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Prochirality Revisited. An Approach for Restructuring Stereochemistry by Novel Terminology

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The importance of orbits (equivalence classes) has been stressed to restructure stereochemistry. The concept of sphericity has been formulated by a new scheme that requires a minimum set of knowledge on point-group theory. The concept of prochirality has been revisited from the viewpoint based on the new formulation of sphericity. A variety of objects such as atoms, ligands, and faces are discussed as the members of such an orbit. In particular, orbits for atoms in tetrahedral molecules and for the faces of carbonyl compounds, ethylene derivatives, and allene derivatives have been examined in terms of the concept of sphericity. The conventional topicity terms of two categories (“topic relationship between two sites” and “topic attribute of a site”) have been effectively replaced by the sphericity terms.

1. Introduction

“Prochirality” was originally proposed as a “geometrical” concept by Hanson:[1] “If a chiral assembly is obtained when a point ligand in a finite nonchiral assembly of point ligands is replaced by a new point ligand, the original assembly is prochiral.” It served as a basis for the *pro-R*/*pro-S* system that specified a relationship between paired ligands such as A’s in the tetrahedral molecules CAAXY. However, Hanson’s “prochirality” turned out not to be a geometrical concept, since such an achiral molecule as $\mathrm{CAAp\bar{p}}$ (A = an achiral ligand; p and $\bar{p}$ = a pair of enantiomeric ligands in isolation) was determined to be “proachiral with prochiral assemblies” in his subsequent paper.[2] Obviously, this determination implies that a molecule $\mathrm{CAXp\bar{p}}$ derived by the process of $\mathrm{CAAp\bar{p}}$ (achiral) → $\mathrm{CAXp\bar{p}}$ (achiral) was regarded as a chiral assembly in terms of the definition cited above, whereas the molecule $\mathrm{CAXp\bar{p}}$ was achiral (more specifically pseudoasymmetric) from a geometrical or stereochemical point of view. Mislow and Siegel[3] recommended the use of the term “prostereogenic” in place of the term “prochiral” on the same line as the term “stereogenic center” proposed earlier by McCasland[4] should be substituted for the term “chiral center” that was originally adopted in the *R*/*S* system of Cahn−Ingold−Prelog (the CIP system).[5,6]

To characterize prochirality as a geometrical concept literally, the term “enantiotopic” was used as widely accepted terminology, along with relevant terms such as “homotopic”, “diastereotopic”, and “constitutionally heterotopic”.[7−9] Thus, the procedure for determining prochirality was based on the enantiotopicity that was characterized by pairwise relationships.[7,10] Later, Mislow and Siegel[3] pointed out the importance of local chirality so as to propose the terms of distinct category, i.e., “chirotopic” and “achirotopic”, which represent the attribute of a site in a molecule. Since the topicity terms of the former type (i.e., topic relationships) are cenceptually distinct from those of the latter type (i.e., topic attributes), organic chemists encountered difficulties in using those terms correctly and distinctly. For example, two homotopic sites can be chirotopic in a chiral molecule and, on the other hand, they can be achirotopic in an achiral molecule. Two chirotopic sites can be homotopic in a chiral molecule and they can be enantiotopic in an achiral molecule. This means that one had to use a correct combination of two kinds of terms to specify the stereochemistry of a molecule.

To remedy the difficulties due to the conventional terminologies, we have proposed the concept of sphericity, where the terms *homospheric, enantiospheric, and hemispheric* have been coined to specify the nature of an orbit (an equivalent class) assigned to a coset representation.[11] Then, prochirality has been defined: *If a molecule has at least one enantiospheric orbit, the molecule is defined as being prochiral*. Thereby, the determination of pro-

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[1] Hanson, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 2731−2472.

[2] Hirschmann, H.; Hanson, K. R. *J. Org. Chem.* **1971**, *36*, 3293−3306.

[3] Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319−3328.

[4] McCasland, G. E. *A New General System for the Naming of Stereoisomers*; Chemical Abstracts: Columbus, 1953.

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

[6] Prelog, V.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 567−583.

[7] Mislow, K.; Raban, M. *Top. Stereochem.* **1967**, *1*, 1−38.

[8] Kaloustian, S. A.; Kaloustian, M. K. *J. Chem. Educ.* **1975**, *52*, 56−58.

[9] Eliel, E. L. *J. Chem. Educ.* **1980**, *57*, 52−55.

[10] Mislow, K. *Bull. Soc. Chim. Belg.* **1977**, *86*, 595.

[11] Fujita, S. *J. Am. Chem. Soc.* **1990**, *112*, 3390−3397.

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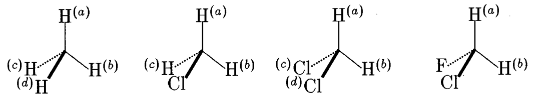
chirality has been ascribed to the presence of an enantiospheric orbit. The members of such an orbit may be any kind of objects, e.g., atoms, ligands, bonds, faces, and so on. Since the concept of sphericity has been originally introduced on the basis of coset representations, it has been necessary to have an intimate acquaintance with the concepts of group theory (point-group and permutation-group theories). Although the group-theoretical features of the original definition enable us to accomplish such quantitative applications as isomer enumerations,[12,13] a more straightforward approach should be developed to expand qualitative discussions on stereochemistry.

As clarified in the preceding paragraphs, the first aim of the present paper is to introduce the concept of sphericity only requiring a minimum set of knowledge on point-group theory. Since the new definition of the sphericity will be more straightforward than the previous one based heavily on group theory,[11] it will provide a succinct basis to the concept of prochirality. The second aim is to show that the conventional topicity terms of two categories can be effectively replaced by the sphericity terms. In other words, a combination of "topic relationship between two sites" and "topic attribute of a site" will be shown to be replaced by a single attribute (sphericity) of an orbit (an equivalence class). Throughout the present paper, the importance of orbits of various types will be stressed so that they give a common viewpoint to integrate "centers", "axes", and "planes", which have been recognized as so-called factorized stereogenic units in the CIP system.[6]

2. Orbits

The symmetry of a molecule is determined by symmetry operations that transform the molecule into itself. If all of such symmetry operations are only rotations (proper rotations), the molecule is determined to be chiral. If such symmetry operations are rotations and rotoreflections (improper rotations), the molecule is determined to be achiral. Let us then consider a set of objects such as atoms, ligands, bonds, and faces in a molecule. If any two objects of such a set coincide with each other under one of the symmetry operations of the molecule, they are determined to be equivalent. Thereby, the set of the objects is called an orbit (an equivalence class).[14]

Figure 1 shows orbits in methane derivatives. It is quite easy to find such orbits, because equivalent atoms can be determined by visual inspection. For example, the four hydrogens of methane ($\mathbf{T}_d$ symmetry) are so equivalent as to construct an orbit, $\Delta(\mathbf{1}) = \{\mathrm{H}^{(a)}, \mathrm{H}^{(b)}, \mathrm{H}^{(c)}, \mathrm{H}^{(d)}\}$. Similarly, three hydrogens ($\Delta(\mathbf{2}) = \{\mathrm{H}^{(a)}, \mathrm{H}^{(b)}, \mathrm{H}^{(c)}\}$) in chloromethane (**2**, $\mathbf{C}_{3v}$ symmetry), two hydrogens ($\Delta(\mathbf{3}) = \{\mathrm{H}^{(a)}, \mathrm{H}^{(b)}\}$) in dichloromethane (**3**, $\mathbf{C}_{2v}$ symmetry), and two hydrogens ($\Delta(\mathbf{4}) = \{\mathrm{H}^{(a)}, \mathrm{H}^{(b)}\}$) in chlorofluoromethane (**4**, $\mathbf{C}_s$ symmetry) construct respective orbits.[15]

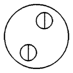
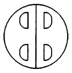
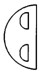


1 **2** **3** **4**

atoms	$\Delta(\mathbf{1})$	=	$\{\mathrm{H}^{(a)},\mathrm{H}^{(b)},\mathrm{H}^{(c)}, \mathrm{H}^{(d)}\}$	homospheric
	$\Delta(\mathbf{2})$	=	$\{\mathrm{H}^{(a)},\mathrm{H}^{(b)},\mathrm{H}^{(c)}\}$	homospheric
	$\Delta(\mathbf{3})$	=	$\{\mathrm{H}^{(a)},\mathrm{H}^{(b)}\}$	homospheric
	$\Delta(\mathbf{4})$	=	$\{\mathrm{H}^{(a)},\mathrm{H}^{(b)}\}$	enantiospheric
edges	$\Delta'(\mathbf{1})$	=	$\{\mathrm{H}^{(a)}\text{-}\mathrm{H}^{(b)}, \mathrm{H}^{(a)}\text{-}\mathrm{H}^{(c)}, \mathrm{H}^{(a)}\text{-}\mathrm{H}^{(d)}, \mathrm{H}^{(b)}\text{-}\mathrm{H}^{(c)}, \mathrm{H}^{(b)}\text{-}\mathrm{H}^{(d)}, \mathrm{H}^{(c)}\text{-}\mathrm{H}^{(d)}\}$	homospheric
	$\Delta'(\mathbf{2})$	=	$\{\mathrm{H}^{(a)}\text{-Cl}, \mathrm{H}^{(b)}\text{-Cl}, \mathrm{H}^{(a)}\text{-Cl}\}$	homospheric
	$\Delta'(\mathbf{3})$	=	$\{\mathrm{H}^{(a)}\text{-}\mathrm{Cl}^{(c)}, \mathrm{H}^{(a)}\text{-}\mathrm{Cl}^{(d)}, \mathrm{H}^{(b)}\text{-}\mathrm{Cl}^{(c)}, \mathrm{H}^{(b)}\text{-}\mathrm{Cl}^{(d)}\}$	enantiospheric
	$\Delta'(\mathbf{4})$	=	$\{\mathrm{H}^{(a)}\text{-Cl}, \mathrm{H}^{(b)}\text{-Cl}\}$	enantiospheric

FIGURE 1. Orbits and sphericities in methane derivatives.

TABLE 1. Sphericity of an Orbit

sphericity	orbit model	definition
homospheric		Among rotoreflections that fix an orbit in an achiral molecule, there exists a rotoreflection that fixes an object (⦶) in the orbit.
enantiospheric		Among rotoreflections that fix an orbit in an achiral molecule, there exists no rotoreflection that fixes an object (◖ or ◗) in the orbit.
hemispheric		There exist no rotoreflections that fix an orbit in a chiral molecule.

The question of *what objects are selected as the members of such an orbit* depends on the purpose of our discussion. Figure 1 also shows the results obtained by considering edges as objects, which are useful in discussing spin–spin coupling phenomena in NMR spectra. For example, the six edge pairs of methane are equivalent to constructing a six-membered orbit, $\Delta'(\mathbf{1}) = \{\mathrm{H}^{(a)}\text{–}\mathrm{H}^{(b)}, \mathrm{H}^{(a)}\text{–}\mathrm{H}^{(c)}, \mathrm{H}^{(a)}\text{–}\mathrm{H}^{(d)}, \mathrm{H}^{(b)}\text{–}\mathrm{H}^{(c)}, \mathrm{H}^{(b)}\text{–}\mathrm{H}^{(d)}, \mathrm{H}^{(c)}\text{–}\mathrm{H}^{(d)}\}$. Similarly, orbits of edges, i.e., $\Delta'(\mathbf{2})$, $\Delta'(\mathbf{3})$, $\Delta'(\mathbf{4})$, can be selected for the other methane derivatives, as shown in Figure 1.

3. Sphericity

In general, an orbit is characterized by its symmetrical nature against proper and improper rotations, which is called *the sphericity of the orbit,* as shown in Table 1. If an object of an orbit in an achiral molecule is fixed (i.e., transformed into itself) by a rotoreflection selected from the rotoreflections that fix the orbit, the orbit is defined as being *homospheric.* If there exists no such rotoreflection, the orbit is defined as being *enantiospheric.* On the other hand, an orbit in a chiral molecule is defined as being *hemispheric*; in this case, the orbit automatically coincides with itself by rotations (proper rotations) only.

As shown at the top of the orbit model column in Table 1, a homospheric orbit is diagramatically represented by a large circle that contains objects expressed by the

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(12) Fujita, S. *Theor. Chim. Acta* **1989**, *76*, 247–268.

(13) Fujita, S. *Symmetry and Combinatorial Enumeration in Chemistry*; Springer-Verlag: Berlin-Heidelberg, Germany, 1991.

(14) Do not confuse "orbit" with "orbital".

(15) The remaining atoms also construct respective orbits in addition to the orbits of hydrogens discussed in the text.

symbol ⌽ (a bisected small circle).[16] Each object is determined to be achiral because it is fixed (coincides with itself) by a rotoreflection. Hence, the local symmetry of the orbit is achiral so that the present definition of homosphericity is shown to be equivalent to the previous one.[11,17] Although the first model for the homospheric orbit in Table 1 indicates a two-membered case, it is easy to extend the model to designate more general cases.

For example, the orbit $\Delta(\mathbf{1})$ in methane is determined to be homospheric, because methane is achiral ($\mathbf{T}_d$ symmetry) and because an object (e.g., $H^{(a)}$) of the orbit $\Delta(\mathbf{1})$ coincides with itself by a reflection due to the mirror plane containing $H^{(a)}-C-H^{(b)}$.[18] Note that each (e.g., $H^{(a)}$) of the four hydgrogens in methane corresponds to one of the bisected small circles (⌽) and the orbit $\Delta(\mathbf{1})$ corresponds to the large circle in the orbit model for the homopheric case (Table 1), although the number of bisected small circles should be increased to four. Similarly, the orbit of the three hydrogens in chloromethane (**2**) is homospheric;[19] and the orbit of the two hydrogens in dichloromethane (**3**) is also homospheric.[20]

A bisected large circle shown at the middle of the orbit model column (Table 1) represents an enantiospheric orbit, which contains objects expressed by a small semicircle (left semicircle or right semicircle). According to the definition, such an object (left half-sphere or right half-sphere) is chiral so that the local symmetry of the orbit is chiral. Note that the left half-sphere and right half-sphere symbols represent a pair of enantiomeric objects. The second model for the enantiospheric orbit in Table 1 illustrates a four-membered case, where one half involves the two objects (left half-sphere) of the same chirality and the other half involves the two objects (right half-sphere) of the opposite chirality. It follows that the present definition of enantiosphericity is equivalent to the previous one.[11,17]

For example, the two hydrogens ($H^{(a)}$ and $H^{(b)}$) in chlorofluoromethane (**4**) are equivalent because they are superimposable with each other by a reflection due to the mirror plane containing F−C−Cl. This means that they construct an orbit ($\Delta(\mathbf{4})$). However, the reflection does not fix each hydrogen ($H^{(a)}$ or $H^{(b)}$) and there exist no other rotoreflections with respect to the orbit $\Delta(\mathbf{4})$. It follows that the orbit $\Delta(\mathbf{4})$ is determined to be enantiospheric, according to the definition shown in Table 1.[21] Note that the orbit $\Delta(\mathbf{4})$ corresponds to the bisected large circle in the orbit model for the enantiospheric case (Table 1), although the number of left and right half-spheres should be decreased to two. Thus the $H^{(a)}$ in the chlorofluoromethane corresponds to one semicircle (left half-sphere) in one half of the bisected large circle, while the $H^{(b)}$ corresponds to one semicircle (right half-sphere) in the other half.

As shown at the bottom of the orbit model column (Table 1), a hemispheric orbit is diagramatically represented as a large semicircle, where the orbit is chiral (i.e. the global symmetry) and objects expressed by the left half-sphere symbol are also chiral (i.e. the local symmetry). Obviously, the present definition of hemisphericity is equivalent to the previous one.[11,17] In this case, the counterpart orbit (the opposite semicircle) that contains enantiomeric objects (right half-sphere) is present in a distinct enantiomeric molecule.

The concept of sphericity is also applicable to orbits of edges. Each of the six edge pairs in methane (**1**) coincides with itself by a reflection. For example, the edge pair $H^{(a)}-H^{(b)}$ is fixed by the reflection due to the mirror plane containing $H^{(a)}-C-H^{(b)}$. Hence, the orbit $\Delta'(\mathbf{1})$ is homospheric in terms of the criterion listed in Table 1.[22] Similarly, the orbit $\Delta'(\mathbf{2})$ in chloromethane is determined to be homospheric.[23]

On the other hand, the orbit ($\Delta'(\mathbf{3})$) of the two edges in dichloromethane is enantiospheric in terms of the criterion shown in Table 1, because the orbit coincides with itself by a rotoreflection (i.e. the global symmetry is achiral) and because each of the edges does not coincide with itself by any rotoreflections (i.e. the localy symmetry is chiral).[24] Similarly, the orbit $\Delta'(\mathbf{4})$ in chlorofluoromethane is determined to be enantiospheric.[25] Such enantiosphericity that has been predicted for $\Delta'(\mathbf{3})$ or $\Delta'(\mathbf{4})$ by the previous math-chemical analysis[11,13] and by the present succinct one (Table 1) has been evidenced by the NMR experiments reported recently.[26]

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[16] Conceptually speaking, an achiral object may be completely structureless as designated by the symbol ○. For the sake of simplicity, we use the symbol ⌽ as the representative for achiral objects of any type.

[17] An orbit is assigned to a coset representation $\mathbf{G}(/\mathbf{G}_i)$, where $\mathbf{G}$ is the global symmetry of the orbit and $\mathbf{G}_i$ is the local symmetry of the orbit. The original definition has been based on the nature of the group $\mathbf{G}$ and its subgroup $\mathbf{G}_i$.[11] If both $\mathbf{G}$ and $\mathbf{G}_i$ are achiral, the orbit is defined as being homospheric. If $\mathbf{G}$ is achiral and $\mathbf{G}_i$ is chiral, the orbit is defined as being enantiospheric. If both $\mathbf{G}$ and $\mathbf{G}_i$ are chiral, the orbit is defined as being hemispheric. The size of the orbit is calculated to be $|\mathbf{G}|/|\mathbf{G}_i|$, where $|\mathbf{G}|$ and $|\mathbf{G}_i|$ represent the orders of the respective groups.

[18] In light of the original definition of sphericity, the orbit $\Delta(\mathbf{1})$ in methane is assigned to a coset representation $\mathbf{T}_d(/C_{3v})$. Since both the global symmetry $\mathbf{T}_d$ and the local symmetry $\mathbf{C}_{3v}$ are achiral, the orbit is determined to be homospheric. The size of the orbit is calculated to be $|\mathbf{T}_d|/|\mathbf{C}_{3v}| = 24/6 = 4$.

[19] The orbit $\Delta(\mathbf{2})$ in chloromethane is assigned to a coset representation $\mathbf{C}_{3v}(/\mathbf{C}_s)$. Since both the global symmetry $\mathbf{C}_{3v}$ and the local symmetry $\mathbf{C}_s$ are achiral, the orbit is determined to be homospheric in light of the original definition of sphericity. The size of the orbit is calculated to be $|\mathbf{C}_{3v}|/|\mathbf{C}_s| = 6/2 = 3$.

[20] The orbit $\Delta(\mathbf{3})$ in dichloromethane is assigned to a coset representation $\mathbf{C}_{2v}(/\mathbf{C}_s)$. Since both the global symmetry $\mathbf{C}_{2v}$ and the local symmetry $\mathbf{C}_s$ are achiral, the orbit is determined to be homospheric in light of the original definition of sphericity. The size of the orbit is calculated to be $|\mathbf{C}_{2v}|/|\mathbf{C}_s| = 4/2 = 2$.

[21] The orbit $\Delta(\mathbf{4})$ in chlorofluoromethane is assigned to a coset representation $\mathbf{C}_s(/\mathbf{C}_1)$. Since the global symmetry $\mathbf{C}_s$ is achiral and the local symmetry $\mathbf{C}_1$ is chiral, the orbit is determined to be enantiospheric in light of the original definition of sphericity. The size of the orbit is calculated to be $|\mathbf{C}_s|/|\mathbf{C}_1| = 2/1 = 2$.

[22] The orbit $\Delta'(\mathbf{1})$ in methane is assigned to a coset representation $\mathbf{T}_d(/\mathbf{C}_{2v})$. Since both the global symmetry $\mathbf{T}_d$ and the local symmetry $\mathbf{C}_{2v}$ are achiral, the orbit is determined to be homospheric. The size of the orbit is calculated to be $|\mathbf{T}_d|/|\mathbf{C}_{2v}| = 24/4 = 6$.

[23] The orbit $\Delta'(\mathbf{2})$ in chloromethane is assigned to a coset representation $\mathbf{C}_{3v}(/\mathbf{C}_s)$. Since both the global symmetry $\mathbf{C}_{3v}$ and the local symmetry $\mathbf{C}_s$ are achiral, the orbit is determined to be homospheric. The size of the orbit is calculated to be $|\mathbf{C}_{3v}|/|\mathbf{C}_s| = 6/2 = 3$.

[24] The orbit $\Delta'(\mathbf{3})$ in dichloromethane is assigned to a coset representation $\mathbf{C}_{2v}(/\mathbf{C}_1)$. Since the global symmetry $\mathbf{C}_{2v}$ is achiral and the local symmetry $\mathbf{C}_1$ is chiral, the orbit is determined to be enantiospheric. The size of the orbit is calculated to be $|\mathbf{C}_{2v}|/|\mathbf{C}_1| = 4/1 = 4$.

[25] The orbit $\Delta'(\mathbf{4})$ in chlorofluoromethane is assigned to a coset representation $\mathbf{C}_s(/\mathbf{C}_1)$. Since the global symmetry $\mathbf{C}_s$ is achiral and the local symmetry $\mathbf{C}_1$ is chiral, the orbit is determined to be enantiospheric. The size of the orbit is calculated to be $|\mathbf{C}_s|/|\mathbf{C}_1| = 2/1 = 2$.

[26] Aroulanda, C.; Merlet, D.; Courtieu, J.; Leset, P. *J. Am. Chem. Soc.* **2001**, *123*, 12059−12066.

4. Prochirality

Now that we have introduced the concepts of orbit and sphericity, we are ready to redefine the concept of prochirality. Before we state this redefinition in general, let us consider the enantiospheric orbit ($\Delta(\mathbf{4})$) in chlorofluoromethane (**4**) as an example. According to the definition of enantiosphericity, $H^{(a)}$ in $\Delta(\mathbf{4})$ does not coincide with itself by any rotoreflections. Instead, such a rotoreflection (i.e. the mirror plane Cl−C−F) transforms $H^{(a)}$ into its mirror image, which is identical with $H^{(b)}$ in this case. In other words, $H^{(a)}$ and $H^{(b)}$ are not superimposed on each other by any rotations (proper rotations). It follows that the orbit is divided into two halves under a chiral perturbation, e.g., such a chiral environment as a chiral solvent or such perturbation as an attack of a chiral reagent. Hence, chlorofluoromethane (**4**) is determined to be prochiral with respect to the orbit $\Delta(\mathbf{4})$.

Let us next examine dichloromethane (**3**). The two hydrogens ($H^{(a)}$ and $H^{(b)}$) in **3** are equivalent even under any chiral perturbations, because of the homosphericity of the orbit ($\Delta(\mathbf{3})$) at issue. In contrast, the enantiospheric orbit ($\Delta'(\mathbf{3})$) of the four edge pairs ($H^{(a)}-Cl^{(c)}$, $H^{(a)}-Cl^{(d)}$, $H^{(b)}-Cl^{(c)}$, and $H^{(b)}-Cl^{(d)}$) in **3** is divided into two halves:

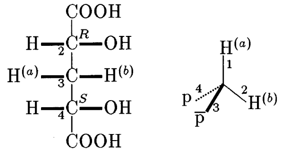
$$\Delta'(\mathbf{3}) \xrightarrow[\text{perturbation}]{\text{chiral}} \{H^{(a)}-Cl^{(d)}, H^{(b)}-Cl^{(c)}\} \text{ and } \{H^{(a)}-Cl^{(c)}, H^{(b)}-Cl^{(d)}\}$$

which are nonequivalent under a chiral perturbation. Hence, dichloromethane (**3**) is determined to be prochiral with respect to the orbit $\Delta'(\mathbf{3})$, although it cannot be determined to be prochiral with respect of the orbit $\Delta(\mathbf{3})$. This type of chiral perturbation has recently been reported in the NMR spectrum of malononitrile.[26]

Now, the definition of prochirality can be obtained by starting from the concept of sphericity redefined in the present paper: *If a molecule has at least one enantiospheric orbit, the molecule is defined as being prochiral*. Consequently, this is the same as the previous definition.[11] Rigorously speaking, such prochirality should be assigned to an orbit at issue. Even if prochirality is stated for a molecule, the orbit at issue should be stated as the origin of the prochirality.

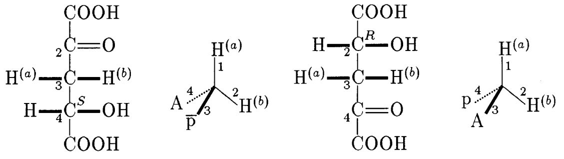
5. So-Called Meso Compounds

Let us examine *meso*-2,4-dihydroxyglutaric acid (**5**). When we use p = *R*-CH(OH)COOH and $\bar{p}$ = *S*-CH(OH)COOH, we obtain a promolecule (**6**).[27] By examining the resulting promolecule **6**, we can discuss most of the symmetrical properties of the original molecule **5**. The pair of p and $\bar{p}$ in **6** constructs a two-membered orbit ($\Delta(\mathbf{6}) = \{p, \bar{p}\}$), which is determined to be enantiospheric by using the criterion listed in Table 1.[29] On the other hand, one hydrogen atom in **6** constructs a one-membered orbit ($\Delta'(\mathbf{6}) = \{H^{(a)}\}$), and another hydrogen atom constructs a distinct one-membered orbit ($\Delta''(\mathbf{6}) = \{H^{(b)}\}$).[30] The orbits are distinctly homospheric according to Table 1.



5 **6**

FIGURE 2. *meso*-2,4-Dihydroxyglutaric acid.



7 **8** **9** **10**

FIGURE 3. Test for prochirality of **5** (or **6**).

Because of the enantiosphericity of the orbit $\Delta(\mathbf{6})$, the promolecule **6** is determined to be prochiral. This means that *meso*-2,4-dihydroxyglutaric acid (**5**) is prochiral with respect to the orbit containing p = *R*-CH(OH)COOH and $\bar{p}$ = *S*-CH(OH)COOH. Under a chiral perturbation, p and $\bar{p}$ are distinguished so that either one can be converted preferably to the remaining one, as shown in Figure 3. Thus, if p (= *R*-CH(OH)COOH) is preferably converted into an achiral (pro)ligand A (= C(=O)COOH), the resulting molecule (**7**) or promolecule (**8**) is predicted to be chiral. If $\bar{p}$ = *S*-CH(OH)COOH is preferably converted into an achiral (pro)ligand A (= C(=O)COOH), the corresponding enantiomeric molecule (**9**) or promolecule (**10**) is generated. It should be noted that the test of prochirality shown in Figure 3 produces a pair of enantiomers (**7**/**9** or **8**/**10**).

The two hydrogens in **6** are chemically nonequivalent (conventionally speaking, diastereotopic), because they belong to distinct orbits, i.e., $\Delta'(\mathbf{6})$ (= $\{H^{(a)}\}$) and $\Delta''(\mathbf{6})$ (= $\{H^{(b)}\}$). They are chemically distinguishable from each other, i.e., even under no chiral perturbation. If the hydrogen $H^{(b)}$ in $\Delta''(\mathbf{6})$ (= $\{H^{(a)}\}$) is preferably replaced by a hydroxyl group, a molecule **11** or a promolecule **12** is generated, as shown in Figure 4.[31] If the hydrogen $H^{(a)}$ in $\Delta''(\mathbf{6})$ (= $\{H^{(b)}\}$) is alternatively replaced by a hydroxyl group, a molecule **13** or a promolecule **14** is generated. It should be noted that the test of stereogenicity shown in Figure 4 produces a pair of diastereomers (**11**/**13** or **12**/**14**).

From the present point of view, Hanson's "prochirality"[2] is found to pay attention to two distinct orbits such as $\Delta'(\mathbf{6})$ (= $\{H^{(a)}\}$) and $\Delta''(\mathbf{6})$ (= $\{H^{(b)}\}$). Note that the differentiation between them requires no chiral perturbation. This is the reason Hanson's "prochirality" should

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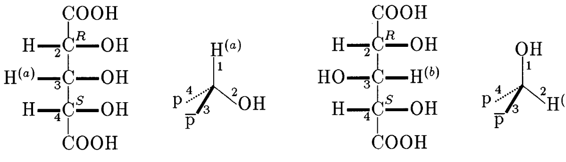
(27) A proligand is defined as a structureless object that has chirality/achirality. This means that the inner structure of a ligand is concealed except chirality/achirality to give the concept of proligand. A promolecule is defined as an object in which such proligands are placed on the positions of an achiral or chiral skeleton. Hence, such a promolecule can be achiral (or sometimes prochiral) or chiral. See ref 28.

(28) Fujita, S. *Tetrahedron* **1991**, *47*, 31−46.

(29) The orbit $\Delta(\mathbf{6})$ (= $\{p, \bar{p}\}$) is assigned to a coset representation $\mathbf{C}_s(/\mathbf{C}_1)$, as for $\Delta(\mathbf{4})$.

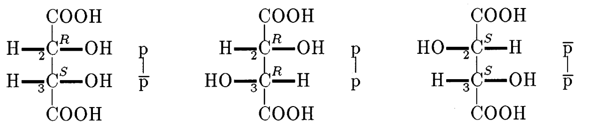
(30) The orbit $\Delta'(\mathbf{6})$ (= $\{H^{(a)}\}$) or $\Delta''(\mathbf{6})$ (= $\{H^{(b)}\}$) is assigned to a coset representation $\mathbf{C}_s(/\mathbf{C}_s)$. The size of the orbit is calculated to be $|\mathbf{C}_s|/|\mathbf{C}_s| = 2/2 = 1$.

(31) Strictly speaking, an achiral proligand (e.g., X) should be used in place of the hydroxyl group. However, such flexible usage is permissible so long as there emerges no confusion.



11 **12** **13** **14**

FIGURE 4. Test for prostereogenicity of **5** (or **6**).



15 **16** **17** **18** **19** **20**

FIGURE 5. *meso*-Tartaric acid and chiral isomers.

be replaced by the concept of prostereogenicity. It should be emphasized that such prostereogenicity (i.e., Hanson's "prochirality") cannot be used to predict the possibility of a chiral synthesis in which an achiral molecule is converted into a chiral molecule (Figure 3). Such chiral syntheses should be treated by the concept of prochirality that is redefined in the present paper. Thus, the concept of prostereogenicity and that of prochirality should be distinctly discussed, as shown in Figures 3 and 4. As found by a careful examination of the procedure by which molecule **5** has been recognized as being "proachiral with prochiral assemblies",[2] Hanson's "prochirality"[1] has exhibited an undesired mix-up of stereochemical aspects (e.g., prochirality) and permutational ones (e.g., prostereogenicity).

The importance of orbits rather than "centers" is further exemplified by examining tartaric acids that have no such "centers". *meso*-Tartaric acid (**15**) is represented by the promolecule (**16**), when we use p = *R*-CH(OH)COOH and $\bar{p}$ = *S*-CH(OH)COOH (Figure 5). The two proligands p and $\bar{p}$ in the promolecule (**16**) construct a two-membered orbit, which is determined to be enantiospheric in terms of the criterion listed in Table 1.[32] Hence, *meso*-tartaric acid (**15**) is prochiral with respect to the enantiospheric orbit that contains p = *R*-CH(OH)COOH and $\bar{p}$ = *S*-CH(OH)COOH.

The chiral isomers of tartaric acid (**17** and **19**) are represented by the corresponding promolecules (**18** and **20**). The two p's in **18** (or $\bar{p}$'s in **20**) construct a two-membered orbit, which is determined to be hemispheric in terms of the criterion listed in Table 1.[33]

6. So-Called Pseudoasymmetric Carbon Atoms

The central carbon atom in diastereomeric 2,3,4-trihydroxyglutaric acids (**11** and **13**) has been conventionally called a "pseudoasymmetric center". It has been assigned to be stereogenic and achirotopic in terms of Mislow–Siegel's criterion,[3] where great importance as a "stereogenic" center has been attached to the central carbon. It should be noted, however, that the stereochemical (point-group theoretical) properties of the two stereoisomers scarcely depend on whether the central carbon atom is achirotopic or not; rather, they mainly depend on the four ligands around the center.

In the present approach, we examine promolecules **12** and **14** that are generated from **11** and **13** by using p = *R*-CH(OH)COOH and $\bar{p}$ = *S*-CH(OH)COOH. Thereby, we focus our attention on an orbit that contains the p and $\bar{p}$ pair in **12** (or **14**). According to the criterion shown in Table 1, the two-membered orbit is determined to be enantiospheric.[34] Hence, **12** (or **14**) is prochiral with respect to the orbit of the p and $\bar{p}$ pair. The prochirality of **12** (or **14**) can be discussed in a similar way as described for **5** (or **6**) in Figure 3. Thus, if p (= *R*-CH(OH)COOH) is preferably converted into an achiral (pro)ligand A (= C(=O)COOH) under the perturbation of a chiral reagent, the resulting promolecule (or molecule) is predicted to be chiral. If $\bar{p}$ = *S*-CH(OH)COOH is preferably converted into an achiral (pro)ligand A (= C(=O)COOH), the corresponding enantiomeric promolecule (or molecule) is generated.

It is here worthwhile to mention Hirschmann–Hanson's criterion[2] applied to such a molecule as **11** (or **13**), which is determined to be "achiral with chiral configurations". Obviously, the characterization of **11** (or **13**) by Hirschmann–Hanson's criterion fails to clarify the possibility of chiral syntheses that stems from the stereochemical nature of the pair of enantiomeric ligands (p = *R*-CH(OH)COOH and $\bar{p}$ = *S*-CH(OH)COOH). Recall also the discussion described for Figures 3 and 4. Ugi et al. have discussed the enumeration of the stereoisomers of trihydroxyglutaric acids such as **11** and **13** by using their concept of chemical identity groups.[35] We have discussed permutation symmetry versus point-group symmetry in the stereogenicity of so-called pseudoasymmetric carbon atoms.[36]

The chiral stereoisomers (**21** and **23**) of 2,3,4-trihydroxyglutaric acid contain a central carbon that is nonstereogenic and chirotopic in terms of Mislow–Siegel's criterion.[3] Note that the stereochemical (point-group theoretical) properties of the two stereoisomers scarcely depend on whether the central carbon atom is chirotopic or not. Instead, such stereochemical properties depend on how the four ligands (i.e., two ligands of *R*-CH(OH)COOH or two ligands of *S*-CH(OH)COOH), H, and OH) construct orbits.

The present approach lays stress on such orbits as contained in the corresponding promolecule (**22** or **24**), where we use p = *R*-CH(OH)COOH or $\bar{p}$ = *S*-CH(OH)COOH. The four proligands (H, OH, p and p) in **22** (or **24**) construct distinct one-membered orbits, each of which is determined to be hemispheric (Table 1).[37] In particular,

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[32] The orbit ({p, $\bar{p}$}) of the promolecule (**16**) is enantiospheric, since it is assigned to a coset representation $\mathbf{C}_{\infty h}(/\mathbf{C}_{\infty})$.

[33] The orbit ({p, p}) of the promolecule (**18**) is hemispheric, since it is assigned to a coset representation $\mathbf{D}_{\infty}(/\mathbf{C}_{\infty})$.

[34] The orbit containing p and $\bar{p}$ in **12** (or **14**) is assigned to a coset representation $\mathbf{C}_s(/\mathbf{C}_1)$. Hence, it is determined to be enantiospheric. The hydroxyl group of **12** (or **14**) constructs a one-membered orbit governed by a coset representation $\mathbf{C}_s(/\mathbf{C}_s)$. The hydrogen ($H^{(a)}$) of **12** (or **14**) constructs a one-membered orbit governed by a coset representation $\mathbf{C}_s(/\mathbf{C}_s)$. The coset representation $\mathbf{C}_s(/\mathbf{C}_s)$ indicates the sphericity of each orbit.

[35] Ugi, I.; Dugundji, J.; Kopp, R.; Marquarding, D. *Perspectives in Theoretical Stereochemistry*; Lecture Notes in Chemistry No. 36, Springer-Verlag: Berlin-Heidelberg, Germany, 1984; pp 146–150.

[36] Fujita, S. *Chem. Rec.* **2002**, *2*, 164–176.

[37] Each of the four proligands (H, OH, p and p) in **22** (or (H, OH, $\bar{p}$, and $\bar{p}$) in **24**) constructs a distinct one-membered orbit, which is hemispheric as assigned to a coset representation $\mathbf{C}_1(/\mathbf{C}_1)$. Although an achiral proligand (e.g., X) should be used in place of the hydroxyl group, the hydroxyl group (OH) is here treated as a proligand because no confusion occurs.

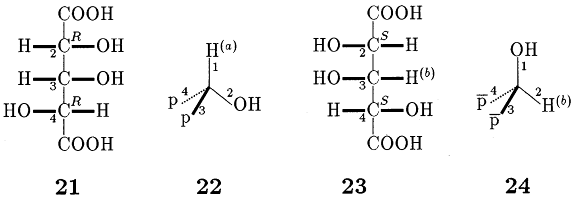

FIGURE 6. Chiral 2,3,4-trihydroxyglutaric acids.

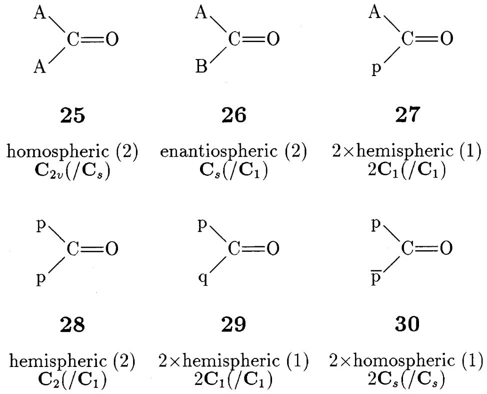

FIGURE 7. Orbits for faces of carbonyl compounds. Uppercase letters such as A and B represent achiral proligands. Lowercase letters with and without an overline (such as p and $\bar{\text{p}}$) represent a pair of enantiomeric proligands, and the symbol q represents another chiral proligand. The number in each pair of parentheses represents the size of the orbit at issue. Thus, "homospheric (2)" represents a two-membered homosperic orbit. A symbol such as $\mathbf{C}_{2v}(/\mathbf{C}_s)$ represents a coset representation assigned to each orbit.

the two p's (or $\bar{\text{p}}$'s) are nonequivalent so that they can be differentiated chemically or spectroscopically.

7. Variety of Orbits

7.1. Faces of Carbonyl Compounds. To show the scope of the present approach, two faces in carbonyl compounds are examined as objects of orbits. Acetone ($A_2C{=}O$, **25**, in general) has two faces, which construct a two-membered orbit (Figure 7). Each of the two faces is fixed by the reflection due to the mirror plane containing the π-bonding of the carbonyl group. According to the criterion shown in Table 1, the orbit of the two faces is determined to be homospheric.[38] In Figure 7, the number in each pair of parentheses represents the size of an orbit at issue. Thus, the orbit of the faces of **25** is designated to be "homospheric (2)", which represents a two-membered homosperic orbit.

On the other hand, two faces in acetaldehyde ($ABC{=}O$, **26**, in general) construct a two-membered orbit of a different type (Figure 7). Each of the two faces is not fixed by the reflection due to the mirror plane containing the skeleton of acetaldehyde. Hence, the orbit is determined to be enantiospheric according to the criterion shown in Table 1.[39] It follows that acetaldehyde is prochiral with respect to the orbit of two faces.

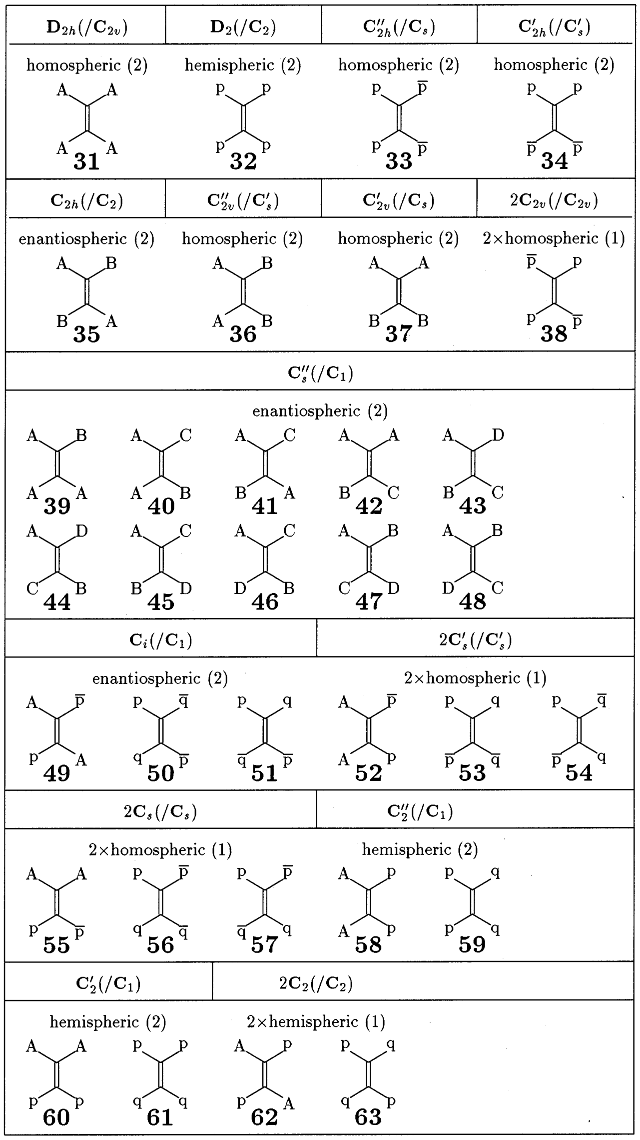

FIGURE 8. Orbits for faces of ethylene derivatives (part I). See the caption for Figure 7.

The faces of other carbonyl compounds are similarly examined and the results are summarized in Figure 7. The two faces in both **25** and **28** are determined to be equivalent (or homotopic) according to Kaloustian–Kaloustian's criterion.[8] The present results show that the two-membered orbit of the faces for **25** is homospheric, while the two-membered orbit for **28** is hemispheric. Note that a relationship "equivalent" (or "homotopic") is replaced by an equivalence class *orbit* and that further classification such as *homospheric* or *hemispheric* is obtained as additional information.

To link the present approach with the previous one,[11] Figure 7 contains the data of respective coset representations (CR's) assigned to the orbits of faces. For example, the two-membered orbit of faces in **25** is assigned to the CR $\mathbf{C}_{2v}(/\mathbf{C}_s)$. Since both the global symmetry ($\mathbf{C}_{2v}$) and the local symmetry ($\mathbf{C}_s$) are achiral, the $\mathbf{C}_{2v}(/\mathbf{C}_s)$ orbit is determined to be homospheric.[17] The size of the orbit is calculated to be $|\mathbf{C}_{2v}|/|\mathbf{C}_s| = 4/2 = 2$. These data are consistent with the present result designated as "homospheric (2)" for **25** in Figure 7. As another example, we

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[38] The two faces of acetone construct a two-membered homospheric orbit, which is assigned to a coset representation $\mathbf{C}_{2v}(/\mathbf{C}_s)$. The size of the orbit is calculated to be $|\mathbf{C}_{2v}|/|\mathbf{C}_s| = 4/2 = 2$.

[39] The two faces of acetaldehyde construct a two-membered enantiospheric orbit, which is assigned to a coset representation $\mathbf{C}_s(/\mathbf{C}_1)$. The size of the orbit is calculated to be $|\mathbf{C}_s|/|\mathbf{C}_1| = 2/1 = 2$.

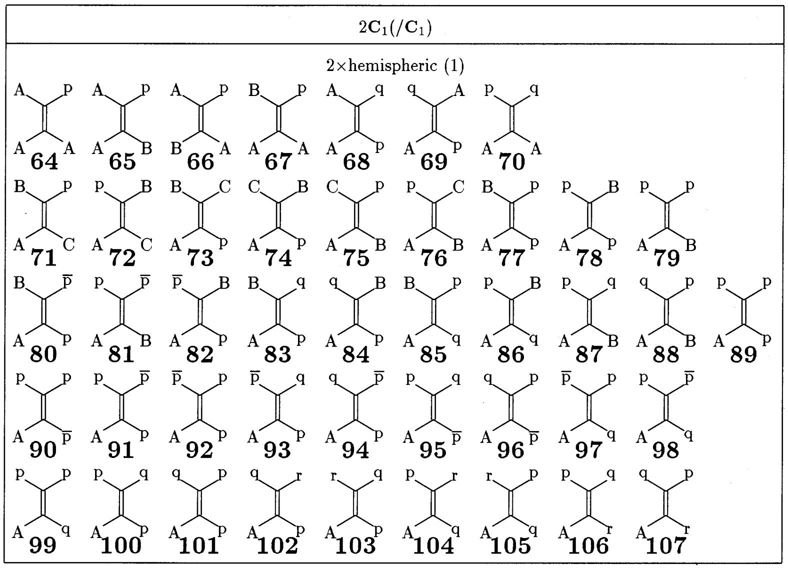

FIGURE 9. Derivatives of ethylene (part II). See the caption for Figure 7.

examine the two-membered orbit of faces in **26**, which is assigned to the CR $\mathbf{C}_s(/\mathbf{C}_1)$. Since the global symmetry ($\mathbf{C}_s$) is achiral and the local symmetry ($\mathbf{C}_1$) is chiral, the $\mathbf{C}_s(/\mathbf{C}_1)$ orbit is determined to be enantiospheric.[17] The size of the orbit is calculated to be $|\mathbf{C}_s|/|\mathbf{C}_1| = 2/1 = 2$. These data are consistent with the present result designated as "enantiospheric (2)" for **26** in Figure 7.

7.2. Faces of Ethylene Derivatives. The faces of ethylene derivatives are examined in terms of the criterion listed in Table 1 and the results are summarized in Figures 8 and 9.

Among achiral derivatives of ethylene listed in Figure 8, a $\mathbf{C}_{2h}$ derivative (**35**), $\mathbf{C}_s''$ derivatives (**39** to **48**), and $\mathbf{C}_i$ derivatives (**49** to **51**) have a two-membered enantiospheric orbit of faces. Hence, they are decided to be prochiral with respect to the respective orbits of faces.

It should be emphasized again that prochirality stems from the presence of an enantiospheric orbit. Hence, a prochiral molecule can contain homospheric orbits along with an enantiospheric orbit. For example, the two proligands A's (or B's) in the $\mathbf{C}_{2h}$ derivative (**35**) construct a two-membered homospheric orbit, which is not a source of prochirality. Note that **35** is prochiral with respect to the orbit of faces, as described above. On the same line, the four atoms of each $\mathbf{C}_s''$ derivative (**39** to **48**) distinctly construct four one-membered homospheric orbits, each of which is not a source of prochirality.

On the other hand, each of the $\mathbf{C}_i$ derivatives (**49** to **51**) contains a p and $\bar{p}$ pair and/or another q and $\bar{q}$ pair. Each of the pairs constructs a two-membered enantiospheric orbit, which can be another source of prochirality in addition to the respective enantiospheric orbit of faces.

Each of the asymmetric derivatives ($\mathbf{C}_1$) listed in Figure 9 contains two one-membered hemispheric orbits of faces. Since the two faces in each derivative belong to the different orbits, they are chemically nonequivalent so that either one can be predicted to be more reactive than the other face.

7.3. Faces of Allenes. Allene (**108**) has four faces ($\pi^{(a)}$ to $\pi^{(d)}$) around its central allene bond (Figure 10). The four faces are equivalent so as to construct a four-membered orbit. Each face is fixed by the reflection due to the mirror plane containing the π-bonding of the double bond at issue. According to the criterion shown in Table 1, the orbit of the four faces in allene (**108**) is determined to be homospheric.[40]

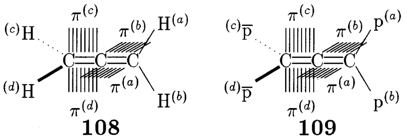

FIGURE 10. Faces for allene derivatives.

An allene derivative (**109**) with two proligands (p's) and two enantiomeric proligands ($\bar{p}$'s) has four faces ($\pi^{(a)}$ to $\pi^{(d)}$) around its central allene bond. The allene derivative **109** has a 4-fold axis of rotoreflection (the S_4 axis) through C=C=C. This axis is the origin of the equivalency of the four faces ($\pi^{(a)}$ to $\pi^{(d)}$). Hence, the four faces construct a four-membered orbit. Because the rotoreflections S_4 and S_4^3 due to the S_4 axis do not fix the four faces and because there are no other rotoreflections, the orbit of the four faces in **109** is determined to be enantiospheric (Table 1).[41] Hence, the allene derivative (**109**) is prochiral with respect to this orbit. Under a chiral environment, the orbit is divided into two halves: $\{\pi^{(a)},\pi^{(b)}\}$ and $\{\pi^{(c)},\pi^{(d)}\}$.

It should be noted that Kaloustian−Kaloustian's criterion[8] is not effective for allene derivatives such as **109**. In other words, the present orbit-oriented approach has a wider scope than do relationship-oriented methods such as Kaloustian−Kaloustian's criterion.[8]

7.4. Ligands and Inner Structures. In the present approach, a ligand is replaced by a proligand, where the inner structure of the ligand is considered in the form of chirality/achirality. This treatment can avoid complicated

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(40) The four faces construct a four-membered homospheric orbit, which is assigned to a coset representation $\mathbf{D}_{2d}(/\mathbf{C}_s)$. The size of the orbit is calculated to be $|\mathbf{D}_{2d}|/|\mathbf{C}_s| = 8/2 = 4$.

(41) The orbit of four faces in **109** is enantiospheric, since it is assigned to a coset representation $\mathbf{S}_4(/\mathbf{C}_1)$. The size of the orbit is calculated to be $|\mathbf{S}_4|/|\mathbf{C}_1| = 4/1 = 4$.

situations due to conformational changes, as found in various cases such as the promolecule **16** for *meso*-tartaric acid (**15**).

A typical conventional treatment of such cases is to consider the highest attainable symmetry of a fixed conformer. The present approach is also effective for discussing the orbit of such a fixed conformer. For example, one of the fixed conformers of *meso*-tartaric acid (**15**) belongs to $\mathbf{C}_s$ symmetry, where the mirror plane is perpendicular to the central C−C bond. As for this fixed conformer, the two hydroxyl groups (2-OH and 3-OH) belong to a two-membered enantiospheric orbit;[42] the two hydrogens (2-H and 3-H) belong to a two-membered enantiospheric orbit;[42] and the two carboxyl groups (1-COOH and 4-COOH) belong to a two-membered enantiospheric orbit.[42] This conclusion is parallel to the one that can be derived from another fixed conformer of $\mathbf{C}_i$ symmetry.[43] It should be noted that an equivalent conclusion can be also derived from the promolecule **16** in the present approach without considering the two conformers.[32]

8. Relationship vs Attribute

In the words of Eliel and coauthors (p 53 in ref 44) on the concept of chirotopicity,[3] "Although the concept of chirotopicity may be of limited practical applicability, it serves to stress the fact that van't Hoff's asymmetric atom has two separate aspects: one, that it is a focus of dissymmetry or chirality (chirotopic), the other, that the exchange of two ligands at the asymmetric atom gives rise to stereoisomers (it is stereogenic)." This statement has implied the problems of the conventional terminology based dually on "topic relationship between two sites" (i.e., homotopic, enantiotopic, diastereotopic, etc.) and "topic attribute of a site" (i.e., chirotopic and achirotopic). Thus, although the topic terms of the two categories have been discussed separately, the separation is incomplete in the practical usage of them by organic chemists. In particular, the term "enantiotopic" of the first category implicitly involves the term "chirotopic" of the second category. In other words, the conventional use of the term "enantiotopic" for discussing prochirality depends on the implicit involvement with the term "chirotopic". This is a reason why "the concept of chirotopicity may be of limited practical applicability", as stated above for the conventional terminology. More precisely speaking, the practical applicability of the concept of chirotopicity has been hidden by the use of the conventional term "enantiotopic".

Moreover, the present formulation of sphericity (Table 1) reveals that the term "homotopic" of conventional terminology indicates three cases without differentiating them, i.e., (1) a relatioship between two objects (two Φ's) in a homospheric orbit, (2) a relatioship between two objects (two left half-spheres or two right half-spheres) in either half of an enantiospheric orbit, and (3) a relatioship between two objects (two left half-spheres or two right half-spheres) in a hemispheric orbit. To avoid the diverse nature of homotopicity, Case 1 is characterized by the term "achirotopic" and Cases 2 and 3 are characterized by the term "chirotopic".[45] The term "enantiotopic" is found to specify a relationship between an object (left half-sphere) in one- half of an enantiospheric orbit and an object (right half-sphere) in the other half of the orbit.[47] The terms "diastereotopic" and "heterotopic" are concerned with two objects belonging to distinct orbits of the same or different types. Thus, the topicity terms are concluded to involve various levels of categories, which should be discussed distinctly.

In light of the present approach, the concept of local chirality/achirality is meaningfully combined with that of global chirality/achirality via the concept of orbit (equivalence classes), as shown in Table 1. The resulting concept *sphericity*, which is recognized as a single attribute of such an orbit, contains information on local and global chirality/achirality. Thereby, the conventional topicity terms of two categories ("topic relationship between two sites" and "topic attribute of a site") have been effectively replaced by the sphericity terms. Thus, the combination of "chirotopic" and "homotopic" has been replaced by the term *hemispheric*, that of "achirotopic" and "homotopic" has been replaced by the term *homospheric*, and that of "chirotopic" and "enantiotopic" has been replaced by the term *enantiospheric*.

The merits of the present approach should be emphasized here:

1. The conventional "topic relationship between two sites" is applicable only to qualitative problems, while the present concept of sphericity has been effectively applied to quantitative stereochemical problems (e.g. isomer enumerations[12] and symmetry-adapted functions[49]), as well as to qualitative stereochemical discussion described in the present paper.
2. Since each "topic" term is mainly concerned with a pairwise relationship, it requires complicated examination in characterizing relationships between three or more objects. In contrast, the present approach is equally applicable to three-membered or more orbits.
3. Conventionally, a combination of "topic relationship between two sites" and "topic attribute of a site" is required to characterize the stereochemistry of a molecule. In contrast, the present approach uses a single attribute (sphericity) after considering an equivalence class (an orbit).
4. Since the concept of sphericity is defined as an attribute of an orbit, it provides a common viewpoint to integrate the conventional "centers", "axes", "planes", etc.

9. Conclusion

The concept of sphericity has been revisited by starting from a minimum set of knowledge on point-group theory, where the importance of orbits (equivalence classes) has been stressed. Thereby, the concept of prochirality has been derived as an alternative definition from the previ-

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[42] Each of these orbits is assigned to a coset representation $\mathbf{C}_s(/\mathbf{C}_1)$. The size of the orbit is calculated to be $|\mathbf{C}_s|/|\mathbf{C}_1| = 2/1 = 2$.

[43] Each of the orbits at issue is assigned to a coset representation $\mathbf{C}_i(/\mathbf{C}_1)$. The size of the orbit is calculated to be $|\mathbf{C}_i|/|\mathbf{C}_1| = 2/1 = 2$.

[44] Eliel, E.; Wilen, S. H.; Mander, L. N. *Stereochemisty of Organic Compounds*; John Wiley & Sons: New York, 1994.

[45] The terms *holotopic* and *hemitopic* have been proposed as to differentiate Case 1 from Cases 2 and 3. See ref 46.

[46] Fujita, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1979−1986.

[47] The membership criterion for detemining topic relationships has been proposed. See refs 11 and 48.

[48] Fujita, S. *Tetrahedron* **1990**, *46*, 5943−5954.

[49] Fujita, S. *Theor. Chim. Acta* **1990**, *78*, 45−63.

ous one that is based heavily on group theory.[11] The conventional topicity terms of two categories ("topic relationship between two sites" and "topic attribute of a site") have been effectively replaced by the sphericity terms. The merit of the present terminology stems from the concept of orbit (equivalence class) that is assigned to a coset representation. More mathematical discussion on the assignment brings quantitative applications such as isomer enumerations and symmetry-adapted functions, as we have shown elsewhere.[13]

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