Leipzig, 1930: (a) p 88; (b) p 69; (c) p 91.

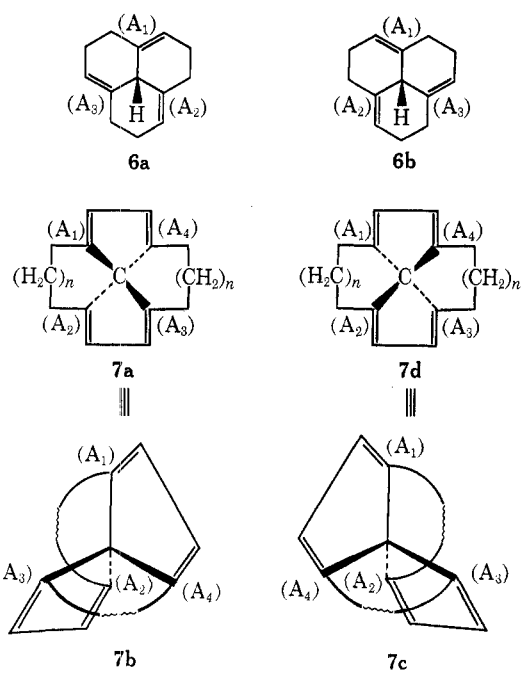
(10) IUPAC 1968 Tentative Rules, Section E. Fundamental Stereochemistry, *J. Org. Chem.*, **35**, 2849 (1970).

(11) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 29.

(12) Examples similar to or identical with structures discussed by Cahn *et al.*[2]

5–7 lie on one or more axes of rotational symmetry. With compound 7 in particular where all four atoms directly linked to the center are homotopic[13a] (they are superposable by operations of rotational symmetry), we face the question as to the nature of the difference between the substituents that allows us to obtain the enantiomer 7c from 7b by an exchange. In spite of its simplicity, Mislow's definition does not seem to be a suitable basis for a general definition of the chiral center. It can be extended to other tetrahedral atoms or to pyramidal triligated atoms. However, it seems inapplicable to trigonal carbon atoms, or to tetragonal or octahedral centers unless one wishes to call any center chiral that gives rise to stereoisomerism.

It is clear from this brief survey that there is no agreement among chemists on what constitutes an asymmetric carbon atom and that we shall need a general principle rather than *ad hoc* rules if we wish to define a chiral center.



A. Steric Centers

1. Centers of Stereoisomerism and Their Ligands. —A major purpose of the factorization of a structure into its steric elements is the development of an efficient procedure for the distinction of stereoisomers.[14] It seems appropriate therefore to begin with a more general concept than chiral center, namely a center of stereoisomerism. This we define according to the following exchange test.

(13) (a) As set forth in greater detail elsewhere,[13b] groups or atoms that are part of the same molecule and are indistinguishable in any chemical or physical test can be superposed by an operation of gyrosymmetry; such groups are called homotopic. The principal operations of gyrosymmetry are operations of rotational symmetry (C_n) and of torsional symmetry and their combinations. Groups (or atoms) that fail these superposition tests for steric reasons alone are called stereoheterotopic and may be subdivided into those that are enantiotopic and those that are diastereotopic. These subclasses were defined by Mislow and Raban,[13c] who initiated this form of description. (b) H. Hirschmann and K. R. Hanson, *Eur. J. Biochem.*, in press. (c) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).

(14) Consistent with Mislow's definition,[7c] we call two different chemical species stereoisomers if their atoms are identically connected but differ in their distribution in space, and if these species are not readily interconverted under the conditions under which their difference is being established.

[1] Centers of Stereoisomerism

[1a] An atom is at a *general* center of stereoisomerism if a stereoisomer can be produced by separating the central atom from its ligands and reconnecting them in such a manner that an exchange in the positions of two atoms directly linked to the center takes place.[15]

[1b] A general center of stereoisomerism is *improper* if the same isomer that can be obtained by the exchange operation [1a] can also be realized by severing only one link to an adjacent atom and by reestablishing the link after a rotation.

[1c] A general center of stereoisomerism is *proper* if the stereoisomer can only be obtained by the exchange operation [1a]. Throughout this paper use of the words "center of stereoisomerism" without qualification will mean that the center is proper.

The central carbon atom of **1** and either of the olefinic carbon atoms in ghC=Cij are general centers of stereoisomerism, but the only proper center is that of **1**; an exchange of the g and h ligands at the olefinic carbon, *e.g.*, would yield the same isomer as would be obtained by severing the double bond and by reconnecting the parts after the =Cij fragment has been rotated by 180°. This second way of isomerization is, of course, equivalent to a conceptual torsion of the double bond. Such improper centers of stereoisomerism will be considered in section B.

In the exchange operation [1a] an unused bonding orbital may be regarded as the equivalent of a bond. Occasionally (**23**) the exchange would result in an isomeric structure with prohibitive strain, whereas a realizable stereoisomer would result if the configuration at one or more other centers were also changed. Such an atom is also called a center of stereoisomerism, a designation which may be qualified, if desired, by the term interdependent.[16]

The exchange operation which produces stereoisomers allows one to determine how ligands ought to be defined for the purposes of factorization. In order not to prejudice the case by prior usage or by usage with different objectives, we shall speak of factorization ligands (abbreviated as *f*-ligands). If the compound is acyclic the *f*-ligands are simply the structures that result if all bonds to the central atom are broken, because these are the pieces that are reconnected to the center in a differ-

(15) (a) This definition is fundamentally similar to that given by McCasland[15b] for a stereogenic atom: "an atom (usually carbon) of such nature and bearing groups of such nature that it can have two non-equivalent configurations." Our definition is not limited to atoms that, like carbon, allow only two configurations. We are not using McCasland's term because we wish to distinguish between centers of stereoisomerism and of prostereoisomerism and find that the etymology of stereogenic fits one of these categories as well as the other. (b) G. E. McCasland, "A New General System for the Naming of Stereoisomers," a pamphlet available from the Chemical Abstracts Service, Columbus, Ohio 43210.

(16) In rare instances where the configuration of two centers cannot be independently altered, the exchange of bonds fails to produce a stereoisomer (*e.g.*, at C-2 and C-3 in 2,3-epoxysuccinic acid anhydride), but the superposition of the model before and after the bond exchange can be accomplished *only* if the center to be examined (*e.g.*, C-2) in the original model is in superposition with a different center (C-3) of the model after the exchange. Clearly, the designation of such a compound does not require the identification and steric description of such centers. However, the exchange test [1] reveals the nature of the steric difference between C-2 and C-3 and justifies their classification as "centers of intramolecular stereoisomerism." Their recognition as such and treatment as ordinary centers of stereoisomerism in nomenclature would provide a way for their differentiation by conventional terms (2*R*,3*S* in the example given).[13b]

ent manner when the stereoisomer is obtained. If we apply this to **4a**, H and OH are *f*-ligands of C-1. This is a center of stereoisomerism because we obtain the trans isomer by exchanging H and OH. We can conduct an analogous operation with a ring ligand if we give it a sense of direction. It may either start with A and end with B or *vice versa*. If the ligand starts with A, we shall call A the proximal atom. We can conduct an exchange if we reconnect in such a way that the proximal atom A takes the place originally occupied by B and *vice versa*. This again gives the trans isomer (**4d**). In obtaining it we have conceptually replaced the bidentate ligand by two *f*-ligands (**4b**, **4c**), with the proximal atoms A and B, respectively, and have exchanged these *f*-ligands. It follows that two *f*-ligands are identical only if they can be superposed in such a way that the positions of the two proximal atoms coincide. Such a superposition is not possible here; the two *f*-ligands are enantiomeric. Therefore, we define:

[2] **Factorization Ligands.**—The *f*-ligands of an atom are the structures that result (aside from the central atom) from the severance of all bonds leading to the atom. This cleavage is not to cause or allow any change of configuration in the ligands. In separating an *n*-dentate ligand, the cleavage can be initiated in *n* different ways. All of these are considered and in each case the first atom separated, the *proximal atom*, is held to be distinct from the $n - 1$ other distal atoms. This distinction is maintained when the *n* separated *f*-ligands are compared in order to determine whether they are superposable, enantiomeric, or otherwise distinct.

It follows from [1c] that stereoisomers at a center of stereoisomerism differ in the spatial distribution of the proximal atoms of this center. It is useful, therefore, to classify the proximal atoms as equivalent or nonequivalent, as this will allow us to determine when their exchange can produce a stereoisomer. Proximal atoms cannot be equivalent unless they belong to superposable *f*-ligands. Until recently this condition might have been thought to be sufficient, but examples **5**–**7** show that it is not.[2,7d] In **6a**, *e.g.*, by severing all bonds to the central carbon we obtain as the *f*-ligands H and three ligands composed of the outer circle with the proximal atoms A_1, A_2, and A_3. These three ring *f*-ligands can be superposed by a rotation through $2\pi/3$ or $4\pi/3$. There is, therefore, no difference between these ligands, but we can discern one between the proximal atoms. In going from A_1 to A_2 through the peripheral bonds we first traverse a double bond, whereas we cross a single bond first if we go to A_3. A_3 and A_2 are therefore not equivalent as they differ in their connectedness to A_1. We have analogous differences in connectedness between the pairs A_1 and A_3 to A_2, and A_2 and A_1 to A_3, and conclude that all three proximal atoms are not equivalent. As a result of this difference we can connect the central atom with A_2 and A_3 in the two nonequivalent ways shown in **6a** and **6b**. In **5a** we have two pairs of superposable *f*-ligands with the proximal atoms A_1, A_2, and B_1 and B_2. We could not have the two isomeric forms **5a** and **5b** if the two A atoms (or B atoms) were equivalent. They are not because, *e.g.*, A_1 but not A_2 is linked to B_1 through an amide bridge. Finally in **7a** we have four superposable *f*-ligands with four nonequivalent proximal atoms because A_1 is differently connected to A_2 and A_4 and unconnected (except through the central carbon or the two other proximal atoms) to A_3. In **5** and **6** at least one *f*-ligand is different from the others, but in case **7** we cannot say that isomer **7d** can be produced from **7a** by an exchange of *f*-ligands because they are indistinguishable. However, in this case as in all others we can attribute the difference between isomers to an exchange of nonequivalent proximal atoms. (**7b** gives **7c** by an exchange of A_3 and A_4.) Definition [1c] accommodates this unusual case. To define these concepts:

[3] **Assemblies of Differentiated Atoms.**—An assembly[17] of differentiated atoms at a center consists of the ligating atom and those directly linked to it. These atoms occupy the same positions they do in the molecular model (except for the customary adjustment of minor inequalities in bond lengths and bond angles). Any two of the proximal atoms are either *equivalent* or *distinct*. They are equivalent only if (1) they belong to superposable *f*-ligands [2], and (2) if their bonding relationships to any other individual proximal atom of the same center are the same.

This differentiation of proximal atoms wil be indicated in the formulas by capital letters. They will receive different letters (A, B, C, ...) if their difference is due to a difference in ligands, and the same capital letter with different subscripts (A_1, A_2, ...) if they differ only in connectedness to another proximal atom.

If we disregard the fact that some potential stereoisomers may be too strained to be realized, we can replace the molecular model by the assembly of differentiated atoms and find that *a ligating atom is at a center of stereoisomerism if and only if these differentiated points can exist in two or more nonsuperposable distributions*. It is easily verified that none of the alternative definitions of ligands that have been proposed would have given a differentiation of the proximal atoms that would have allowed this generalization.

2. Chiral and Achiral Centers of Stereoisomerism.—In examining a fully defined object, such as a molecular model, one can test whether it can or cannot be superposed on its mirror image and therefore state, without ambiguity, whether it is achiral or chiral.[10] If one subjects a center of stereoisomerism to such a reflection test, one can conduct the test in two distinct ways which reveal different properties of the center. We are presenting both before proposing a definition of the chiral center.

One may wish to determine whether the configura-

(17) The "reference assembly of point ligands" employed previously[3] in defining prochiral centers and the "assembly of differentiated atoms" discussed here are based on essentially the same concept. In both cases the individual ligands are replaced by points that are either equivalent or distinct and that occupy defined positions in three-dimensional space. The two approaches differ in the way the equivalence or difference of these points is established and in the conclusions that are drawn from this form of examination. For example, a center was previously held to be chiral if the assembly of point ligands was chiral, whereas the chirality of an assembly of differentiated atoms is now used as an index of a chiral configuration [4]. We are including the ligating center in the assembly of differentiated atoms to accommodate cases where the proximal atoms are at the base and the center at the vertex of a pyramid.

tion of a center of stereoisomerism, viewed apart from that of any other center of stereoisomerism of the same molecule, can be described only by reference to a chiral object with a defined sense of chirality. Such a chiral descriptor is needed if the assembly of differentiated atoms [3] cannot be superposed on its mirror image. If it cannot be superposed, two enantiomeric configurations are possible and these, obviously, can be distinguished only by chiral descriptors. Therefore, by subjecting the assembly of differentiated atoms to a reflection test we determine a fundamental property of the center which can be expressed as follows:

[4] **Chiral and Achiral Configurations.**—A center of stereoisomerism [1c] has a chiral configuration if its assembly of the differentiated atoms [3] cannot be superposed on its mirror image. If superposition is possible the assembly and therefore the configuration is achiral.

If we apply this to the central carbon atoms of the enantiomers of glyceraldehyde, of the optically inactive diastereomers of the trihydroxyglutaric acids (example of **1**), or to the carbinol carbon atoms of 1,4-cyclohexanediol (**4**), we find that all these have chiral configurations.[18]

Ebel[19] did not regard the carbon atom shown in **1** as asymmetric because it can "keine selbständige optische Aktivität hervorrufen." This indicates a different concept because it seems to imply that an asymmetric carbon atom is one that can contribute to the chirality of the structure. Such a contribution can be revealed by a second type of reflection test that would reflect the whole molecular model. As a chiral structure is being reflected into its enantiomer, any element of stereoisomerism that contributes to the chirality of the whole would undergo a change in configuration. If we adopt this as our test for a chiral center, we need a fixed and incontestable procedure for determining whether the configuration is retained or not. We face no choice if the set of ligands attached to the center remains unchanged on reflection of the model. This is the case in examples **1** and **3**. We can superpose the assemblies of differentiated atoms derived from the original (**1a**, **3a**) and from the reflected model (**1b**, **3b**) in case **1** but not in **3**. Therefore, the configuration of the central atom of **1** but not of **3** is retained on reflection of the whole structure. As example **2** shows, the set of ligands need not remain unaltered by the reflection and we shall have to decide whether the h^- or i^+ ligand of the reflected set corresponds to the h^+ of the original one. The proper procedure can be deduced from the case $Cg^+g^-hi^+$ which on reflection changes to $Cg^-g^+hi^-$. As the three ligands which are common to both sets fully determine the configuration, it follows that the fourth ligand of the original set (i^+) corresponds to the i^- ligand of the reflected set. As a reflection of the model can only invert a ligand or leave it unchanged, no other alternative will ever have to be faced. Consistency demands that we adopt the following rule in order that the configurations of a center of stereoisomerism may be compared before and after the reflection of a molecular model [6].

[5] **Corresponding Proximal Atoms.**—Proximal atoms at a center in an original and a reflected model correspond if the *f*-ligands [2] that contain them are superposable. If there remain proximal atoms that cannot be paired according to this rule, a proximal atom in the reflected model corresponds to that proximal atom in the original model that is associated with an enantiomeric *f*-ligand.[20] If proximal atoms in the original model are differentiated only by different bonding relationships to another proximal atom of the same center, these relationships must be preserved when choosing the corresponding proximal atoms in the reflected model.

Case **2** serves to illustrate the first part of this rule. Ligands g^+ and g^- are common to both the original (**2a**) and the reflected (**2b**) model. This determines the location of the proximal atoms that are labeled A and B. The remaining two ligands, h^+ and i^-, are found only in **2a**. According to [5] the proximal atoms of h^+ and h^- correspond and were, therefore, given the same designation (C). Similarly the corresponding proximal atoms of i^- and i^+ are designated D. As the two assemblies can be superposed, the configuration of the central atom of **2** is retained. According to the criterion under consideration, this center is achiral although the compound is not. Its chirality is due to the uncompensated chirality of the steric elements of the h^+ and i^- ligands.

The second part of [5] was justified when the stereoisomerism of examples **5**–**7** was discussed. In applying it we find that the selection of A_1 in the reflected models of **5**–**7** allows a choice which, however, has no effect on the outcome of the superposition test because the proximal atoms labeled with the same letter are homotopic.[13a] Once this choice has been exercised, the locations of the remaining proximal atoms (B_1, A_2, B_2 in **5**; A_2, A_3 in **6**; or A_2, A_3, A_4 in **7**) are unambiguously determined by their bonding relationships. The assemblies of the corresponding atoms derived from the original and reflected models of these compounds are enantiomeric and the central atoms are, therefore, chiral centers of stereoisomerism according to both criteria. No other conclusion would be acceptable, as the only element of realizable stereoisomerism present in these compounds is the center, which is, therefore, the only element which can be held to be responsible for the chirality of the whole.

If a center of stereoisomerism is directly ligated to three atoms or tetrahedrally to four, only two configurations are possible, and if a reflection causes a change of configuration it necessarily changes it to the enantiomeric one. As these enantiomeric configurations can be distinguished only by chiral descriptors it follows that such a center meets both criteria that we have con-

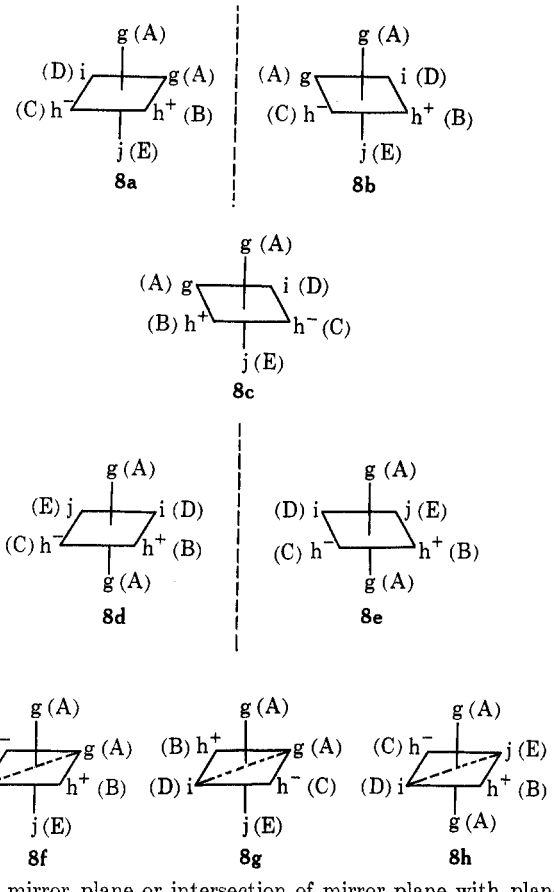
(18) Of these, only the configurations of the glyceraldehydes and of the pentaric acids are specified by chiral descriptors (*R*/*S* or *r*/*s*, respectively) under the rules of Cahn, *et al.*[2] Although it would be quite simple to design a system that would allow one to describe also the configurations of C-1 and C-4 of **4** by relating each individually to an external chiral reference standard, there is no incentive to do this because we can combine both carbinol carbons into a single steric unit and call the isomers cis and trans. This form of analysis is discussed further in section B.4.

(19) F. Ebel in "Stereochemie," K. Freudenberg, Ed., F. Deuticke, Leipzig, 1933, p 599.

(20) This rule is unambiguous if the center is tetrahedral but may require a supplementary statement in other cases. An example (**24**) will be discussed at the end of section A.4.

sidered for a chiral center: the configuration is chiral and it changes on reflection of the model.

However, if the four proximal atoms occupy the corners of a tetragon or if more than four atoms are directly ligated to a center, permutation of their distribution about the center allows more than two nonequivalent configurations. In such a case a reflection of the molecular model may change the configuration to one that is the *diastereomer* of the original one. This is illustrated by example **8** which shows eight of the 15 stereoisomers of the octahedral center Xggh$^+$h$^-$ij. In any one of the isomers **8a–e**, the configuration, as defined by



(-----) mirror plane or intersection of mirror plane with plane shown in formula

the assembly of corresponding atoms and indexed by capital letters, is changed upon reflection of the model to a diastereomeric one. The configuration[21] itself may be chiral, as in **8a–c** (the reflection of **8a** gives the enantiomer **8b** with a diastereomeric configuration,whereas **8c** is the diastereomer that has the configuration enantiomeric to that of **8a**), or achiral, as in the pair of enantiomers **8d** and **e**. All these isomers are themselves chiral and we must acknowledge that their chirality depends upon the configuration of the central atom because we can obtain achiral isomers (**8f–h**) by a different spatial distribution of the same ligands. This supports our contention that a center that undergoes any change in configuration on reflection of the model can contribute to the chirality of the whole—it is not necessary that the change is to an enantiomeric configuration. The configuration of the central atoms of the achiral isomers (*e.g.*, **8f–h**) is retained on reflection of the model. Again the configuration[21] of the centers may be chiral, as in **8f** and **g**, or achiral (**8h**). The relationship between **8f** and **g** is analogous to the diastereoisomerism that results from a change of configuration of the so-called pseudoasymmetric carbon atom of **1**.

We have thus observed all four categories that can result from applying the two reflection tests: centers of stereoisomerism either do or do not change configuration on reflection of the molecular model and each of these types has either a chiral or an achiral configuration. The criteria which determine these properties were formulated without an arbitrary choice, but we are unable to deduce from basic principles whether one ought to call a center chiral if it changes configuration on reflection of the model (*i.e.*, can contribute to the chirality of the whole), or if its configuration is chiral (*i.e.*, requires a chiral descriptor), or if it meets both criteria. A choice might be based on greater utility or on tradition. Although utility would suggest otherwise, tradition has set up the central carbon of glyceraldehyde as the paradigm of an asymmetric center and distinguished such atoms from pseudoasymmetric atoms of type **1**. This view was upheld by Cahn, *et al.*[2], who called only the former centers chiral. As the chiral center of glyceraldehyde meets both criteria for chirality, we merely continue this tradition if we suggest that both be used for the general definition of a chiral center. To formalize:

[6] **Chiral and Achiral Centers of Stereoisomerism.** —A center of stereoisomerism is chiral if (1) it has a chiral configuration [4] and (2) the configuration changes on reflection of the molecular model; it is achiral if it fails to meet either test. The configuration changes if the assembly of differentiated atoms [3] cannot be superposed on the assembly of corresponding atoms [5] derived from the reflected model.

According to these definitions isomers **8a–c** have chiral and **8d–h** have achiral centers of stereoisomerism. The configurations of **8a–c** and **8f,g** are chiral, those of **8d,e,h** are achiral. As we have seen, the type of nomenclature required depends more on the character of the configuration than on the classification of the center itself. It will be useful, therefore, to consider configurations as well and to subdivide the class of achiral centers of stereoisomerism. One category [7] is a traditional one, another [11] will be described in the next section.

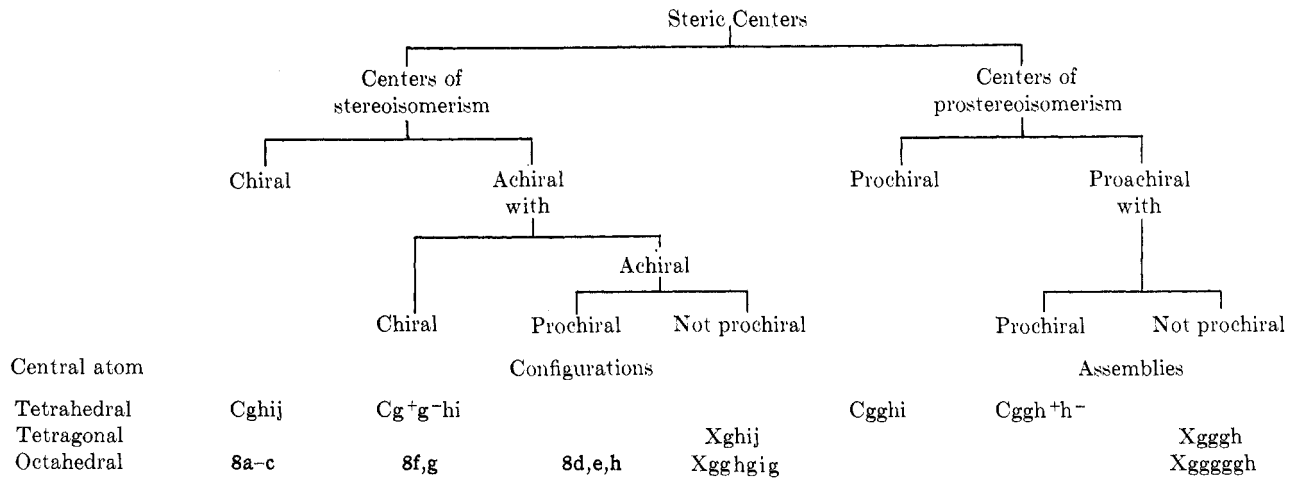
[7] Atoms that are being termed pseudoasymmetric can be defined as atoms at achiral centers of stereoisomerism [6] that have chiral configurations [4].[23]

(21) The descriptions of the configuration of **8a–c,f,g** must include an index with a defined sense of chirality. Such an index is provided by the octahedral chirality rule[2,22] and serves as the sole distinguishing mark for the pairs **8a,c** and **8f,g**. It is neither necessary nor possible to use a chiral descriptor for specifying the configuration of the centers with achiral configurations (**8d,e,h**). Of course, we need to know what is meant by h$^+$ and h$^-$, but this is clearly a separate question. We can distinguish between the enantiomers **8d** and **8e** by stating which h ligand is opposite to i or j, either directly or by means of the numbering system advocated by Cahn, *et al.*[2]

(22) The problem of ascertaining without an arbitrary convention whether two stereoisomers at an octahedral chiral center have the same or inverted sense of chirality has been discussed by E. Ruch, *Theor. Chim. Acta*, **11**, 183 (1968); also E. Ruch and A. Schönhofer, *ibid.*, **19**, 225 (1970).

(23) Cahn, *et al.*,[2] have noted that the configurational symbols for pseudoasymmetry (*r* and *s*) are unchanged on reflection of the model. This observation would be in keeping with our definition but cannot be used as a definition in its place because exceptions to their rule exist (*e.g.*, C-2 of **22**). Moreover, under the sequence rule some chiral centers also retain their configurational symbols on reflection. Such a case (C-1 of **22**) is discussed in section A.4 (examples).

CHART I[a]



Central atom	Configurations				Assemblies		
Tetrahedral	Cghij	$Cg^{+}g^{-}hi$			Cgghi	$Cggh^{+}h^{-}$	
Tetragonal				Xghij			Xgggh
Octahedral	**8a–c**	**8f,g**	**8d,e,h**	Xgghgig			Xgggggh

[a] No entry means that no example is possible for the type of central atom and class of steric center under consideration.

3. Centers of Prostereoisomerism and Prochirality.—As we have discussed elsewhere,[13b] there exist superposable *f*-ligands of the same central atom that can be differentiated from each other by suitable chemical or physical probes. A common example is provided by the ligands designated g in Cgghi. These ligands have been termed stereoheterotopic,[13a] as they reside in sterically distinct environments, and the center to which they are attached has been said to be prochiral[3] because the center is achiral but would become chiral if one of the g ligands was held to differ from the other and from h and i. One often has need to distinguish such ligands in nomenclature and, in the example given, can obtain the required pair of distinctive descriptors by determining whether the center would acquire the *R* or *S* configuration if one of these ligands (g) were given sequence rule priority over the other.[3] Such a center is not a center of stereoisomerism. Therefore, in general, if we wish to carry out a complete steric description of compounds and their constituent parts we will need to identify some sterically relevant centers that are not centers of stereoisomerism. We wish to call examples of this second type of steric center centers of prostereoisomerism and to classify them by relating them to centers of stereoisomerism as follows:

[8] **Centers of Prostereoisomerism.**—An atom is at a center of prostereoisomerism if it is not at a center of stereoisomerism [1c] and if it is linked to two superposable *f*-ligands [2] that are so located that the center would be a center of stereoisomerism if one member of this pair of superposable *f*-ligands were considered to be wholly different from all others at that center; *i.e.*, it is neither superposable upon nor enantiomeric to any other *f*-ligand.

[9] **Prochiral and Proachiral Centers of Prostereoisomerism.**—A center of prostereoisomerism [8] is prochiral or proachiral, respectively, if the center that results from the change [8] of one of the superposable *f*-ligands is chiral or achiral [6].

One can determine the chiral or achiral character of the stereoisomerism that would result if one or the other of the superposable *f*-ligands underwent the same change [8], if one examines the assembly of differentiated atoms (*cf.* [4]).

[10] **Prochiral Assemblies.**—An assembly of differentiated atoms at a center [3] is prochiral if it is superposable upon its mirror image (*i.e.*, is achiral) and if it contains two equivalent proximal atoms [3] so located that it would become chiral if either member of the pair were considered to differ from all others in the assembly.

If the assembly is prochiral, a chiral terminology is required for differentiation between the *f*-ligands associated with such a pair of equivalent proximal atoms. As a chiral center always has a chiral assembly [6], a prochiral center (which would change to a chiral one on substitution [9]) must have a prochiral assembly. If the center is proachiral the assembly may or may not be prochiral.[24] Simple examples of these categories will be shown in Chart I.

If two superposable *f*-ligands are stereoheterotopic[13a] and attached to a tetrahedral center, this center is necessarily a center of prostereoisomerism. However, if the center is tetragonal or bonded to more than four proximal atoms, the two superposable *f*-ligands can also be found at centers of stereoisomerism. Example **8** gives an illustration of this, because the centers were shown to be centers of stereoisomerism and because the two *f*-ligands designated as g are stereoheterotopic as they cannot be superposed by an operation of gyrosymmetry.[13a] If we fully specify the chiral configurations of isomers **8a–c,f,g** (*e.g.*, by the combination of numbering and a chiral descriptor assigned by the octahedral chirality rule, as advocated by Cahn, *et al.*[2]), we have also specified the position of every ligand in these molecules and can refer individually to either one of the pair of the superposable ligands. This approach will not distinguish the positions of the superposable *f*-ligands in the isomers with achiral configurations (**8d,e,h**). We note, however, that their configurations would become chiral if one of the equivalent proximal

(24) In the system proposed by Hanson[3] different chiral descriptors are used in the two cases. Superposable *f*-ligands at a prochiral center are distinguished by the terms *pro-R* and *pro-S*, whereas *pro-r* and *pro-s* are used if the center is proachiral [9] and the assembly of differentiated atoms is prochiral [10].

atoms were considered to be different from any other. We could therefore characterize the position of this altered proximal atom and its associated *f*-ligand by specifying the sense of chirality (*e.g.*, *R* or *S*) that would result from the change. It is useful therefore to delineate a further subclass of an achiral center of stereoisomerism as follows:

[11] An achiral center of stereoisomerism [6] has a *prochiral configuration* if it has a prochiral assembly [10].

Achiral centers of stereoisomerism with prochiral configurations can occur only if at least five *f*-ligands are joined to the center.[25]

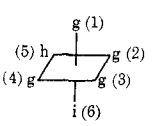
4. Examples.—The full classification presented in the above sections is summarized in Chart I. All criteria used to delineate the various categories were given above ([1c]–[11]); illustrations are shown in Chart I and Tables I and II.

It seems desirable to shorten the names of the four main classes; the chiral and achiral centers of stereoisomerism and the prochiral and proachiral centers of prostereoisomerism. We shall speak instead of chiral, achiral, prochiral, and proachiral centers with the understanding that the term center, if used in this context, always refers to a steric center, *i.e.*, a center which is either a center of stereoisomerism or of prostereoisomerism.

We are not suggesting at this time concise terms for the various subclasses shown in Chart I. The full classification of a steric center according to our criteria will rarely be required as it will usually suffice to indicate the relevant property (*e.g.*, a center with a chiral or with a prochiral configuration).

According to the exchange test [1c] examples **9**, **10**, and **1**–**3** are centers of stereoisomerism. All have four distinct *f*-ligands and therefore chiral configurations. These configurations are inverted on reflection of **9**, **10**, and **3** but not of **1** and **2**. Only the former group, therefore, has chiral centers. Examples **11**–**13** are not centers of stereoisomerism but of prostereoisomerism. On replacing one of the pair of superposable ligands by a new ligand (h), example **11** would change to **9** and is, therefore, prochiral. Examples **12** and **13** are proachiral centers as they would change to **1**.

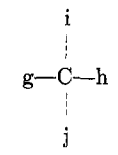
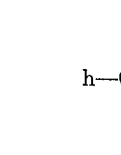
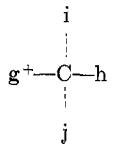
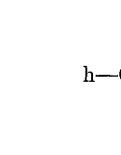
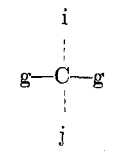
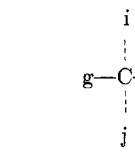
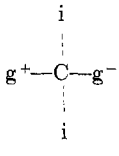
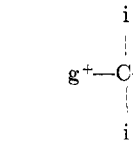
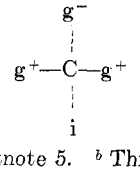
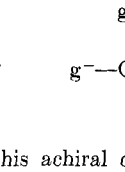
(25) An achiral center with a prochiral configuration [11] may have more than two superposable *f*-ligands. In testing [10] whether a chiral assembly results if one of these *f*-ligands is altered we must not pick this ligand at random. In the following example a replacement of a g by j would not result in a chiral assembly of proximal atoms if the change were made at positions 1 or 3, but it would at 2 or 4.



The proximal atoms at 2 and 4 lie across the plane of symmetry of the assembly and can receive alternative numbering under the rules proposed by Cahn, *et al.*[2] (assumed priority order g > h > i). No specific suggestions have been made for the distinction in nomenclature of stereoheterotopic[13a] superposable *f*-ligands at octahedral centers. We think it most convenient to distinguish their position by numbers using as far as possible the above rules.[2] If these rules leave a choice between two alternatives, the one is chosen that would result in the *R* (or *r*) configuration if at the first point of difference the ligand with the lower number had sequence-rule priority over the superposable *f*-ligands with the higher numbers. The symbols *R*-n for *R*-numbered, or *r*-n for *r*-numbered, would be used to indicate that this subsidiary rule has been applied. In the above example *R*-numbering is shown, as the configuration would be *R* if the *f*-ligand numbered 2 had priority over those at 3 and 4. In **8d**,**e**,**h** position 1 is on top if **8d** and **8e** are *R*-n and **8h** is *r*-n and the priority sequence is g > h^+ > h^- > i > j.

TABLE I

STERIC CENTERS WITH UNIDENTATE LIGANDS[a]

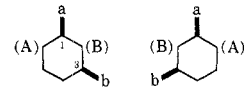
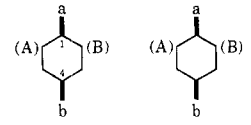
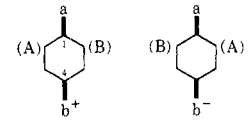
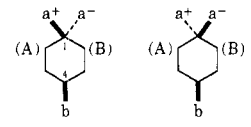
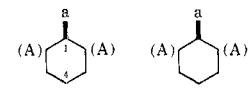
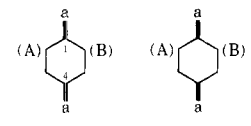
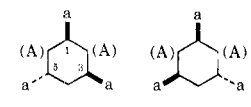
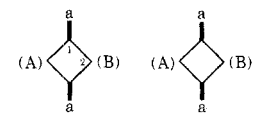
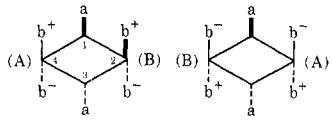
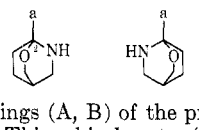
	Model (object, *O*)	Reflection (image, *I*)	Assignment of center
9			Chiral
10			Chiral
1	See text		Achiral[b]
2	See text		Achiral[b]
3	See text		Chiral
11			Prochiral
12			Proachiral[c]
13			Proachiral[c]

[a] See *footnote 5*. [b] This achiral center (of stereoisomerism) has a chiral configuration [4]. [c] This proachiral center (of prostereoisomerism) has a prochiral assembly [10].

The carbon atom numbered C-1 of **20** is not at a center of stereoisomerism because an exchange of its ligands H and a does not produce a stereoisomer. Its two other *f*-ligands which constitute the ring can be superposed with their proximal atoms coinciding. Both C-2 and C-6 are therefore equivalent proximal atoms of C-1 and receive the same designation (A). As C-1 would be a chiral center if these ring ligands were distinct (as those of C-1 in **14**), this center is classed as a prochiral center. In contrast, C-5 of **20** is a center of stereoisomerism because an exchange of *f*-ligands would yield the all-cis isomer. Its ring *f*-ligands are enantiomeric. If we reflect the molecular model in a plane perpendicular to the ring through C-2 and C-5, the corresponding proximal atoms of C-5 keep their positions. This shows that the configuration of C-5 is retained on reflection of the model and that C-5 is at an achiral center. The same classification applies to any center of stereoisomerism that lies in a plane of symmetry of the molecule.

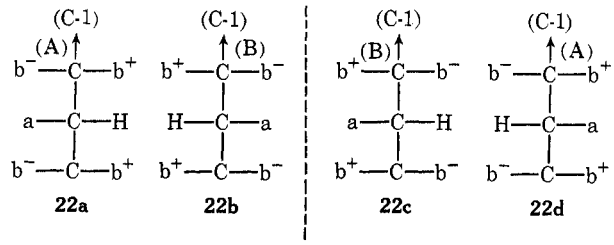
Example **22** is of interest because C-1 and C-3, which lie across a center of symmetry, receive in the *R*/*S* system the same configurational symbols which therefore do not change upon reflection. Nevertheless, analysis shows that these are chiral centers of stereoisomerism. As the two ring *f*-ligands of C-1 in **22**-(*O*) are distinct (**22a**,**b**), their proximal atoms are nonequivalent. On reflection of the model these *f*-

TABLE II
STERIC CENTERS WITH PLURIDENTATE LIGANDS[a]

	Model (object, O)	Reflection (image, I)	Assignment of center	
14			C-1 C-3	Chiral Chiral
15			C-1 C-4	Achiral[b] Achiral[b]
16			C-1 C-4	Chiral Achiral[b]
17			C-1 C-4	Chiral Chiral
18			C-1 C-4	Prochiral Proachiral[c]
19			C-1 C-4	Achiral[b] Achiral[b]
20			C-1 C-2 C-3 C-4 C-5	Prochiral Proachiral[c] Prochiral Prochiral Achiral[b]
21			C-1 C-2	Achiral[b] Proachiral[c]
22			C-1 C-2	Chiral Achiral[b]
5–7	See text		Central C	Chiral
23			C-2	Chiral

[a] The markings (A, B) of the proximal atoms refer to C-1; see footnote 5. [b] This achiral center (of stereoisomerism) has a chiral configuration [4]. [c] This proachiral center (of prostereoisomerism) has a prochiral assembly [10].

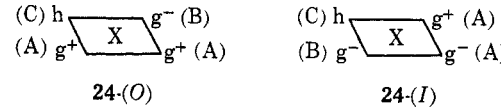
ligands change to **22c,d** which cannot be superposed on the original pair. In this case [5] the enantiomeric pairs, **22a,d**, and **22b,c** correspond. The corresponding proximal atoms (A and B) of the reflected model **22**-(*I*) are therefore located as shown. It is evident that



ligands of **22**-(*O*) ligands of **22**-(*I*)
(--- mirror plane)

the two assemblies of differentiated atoms cannot be superposed and that the center is chiral.

In this as in the other examples shown in these tables, the pairing of the proximal atoms of chiral ligands before and after reflection is unambiguously defined by the criterion given [5]. This need not be true if the center is tetragonal or octahedral rather than tetrahedral. Example **24** illustrates such a case. The central atom of **24**-(*O*) is a center of stereoisomerism which changes to **24**-(*I*) on reflection. We can pair the h and g^- and one of the g^+ ligands of **24**-(*O*) with superposable ligands of **24**-(*I*), but we must make a choice as to which of the two g^+ ligands of **24**-(*O*) is thought to be paired with the sole g^+ of **24**-(*I*). As we always conduct the superposition test between a model containing two achiral superposable *f*-ligands and its mirror image in such a way that superposition of the corresponding proximal atoms results if this is possible, we regard it as consistent if we exercise the option in pairing proximal atoms in such a way that whenever possible superposition of their assemblies can be achieved. Superposition is possible if the g^+ ligand adjacent to h in **24**-(*O*) is paired with the one in **24**-(*I*), which means that the g ligands diagonal to h in **24**-(*O*) and **24**-(*I*) are the ones that are not common to the two structures and which consequently are to be paired as enantiomers. This pairing is presented with **24** and shows that the two assemblies (XAABC) can be superposed by a rotation of a diagonal axis through the proximal atom C. The center of **24** is therefore achiral. As the plane of the tetragon is a symmetry plane of the assembly of differentiated atoms, the configuration is likewise achiral; the compound, of course, is not.



24-(*O*) **24**-(*I*)

Cahn, *et al.*,[2] have given numerous examples of chiral and of achiral octahedral centers of stereoisomerism. All would receive the appropriate classification under the definitions which we have presented.

B. Other Elements and Units of Stereoisomerism and of Prostereoisomerism

It follows from [1b] that the stereoisomers resulting from an exchange of *f*-ligands at an improper center of stereoisomerism have superposable assemblies of differentiated atoms for the center. These stereoisomers usually contain a second improper center such that the two isomers are also interconverted by an exchange of *f*-ligands at this center. By constructing an assembly containing both centers and their proximal atoms one can obtain a larger entity that differs for the two isomers. This allows their distinction and represents an *element of stereoisomerism*[26] if, in case of a choice, the two improper centers are as close as possible. The isomerism of the olefins provides a simple example. The olefinic carbons are the improper centers of stereoisomerism which singly do not permit a descrip-

(26) An element of stereoisomerism may be defined as a structural type equivalent to the most compact assembly that permits stereoisomerism by a different spatial distribution of differentiated proximal atoms.

tion of configuration. The element of isomerism consists of the two atoms linked by the double bond and the differentiated proximal atoms singly bonded to these centers.

Occasionally a structure contains two proper centers of stereoisomerism [1c] that are so interrelated that a change of configuration at either center produces the same isomer and a change at both restores the original structure. In many such cases it is convenient to describe a larger entity that combines the individual centers and their proximal atoms into a steric unit as this will permit the use of a single descriptor of configuration. The cis–trans isomerism of the 1,4-disubstituted cyclohexanes has long been recognized as such a case. Although geometrically related to the cis–trans isomerism of the olefins, the two cases differ in that an entity that can be resolved into elements of the same stereoisomerism is not, strictly speaking, an element and is more suitably termed a unit. Such *units of stereoisomerism* may contain elements besides proper centers.

Among the larger entities that contain general centers of stereoisomerism [1a] the axis and plane of stereoisomerism became important when Cahn, *et al.*,[2] showed that the chirality of many structures that had been classed as having only "molecular asymmetry" could be attributed to chirality with respect to a line (axis) or a plane. These latter two concepts are not necessarily mutually exclusive, as the same partial structure can often be viewed as either a chiral axis or a chiral plane.

1. Axes of Stereoisomerism and of Prostereoisomerism.—Cahn, *et al.*,[2] derived axial chirality and axial pseudoasymmetry by giving one dimension to the corresponding tetrahedral centers. They observed such axial chirality among the chiral allenes, alkylidenecycloalkanes, spirans, biaryls, and adamantoids, but excluded some chiral spirans although the four ligands occupied the four corners of an elongated tetrahedron. One of these is **25**, which was excluded because C-4 is a chiral center; others are spirans of type **5** where the axis which may be thought to be desymmetrized by the C=O and NH groups is occupied by only one atom, the chiral carbon at the center. It seems that the chiral axis and related achiral structures can be defined by an approach closely analogous to the one used in defining and classifying steric centers and in a manner that would exclude such cases as **5** and **25**. The axis of chirality was introduced as a geometric concept and illustrated by examples[2] that we would classify as either elements (*e.g.*, allenes) or units (*e.g.*, alkylidenecycloalkanes) of axial stereoisomerism. We have therefore phrased our definition to cover both types.

[12] **Axes of Stereoisomerism.**—An axis of stereoisomerism is a structure that contains two general centers of stereoisomerism [1a] (1) so interrelated that an exchange of differentiated proximal atoms [3] at either center produces the same stereoisomer and an exchange at both restores the original structure and (2) so oriented that the planes defined by the centers and the proximal atoms specified in [13] intersect at a large angle (usually 90°). The general centers, which should be as close to each other as possible, may be either trigonal or tetrahedral and an unused bonding orbital may be treated as a proximal atom for the purposes of the above tests. The straight line between two such centers of stereoisomerism is termed an axis of stereoisomerism with the two centers as its *terminal atoms*. These atoms, the bond(s), and any other atoms that connect them by the shortest path we term the *core*, and, if there are two or more alternative paths of equal length, no distinction is made between them but all are included in the core.

Cores analogous to the ones described for the axis of stereoisomerism will be defined below (B.2–4) for other steric elements and units. Definitions [13]–[17] have been so phrased that they are applicable to any of these elements and units. In these we shall, for the sake of brevity, speak of the steric character of a core in the same general sense as one customarily speaks of the chirality or configuration of an atom or center. The correspondence between these definitions and the definitions for a steric center will be apparent: [13] to [2], [14] to [4] and [3], [15] to [6] and [5], [16] to [8] and [9], and [17] to [10].

[13] **Core-Factorization Ligands.**—The *cf*-ligands of a core are the structures that result from separating from the core that part of the molecule that is bonded to the terminal atoms. A *proximal atom* of a core is part of a *cf*-ligand and is directly attached to a terminus. A ligand joined to terminal atoms in n bonds is treated as n separate factorization ligands each with its proximal atom as described [2].

[14] **Cores with Chiral and Achiral Configurations.**—A core of stereoisomerism has a chiral or achiral configuration, respectively, if its assembly of differentiated atoms cannot or can be superposed on its mirror image. The assembly consists of the core and its differentiated proximal atoms. The proximal atoms are differentiated as at the center [3].

[15] **Chiral and Achiral Cores of Stereoisomerism.**—A core of stereoisomerism is chiral (1) if it has a chiral configuration [14] and (2) if the configuration changes on reflection of the molecular model; it is achiral if it fails to meet either test. The configuration changes if the assembly of differentiated atoms [14] cannot be superposed on the assembly of corresponding atoms derived from the reflected model. Corresponding proximal atoms are determined as described for the center [5]. Again, special bonding relationships must be preserved. These exist if two or more *cf*-ligands are attached to the same terminal atom, if there is bonding between proximal atoms besides that through the core, or if proximal atoms are attached to different terminal atoms that cannot be superposed by an operation of gyrosymmetry[13a] performed on the core. Therefore, whenever such special bonding relationships exist, each terminal atom is examined individually as for the center [5] when the corresponding proximal atoms of the core are determined.

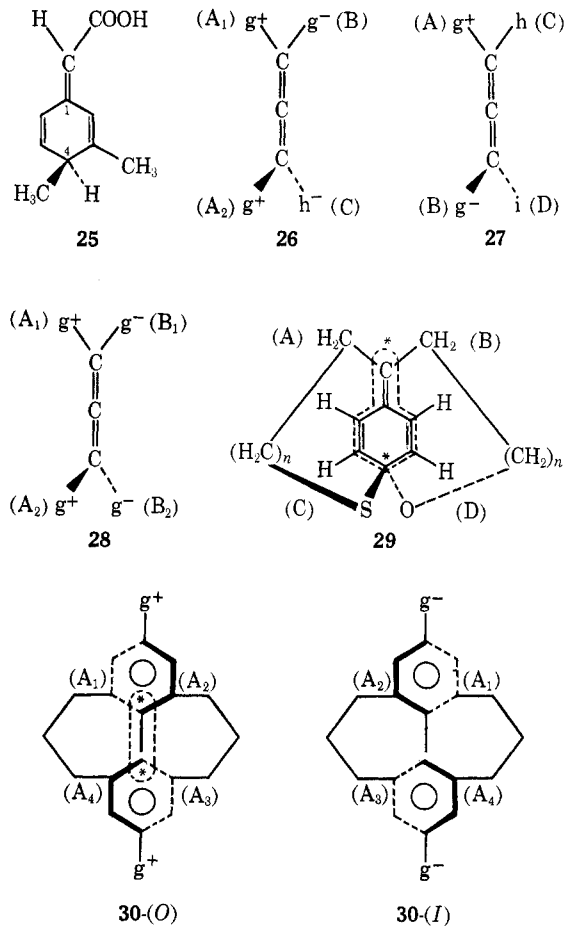
[16] **Prochiral and Proachiral Cores of Prostereoisomerism.**—A core of prostereoisomerism is not a core of stereoisomerism, but would change to such a core if one member of a pair of superposable *cf*-ligands [13] of the core were considered to be wholly different (*cf.* [8]) from all others of the same core. A core of prostereoisomerism is prochiral or proachiral, respectively, if the resulting core is chiral or achiral [15].

[17] **Prochiral Assemblies.**—An assembly of a core [14] is prochiral if it is achiral but would become chiral if one of a pair of equivalent proximal atoms were thought to be different from all others in the assembly.

If one applies these criteria to any axis of stereoisomerism [12], one finds that, as in the case of the tetrahedral center, all have chiral configurations [14], but that the configuration may or may not change to an enantiomeric one upon reflection of the molecular model, *i.e.*, the axis may be chiral or achiral. As would be anticipated from our analysis of centers of stereoisomerism [7], axes that were termed by Cahn, *et al.*,[2] pseudoasymmetric are achiral axes of stereoisomerism [15] with chiral configurations [14]. Axes of prostereoisomerism [16] fail to yield a stereoisomer upon exchange of differentiated proximal atoms at either terminus of the axis; the superposable *cf*-ligands that are held to be different in carrying out the tests for prostereoisomerism and prochirality are attached to the same terminus. As all axes of stereoisomerism have chiral configurations, all axes of prostereoisomerism have prochiral assemblies [17].

Example **26** meets the definitions of an axis of stereoisomerism [12]. Its core consists of the chain of doubly bonded carbon atoms; the terminal atoms are the trigonal carbons at the end of this chain. Both are improper centers of stereoisomerism [1b] that yield the same isomer by exchange; also the bonds connecting the *cf*-ligands g and h to these terminal atoms lie in two perpendicular planes. As the two superposable *cf*-ligands g^+ are in a different bonding relationship to g^- their proximal atoms are distinguished as A_1 and A_2. The distribution of the corresponding proximal atoms does not change if the model of **26** is reflected in the plane g^+Ch^-; therefore the axis is achiral [15], but, as expected, the elongated tetrahedron occupied by the proximal atoms A_1B, A_2C cannot be superposed on its mirror image, *i.e.*, the achiral axis has a chiral configuration. In contrast, **27** and **28** both contain chiral axes of stereoisomerism. These examples show, as do the isomers of **8**, that the description of a pseudoasymmetric carbon atom in the IUPAC rules[10] cannot be applied without revision to steric elements other than the tetrahedral center. Example **25** does not meet the definition of an axis of stereoisomerism [12] as an exchange of the H and CH_3 ligands at C-4 or of the H and COOH ligands at the olefinic carbon does not produce the same stereoisomer. Examples **29** and **30** are somewhat more complex. Their cores are circumscribed by the loops of dashes; their terminal atoms are marked by asterisks. Both are chiral axes of stereoisomerism by the criteria given. For **29** the *cf*-ligands and therefore the differentiated proximal atoms are all nonequivalent.

As in examples **26**–**28** and **30**, an exchange of the *cf*-ligands at either terminal yields the same stereoisomer. Its configuration can be completely described either by specifying that of the chiral axis or by stating that of the tetrahedral terminal atom. This is possible for **29**, because this carbon is a proper center of stereoisomerism. It is chiral when tested according to [6]. Because of their bonding relationships the proximal atoms of **30**-(*O*) are nonequivalent although their *cf*-ligands are superposable. They are enantiomers of the *cf*-ligands of **30**-(*I*) which is the mirror image of **30**-(*O*). If one proximal atom (A_1) of **30**-(*O*) is arbitrarily paired with A_1 of **30**-(*I*), the pairing of the remaining three pairs of proximal atoms is uniquely determined by their bonding relationships to A_1. The superposition test [15] shows that the two assemblies are enantiomeric and therefore that **30** has a chiral axis. The case is closely related to one discussed by Mislow, *et al.*,[27] and later by Cahn, *et al.*,[2] but shows in addition that the chirality of an axis can be deduced in such a case by our criterion even when chiral ligands are also present and when, therefore, this deduction cannot be based on the chirality of the whole structure.



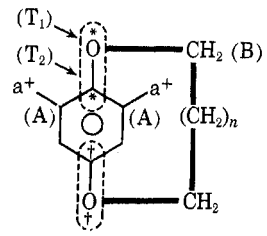
2. **Planes of Stereoisomerism and of Prostereoisomerism.**—In the plane, as in the axis of stereoisomerism, a core structure with two terminal atoms can

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

be identified.[28] One of these (T_1) is an atom that lies in the plane and is directly joined to an out-of-plane group that is limited in its orientation to one side of the plane. The second terminal atom (T_2) is the nearest improper center of stereoisomerism [1b] that is linked to the first by bonds lying in the plane and so related to T_1 that the same stereoisomer can be produced by a change of orientation of the out-of-plane group from one side of the plane to the other or by an exchange of differentiated proximal atoms [3] at T_2. If both of these changes are made the original structure is restored. The core consists of these two terminal atoms together with the bond(s) and any atoms that connect them by the shortest path. In applying [13]–[17] one finds that, as for the axis, all planes of stereoisomerism have chiral configurations [14] and all planes of prostereoisomerism [16] have prochiral assemblies [17]. Although proachiral planes can be conceived, it appears that such structures can alternatively be factorized into proachiral axes.

If the out-of-plane group that induces stereoisomerism is a simple bridge, as is generally the case, two cores usually can be identified that are interrelated in the sense that the plane has the same basic character relative to each core, *i.e.*, it is either a chiral or an achiral plane of stereoisomerism or a plane of prostereoisomerism. The latter is illustrated by example **31**. The two core structures are enclosed by dashes; their two sets of terminal atoms are indicated by the asterisks and by the daggers. The proximal atoms marked A and B refer to the former core. It is evident that the two *cf*-ligands which start at either one of the A's and which end at the other A and at B are superposable. Their exchange would produce a stereoisomer only if they were thought to be different. In this case the core would invert its configuration on reflection. The core, therefore, is prochiral. An analogous examination of the starred core of **32** shows that it is an achiral plane of stereoisomerism with a chiral configuration. The core and its proximal atoms can be superposed on the assembly of corresponding points that result from the reflection of the molecular model, but there is no plane of symmetry through the core and its proximal atoms if all three are distinct. Cahn, *et al.*,[2] have termed such a case a pseudoasymmetric plane. In these cases the ligands at the alternate cores differ constitutionally from the original ones, but this causes no change in the classification of the plane. Example **33** shows a case which, unlike **32**, has two chiral cores, but which resembles **32** in its lack of overall chirality. Example **34**, like **33**, has two chiral cores. As in **33** the *cf*-ligands of one core are the enantiomers of those at the other, but **34** represents a chiral compound. We therefore find that the two cores of a plane of stereoisomerism with such sets of enantiomeric ligands may either compensate (**33**) or not compensate (**34**) each other, and conclude that the elements of chirality are the individual cores and their proximal atoms rather than the larger entity that would result from the combination of two or more such cores.[29] This is, of course, consistent with our definition of an element of stereoisomerism.[26]

The above view is further strengthened by consideration of the examples **35** and **36**. If the planar part



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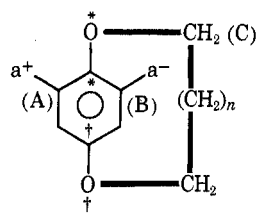

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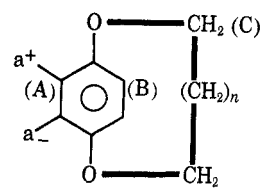

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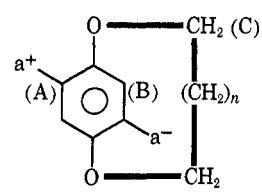

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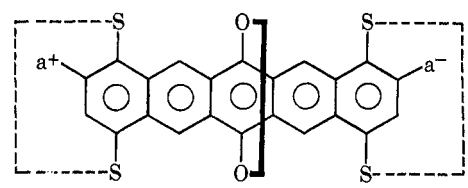

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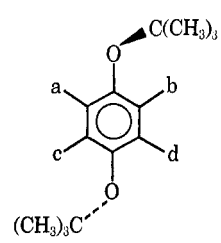

36

of the structure is wide enough to allow multiple bridging, the plane can be achiral relative to some of these bridges but chiral relative to others. In **35**, *e.g.*, the two central cores are achiral and the four lateral ones chiral. In most cases studied the out-of-plane group that induces chirality is a single bridge of such span that it cannot swing past the plane to the other side. This fixes the cis relationship of the two out-of-plane proximal atoms of the two cores and thereby ties their configurations. However, one can

(28) The present discussion is limited to structures that maintain their integrity by linking all their parts through at least one bond between *identifiable* atoms. This restriction excludes ferrocenes if these are pictured as having a π bond between the iron and the cyclopentadienyl ring. Such structures can have planes of stereoisomerism which would have to be studied by a core structure different from the one here presented. Alternatively, one can adopt the convention, as Cahn, *et al.*,[2] have done, that there are bonds between Fe and the individual carbon atoms of the cyclopentadienyl ring. From this point of view the elements of chirality present in the chiral ferrocenes are not chiral planes, but chiral centers which fall within the scope of this paper.

(29) In the *R*/*S* system[2] the choice of the pilot atom on the basis of sequence rule priorities—or an arbitrary choice if the alternative pilot atoms are homotopic[18]—in effect selects one core as the dominant one. This approach greatly simplifies the specification of the configuration but could lead to complications if, *e.g.*, the plane is chiral relative to two enantiotopic[13] cores (*cf.* **33**). Cahn, *et al.*,[2] have not yet discussed such a case. One might attempt to meet this problem by a rule that a plane should be regarded as pseudoasymmetric if the choice of the pilot atom depends on the priority sequence $R > S$. Unfortunately, this criterion would fail in the closely related case **34** which is chiral while **33** is not. After considering examples **35** and **36**, we see little prospect of evolving a general system (as distinct from a specific nomenclature) that could properly characterize *any* plane by a single term expressing its steric character as the composite of its relationship to all its cores.

conceive planes (*e.g.*, **36**) that still owe their stereoisomerism to restricted torsion (in this case by the bulky *o*-groups, a, b, ...) but that allow the independent variation of the configuration of the two cores. Therefore, the term chiral plane may not only allow but even require further factorization into the individual cores.

3. Torsional Stereoisomerism and Prostereoisomerism.—The existence of two or more nonsuperposable structures that differ only in torsional angles and that do not interconvert readily during the period of observation is a manifestation of torsional stereoisomerism. It can be analyzed for chirality or achirality in analogy to the elements already discussed if the barrier which restricts torsion is considered to be absolute and if conformational changes are allowed only within these limits. As we are usually concerned with differences about a particular bond,[29a] the core consists of the bond about which rotation is restricted and its two terminal atoms. Definitions [13]–[17] may be applied to this core. The three staggered forms of 1,2-dibromoethane, if considered to be fixed, would constitute a well-known example of torsional stereoisomerism. Of these, either one of the two synclinal (gauche) forms is a chiral element and chiral descriptors are needed for their distinction. The antiperiplanar (trans) form is an achiral element of torsional stereoisomerism [15]. It has an achiral configuration and the descriptor is, of course, achiral. These classifications would remain unaltered if the bromine atoms were replaced by chiral ligands such as g^+ and g^+, g^+ and g^-, or g^+ and h^+. Cahn, *et al.*,[2] have provided many other examples of torsional chirality and discussed them in detail. If the rotation around the C–C bond in Chij–Cggg is severely restricted, this bond is an element of torsional prostereoisomerism. A manifestation of such prostereoisomerism was observed during an nmr study of an olefin ijC=Ch[$C(CH_3)_3$], which showed a distinct signal for one of the three methyl groups.[30]

The torsion which produces the stereoisomer should be regarded as a purely conceptual operation. It ought not to be limited to cases where such an event can be realized experimentally any more than we contemplate whether the direct exchange of ligands at a center of stereoisomerism can be an actual phenomenon. In either case the sole criterion of isomerism is the stability of the final product and not the probability of the operation which relates the original structure to its isomer.[31] On this basis alternative forms of analysis are frequently possible. We can thus regard the isomerism of the olefins either as a manifestation of torsional isomerism or as an example of the steric element mentioned before and discussed further in the next section. Similarly, some forms of axial stereoisomerism (allenes, biaryls) and of planar stereoisomerism can be regarded as torsional stereoisomerism. A similar view was expressed by Cahn, *et al.*,[2] who spoke of conformational chirality. According to our presentation the distinction between these alternative forms of analysis is rather unimportant, as the difference lies solely in the operation (torsion or exchange) that is thought to produce the stereoisomer. The actual examination of the isomer, its core, and the *cf*-ligands are the same.

4. Other Steric Elements and Units.—As indicated above, the steric element of the olefins and of other sterically analogous structures can also be regarded as the composite of two improper centers of stereoisomerism [1b]. The core consists of the double bond and of the two double-bonded atoms which are the terminal atoms of the core. Such a double bond regarded as an element of stereoisomerism is always achiral; special comment is indicated only for the type g^+g^-C=Chi, which is a chiral structure. The assemblies of this double bond and its four differentiated proximal atoms derived from the original and the reflected model are diastereomeric. Each individual assembly, however, is achiral and thus the element is classed as achiral in conformity with [15]. Compound *37* of Cahn, *et al.*,[2] is similar to this type and was factorized by them in a manner which seems consistent with this deduction. The situation is analogous to **8d,e** which was discussed in greater detail above.

The cis/trans nomenclature for a 1,4-disubstituted cyclohexane (*e.g.*, **15–17**) treats the two centers of stereoisomerism of such a compound as a unit. Its core would consist of the ring carbon atoms with C-1 and C-4 functioning as the terminal atoms. This unit is achiral in all cases. In **15** and **16** the assemblies of the core and of the corresponding proximal atoms obtained before and after reflection are superposable; in **17** they are diastereomeric, but the individual assembly is achiral. Examples **16** and **17** illustrate, therefore, that the steric character of the unit may differ from that of the individual centers contained therein. Although the unit treatment serves well for the distinction of stereoisomers, full factorization of **15–17** into their centers of stereoisomerism is needed for the naming[13b] of the stereoheterotopic methylene groups that are attached to these centers.

Finally, Cahn, *et al.*,[2] have noted that adamantanes substituted at the four tertiary positions with four different ligands can exist in only two enantiomeric configurations. The four chiral centers can be combined into a single steric unit having as its core the adamantane carbon skeleton and as its terminal atoms the four tertiary carbon atoms. In applying [15] to this unit it should be noted that there are no special bonding relationships between proximal atoms through the core, as all of the termini can be superposed by simple rotations of the core and only one proximal atom is attached to each terminus.

Concluding Remarks

The creation of a universal system for the specification of chiral configurations and conformations by Cahn and his collaborators[2] represented a major advance toward a unique description of chemical structures. If the task of coding for structural infor-

(29a) NOTE ADDED IN PROOF.—This need not be the case if there is a continuous series of collinear bonds as, *e.g.*, in a cummulene. In such a case of torsional stereoisomerism the core would consist of this linear sequence of atoms, while the ends of this chain would constitute the terminal atoms of the core. It seems appropriate, therefore, to refer to any core of torsional isomerism as a *line of torsion*.

(30) A. F. Casy and R. R. Ison, *Tetrahedron*, **25**, 641 (1969).

(31) The probability of a torsional change is, of course, an important question in chemistry, but a distinctive nomenclature is available: *conformational changes* are those changes in the internal coordinates of the nuclei that occur freely during the period of observation and that do not involve changes in bonding; *conformers* are those states of a molecule that differ in conformation and that represent minima of energy (*cf.* ref 10). This definition of conformation is similar to one given by Barton [D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953)].

mation is to be entrusted entirely to machines, they will have to be instructed not only how to examine ligands in order to determine the sense of chirality[2] but also how to decide when such an examination is appropriate and whether, for example, a sinister sense of chirality is to be expressed as *S* or as *s*. These additional problems also call for precise definitions and alone provide sufficient practical justification for an inquiry as to what constitutes a chiral or a prochiral element. We faced no arbitrary choices in formulating relevant criteria and are presenting these tests with the expectation that they can serve their stated objectives. However, we found that an appropriate definition of a chiral element can be based on the outcome of either one or both of two distinct reflection tests. Our decision to use both tests in the definition of a chiral element was prompted by the realization that only this choice provided a classification that would be compatible with the Cahn–Ingold–Prelog system which, in turn, is firmly based on tradition. We present this choice not as the necessarily best solution, but rather as a point of departure for a fuller discussion which might concern itself more with the tasks of the future than with preserving the concepts of the past. Unfortunately we see no *single* answer as to what would be the most useful definition of a chiral element; those who are cataloguing and comparing stereoisomers will have to identify the partial structures that can only be described in chiral terms and these structures are not necessarily the same entities that enter the equations of those who calculate such chiral properties as optical rotation.

In factorizing a structure into the components relevant to the distinction of stereoisomers we have adhered, as far as possible, to the categories set forth by Cahn, *et al.*[2] These classes may allow alternative ways of factorizing a structure. We observed, however, that as long as the assembly of differentiated atoms met our definition of an element of stereoisomerism[26] the use of alternative classifications did not change the nature of either the *f*-ligands or of the framework to which they are attached. Moreover, only two basic types of the elemental assembly are needed to describe all forms of stereoisomerism that we have considered: (1) the assembly of the proper center and (2) the assembly of the line of torsion (B.3). Although the traditional geometric concepts (center, axis, plane, helix,[2] cis–trans isomerism[10]) are serving well as a basis of a comprehensive nomenclature of stereoisomerism, it remains an aim of fundamental stereochemistry to provide a unique mode of factorization for any stereoisomer. The two elemental assemblies of the center and of torsional isomerism appear to meet this objective for any compound that has a fully defined pattern of connectedness[28] between its constituent atoms.

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Metal–Ammonia Reduction. XI. Regiospecific and Stereoselective Reduction in the Chrysene Series

RONALD G. HARVEY

The Ben May Laboratory, University of Chicago, Chicago, Illinois 60637

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Metal–ammonia reduction of chrysene through the hexahydro stage proceeds regiospecifically *via* 5,6-dihydro- (**1**) and 4b,5,6,12-tetrahydro- (**2**) to 4b,5,6,10b,11,12-hexahydrochrysene (**3**). Existence in liquid ammonia of stable monoanionic intermediates related to **1** and **2**, but not **3**, is demonstrated by reductive methylation. Cis stereoselectivity observed in reduction of both **2** and 5,6,11,12-tetrahydrochrysene to **3** is dependent upon olefin structure. Conformational analysis of **3** indicates three possible conformations of *trans*-**3**, a boat–boat, a boat–chair, and a chair–chair form, and two sets of three similar configurations for *cis*-**3**, a "folded" set and a "twisted" set. The relative importance of thermodynamic, steric, and ion-pair factors in determining product stereochemistry is discussed.

In the previous papers of this series,[1,2] methods for the efficient, controlled reduction of representative polycyclic aromatic hydrocarbons by means of solutions of alkali metals in liquid ammonia were described. These transformations proved uniquely regiospecific (*i.e.*, only a single dihydro isomer formed at each stage), uncomplicated by secondary processes (*e.g.*, isomerization, disproportionation, dimerization, etc.) and frequently also stereospecific;[3–5] moreover, the sites of reduction were in general accord with predictions of molecular orbital theory.[6,7] Analogous reductive alkylations of polycyclic aromatic carbanions in liquid ammonia were found to exhibit similar regiospecificity but generally contrary stereoselectivity.[8–10]

We report now extension of these studies to the chry-

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