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Systematic Characterization of Prochirality, Prostereogenicity, and Stereogenicity by Means of the Sphericity Concept

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Abstract—A systematic method for characterizing prochirality, prostereogenicity, and stereogenicity is described. Any set of equivalent ligands is regarded as an orbit governed by a coset represention, by which the orbit is classified into homospheric, enantiospheric, or hemispheric. A molecule containing at least one enantiospheric orbit is defined to be prochiral (Rule A). After the definition of the topicity terms, a prostereogenic center is defined as a center or atom having two ligands that are indistinguishable in isolation and not homotopic (i.e. either enantiotopic, diastereotopic or heterotopic) in a molecule (Rule B). Then, Rule C for characterizing a stereogenic center is defined subsidiarily from Rule B; these rules are discussed by using several molecules of stereochemical interest. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

From the proposal of a tetrahedral model by van't Hoff,[1] the term 'asymmetric carbon center' has been used widely by organic chemists and biochemists, though it does not always correspond to the chirality of molecules. The term 'pseudoasymmetric' has later been coined to designate a carbon atom that is attached to four different ligands ($ABQ\bar{Q}$) but does not show chirality, where Q and $\bar{Q}$ are enantiomeric chiral ligands and A and B are achiral ligands.[2] Typical examples for $ABQ\bar{Q}$ are achiral 2,3,4-trihydroxyglutaric acids, in which Q and $\bar{Q}$ are enantiomeric ligands with the formula –CH(OH)COOH and A and B represent a hydrogen atom and a hydroxyl group. Because of the lack of an appropriate mathematical or logical framework, these and related molecules have been a source of contention ever since.[3] This contention has been revived after the proposal of the sequence rule[4] and of prochirality.[5] According to Hirschmann and Hanson,[6] a pseudoasymmetric center has been defined as 'a center of stereoisomerism with a configuration that can be specified (without reference to other steric elements in the molecule) only by a chiral descriptor but whose configuration does not change on the reflection of the molecular model'. Prelog and Helmchen[7] have adopted another type of definition of such terms as prochiral, pseudoasymmetric, and propseudoasymmetric. As summarized in Table 1, main differences between the two types of definitions are concerned with AABQ and $AQ\bar{Q}R$, where R represents another chiral ligand. On the other hand, Mislow and Siegel[8] have discussed pseudoasymmetric carbon atoms and concluded that the term 'pseudoasymmetric' lacks any meaningful reference to symmetry and geometry and should be replaced by stereogenicity and local chirality.

More recently, we have discussed the importance of a coset representation $G(/G_i)$ and of its subduction into a subgroup G_j, i.e. $G(/G_i)\downarrow G_j$.[10] The key point is that such a coset representation $G(/G_i)$ can be assigned to an orbit, i.e. a set of equivalent objects (atoms, ligands, etc.), where G is the global symmetry of the molecule and G_i is the local symmetry of each ligand of the orbit. Thereby, we have further proposed the concept of sphericity which controls the chirality fittingness of an orbit consisting of equivalent ligands (or other objects) in a molecule.[11] We have coined the sphericity terms ('homospheric', 'enantiospheric' and 'hemispheric'), which have been successfully applied to the redefinition of prochirality,[11] topicity,[12,13] stereogenecity,[13] and anisochrony.[14]

The task of the present paper is to discuss chiral centers, pseudoasymmetric carbon centers and related matters in terms of the sphericity concept with consistent terminology. During this task, we shall exemplify the merits of the sphericity concept as a tool for characterizing stereochemical phenomena. In particular, a stepwise procedure for characterizing prochirality, prostereogenicity, and stereogenicity is proposed as a convenient tool of discussing stereochemistry.

Results and Discussion

Terminology for stereochemistry

The term 'prochirality' proposed by Hanson has been

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Table 1. Tetrahedral carbon atom with ligands

Ligands attached to Carbon	Hirschmann and Hanson[6,9]	Prelog and Helmchen[7]	Our Results (Pro)chirality[a] (Genecity)	Examples
ABCD	Chiral center of stereoisomerism	Chiral	Chiral (stereogenic)	**21**
AABC	Prochiral center of prostereoisomerism	Prochiral	Achiral, prochiral (prostereogenic)	**2**, **20**
AABQ	Prochiral center of prostereoisomerism	(Chiral)	Chiral (prostereogenic)	**3**[b]
AQQ̄R	Pseudoasymmetric[6]	(Chiral)	Chiral (stereogenic)	
QQ̄AB	Achiral center of stereoisomerism with chiral configuration	Pseudoasymmetric	Achiral, prochiral (stereogenic)	**7**, **8**
QQ̄AA	Proachiral center of prostereoisomerism with prochiral assembly	Propseudoasymmetric	Achiral, prochiral (prostereogenic)	**9**

[a] Under the condition that the symmetry of a promolecule is superior to the one of the corresponding molecule.
[b] This is regarded as a promolecule without linking to the molecule **1**.

criticized from a stereochemical point of view, as pointed out by Mislow and Siegel[8]: 'We thus recognize that 'elements of prochirality' suffer from the same lack of correspondence to local symmetry characteristics as 'elements of chirality'. This problem can be easily avoided if the usage of 'prochirality' with reference to prostereoisomerism is altogether abandoned, and such a course of action seems at least worthy of consideration.' Along the same line, the term 'prochiral' due to the IUPAC Rule E-4.12(a) and Rule E-4.12(b),[15] the latter of which has been defined as the successor of Hanson's proposal, has polysemous nature, as discussed by us.[16]

In this paper, we use the revised definitions of prochirality and related matters, as summarized in Rules A–C. Thereby, the terms *chirality* and *prochirality* have purely stereochemical meanings so that they can be used to describe the global symmetry of a molecule. Even if the terms are used to designate a part of such a molecule, the global symmetry of the molecule and the local symmetry of the part are well defined from a stereochemical point of view.

Rule A (Prochiral): The prochirality defined by Rule E-4.12(a) is preserved to be the revised definition of the term *prochiral*. This means that such a description as 'a molecule is prochiral' is permitted like the one 'a molecule is chiral'. In terms of the sphericity concept (Table 2), *a molecule containing at least one enantiospheric orbit is defined to be prochiral*.[11]

Rule B (Prostereogenic): The term 'prochiral center' defined by Rule E-4.12(b)[17] is replaced by the term *prostereogenic center*. In terms of the sphericity concept (Table 3), *if a center or atom has two ligands that are indistinguishable in isolation and not homotopic (i.e. either enantiotopic, diastereotopic or heterotopic) in a molecule, it is called a prostereogenic center.*

Rule C (Stereogenic): In addition, the term 'chiral center'[4,18] is replaced by the term *stereogenic center*.[19] Thus, the term *stereogenic center* is defined by starting from Rule B. *If a center or atom has two ligands that are distinguishable in isolation and if it can be transformed (even if virtually) into a prostereogenic center where the ligands are converted into two ligands indistinguishable in isolation, it is called a stereogenic center*.[13]

The test for prochirality, prostereogenicity and stereogenicity can be systematically carried out by the tools derived from the sphericity concept (Tables 2 and 3). The test is based on the fact that an orbit (a set of equivalent atoms or ligands) is assigned to a coset representation $G(/G_i)$.

1. Consider an appropriate conformer of the highest attainable symmetry G or the corresponding promolecule belonging to G.[20]

Table 2. Sphericity of a $G(/G_i)$-orbit[11]

Coset representation $G(/G_i)$	Global symmetry G	Local symmetry G_i	Chirality fittingness (ligands allowed)
Homospheric	Achiral	Achiral	Achiral ligands
Enantiospheric	Achiral	Chiral	Achiral ligands or a pair of chiral ligands and their enantiomers in the two halves
Hemispheric	Chiral	Chiral	Achiral or chiral ligands

Table 3. Membership criterion for topicity

Topicity		Membership criterion[11,12]
Homotopic	Holotopic	Between two sets of members in a homospheric orbit
	Hemitopic	Between two sets of members in either half of an enantiospheric orbit or in a hemispheric orbit
Enantiotopic		Between a set of members of one half and the corresponding set of members of the other half in an enantiospheric orbit
Diastereotopic		Between a set of an orbit and a set of a related orbit, where the two related orbits are governed by the same kind of coset representations

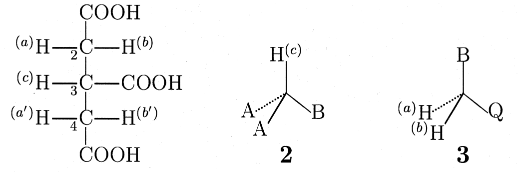
2. Collect equivalent ligands to give a respective orbit.
3. Assign each orbit to a coset representation $G(/G_i)$.
4. Classify the sphericity of the orbit according to Table 2.
5. Assign the topic relationship between a pair of orbits to be considered by virtue of Table 3.
6. Refer to Rule A for prochirality, to Rule B for prostereogenicity, or to Rule C for stereogenicity.

The assignment (Steps 1–3) can be accomplished by Method I or Method II described in Chapter 6 in Ref. 12, where the coset representation is treated directly as a permutation representation. In the present paper, we have adopted a more intuitive method, in which the local symmetry G_i of a site in an orbit can be obtained by inspection, giving the symbol $G(/G_i)$ for the coset representation. It should be added here that the number of members (sites) in the $G(/G_i)$-orbit is equal to $|G|/|G_i|$, where $|G|$ and $|G_i|$ represent the orders of the groups G and G_i, respectively. This proposition is useful to test the validity of the assignment.

Systematic test for prochirality and prostereogenicity

The latter intuitive method takes account of the symbol $G(/G_i)$ only, since the sphericity can be determined by comparing the chirality/achirality of the global symmetry G with that of the local symmetry G_i (Table 2). For example, the four hydrogen atoms of methane (CH_4) construct an orbit, which is determined to be governed by $T_d(/C_{3v})$. Note that the global symmetry of methane is characterized as T_d (Step 1), while the local symmetry for the orbit of the four hydrogen atoms (picked up in Step 2) is determined to be C_{3v} by fixing one hydrogen atom or, in other words, by distinguishing one hydrogen atom from the remaining hydrogens (Step 3). More precisely speaking, the hydrogen atom distinguished is left unchanged under all the operations of the C_{3v}-group. This assignment is verified by calculating the number of members in the $T_d(/C_{3v})$-orbit; thus we have $|T_d|/|C_{3v}|=24/6=4$. Since T_d and C_{3v} are achiral, the orbit of the four hydrogens is determined to be homospheric by virtue of the criterion described in Table 2 (Step 4). Table 2 shows that such a homospheric orbit can accommodate achiral ligands, as exemplified by the four hydrogens in this case. According to Table 3, the relationship between any pair selected from the four hydrogens is determined to be homotopic (Step 5). Then Step 6 can be traced by referring to Rules A–C, none of which applies to this case.

On the other hand, the two hydrogen atoms of chlorofluoromethane (CH_2ClF) construct an orbit, which is determined to be governed by $C_s(/C_1)$.[22] In this case, the global symmetry of chlorofluoromethane is characterized as C_s, while the local symmetry is determined to be C_1 by fixing one hydrogen atom. Note that the size of the orbit is calculated to be $|C_s|/|C_1|=2/1=2$, which is equal to the number of the hydrogen atoms of CH_2ClF. Since C_s is achiral and C_1 is chiral, the orbit of the two hydrogens is determined to be enantiospheric (Table 2). Table 2 shows that such an enantiospheric orbit can accommodate achiral ligands, as exemplified by the two hydrogens in this case. The enantiosphericity is then related to prochirality (Rule A) and to prostereogenicity (Rule B).



1

$H^{(a)}H^{(a')}$: $\mathbf{C}_s(/\mathbf{C}_1)$
$H^{(b)}H^{(b')}$: $\mathbf{C}_s(/\mathbf{C}_1)$
$H^{(c)}$: $\mathbf{C}_s(/\mathbf{C}_s)$

2

A_2: $\mathbf{C}_s(/\mathbf{C}_1)$
$H^{(c)}$: $\mathbf{C}_s(/\mathbf{C}_s)$
B: $\mathbf{C}_s(/\mathbf{C}_s)$

3

$H^{(a)}$: $\mathbf{C}_1(/\mathbf{C}_1)$
$H^{(b)}$: $\mathbf{C}_1(/\mathbf{C}_1)$
B: $\mathbf{C}_1(/\mathbf{C}_1)$
Q: $\mathbf{C}_1(/\mathbf{C}_1)$

Figure 1. Citric acid and promolecules.

In comparison with the rigid molecules described above, the stereochemical characterization of non-rigid molecules requires more sophisticated procedures. To characterize the prochirality of citric acid (**1**), for example, we consider orbits (sets of equivalent atoms) appearing in its appropriate conformer of the highest attainable symmetry. Thus, $H^{(a)}$ and $H^{(a')}$ belong to a two-membered orbit governed by $C_s(/C_1)$, while $H^{(b)}$ and $H^{(b')}$ belong to another two-membered orbit governed by $C_s(/C_1)$. The other paired parts of the two ligands CH_2COOH, i.e. C(2) and C(3); and (1)COOH and (5)COOH, are also assigned to $C_s(/C_1)$-orbits. The symbol $C_s(/C_1)$ shows that the global symmetry of **1** is C_s, while the local symmetry assigned to the orbit is C_1. Because the former is achiral and the latter is chiral, the $C_s(/C_1)$-orbit is determined to be enantiospheric in the light of Table 1. Hence, citric acid itself is concluded to be prochiral as an achiral object defined in Rule A (the revised IUPAC E-4.12(a)) (Fig. 1).

Alternatively, let us regard the two ligands CH_2COOH in citric acid (**1**) as proligands (A), as shown in **2**. The proligands A in the resulting promolecule **2** construct a two-membered enantiospheric orbit governed by $C_s(/C_1)$. Hence, citric acid is again concluded to be prochiral by virtue of Rule A. Our results for representative promolecules such as **2** are collected in the two columns of the right-hand side of Table 1.

It should be emphasized that the first method characterizes the prochirality of **1** by means of the sphericities of the orbits involved, but not by the nature of the central carbon atom C(3). Again in the alternative method, only the sphericity of the orbit of the ligands (A) is taken into consideration.

In order to test the prostereogenicity of citric acid, we take account of the two ligands (CH_2COOH) in **1** as well as the two proligands (A) in **2**. Rule B indicates that the C(3) is a prostereogenic center. Obviously, the prostereogenic center is associated with the prochirality due to the enantiospheric orbit of the two As.

When we focus our attention on C(2) in **1**, the hydrogens $H^{(a)}$ and $H^{(b)}$ selected from the four ligands ($H^{(a)}$, $H^{(b)}$, CH_2COOH and $CH(OH)CH_2COOH$) are indistinguishable in isolation. By an intimate inspection on the molecule **1**, the relationship between the $C_s(/C_1)$-orbit of $H^{(a)}$ and $H^{(a')}$ and the $C_s(/C_1)$-orbit of $H^{(b)}$ and $H^{(b')}$ is determined to be diastereotopic in terms of the membership criterion (Table 3). Hence, the carbon C(2) is a prostereogenic center in agreement with Rule B. More simply, we can consider the corresponding promolecule **3**, where the relationship between $H^{(a)}$ and $H^{(b)}$ is diastereotopic because $H^{(a)}$ and $H^{(b)}$ belong to distinct $C_1(/C_1)$-orbits (Table 3). It should be noted that the promolecule **3** is here characterized by linking to the molecule **1**. This means that the global symmetry cannot be discussed by this simple procedure.

Systematic test for stereogenicity

Stereogenic centers are concerned with the so-called pseudoasymmetric carbon centers. Let us begin with two achiral 2,3,4-trihydroxyglutaric acids (**4** and **5**) that have been frequently cited as typical examples.

In order to test the stereogenicity of the central carbon of **4** or **5**, we first take the corresponding promolecule into consideration. When chiral proligands Q and $\bar{Q}$ are substituted for the ligands –CH(OH)COOH (*R* and *S*) in **4** and **5** and the hydroxyl group is replaced by an achiral proligand A,[21] we have the corresponding promolecules **7** and **8**, both of which belong to the point group C_s. Note that these promolecules are diastereomeric to each other. The chiral proligands Q and $\bar{Q}$ of **7** (or **8**) construct a two-membered orbit governed by the coset representation $C_s(/C_1)$, which is determined to be enantiospheric (Table 2). On the other hand, the proligand H (hydrogen atom) in the promolecule **7** (or **8**) belongs to a one-membered orbit governed by $C_s(/C_s)$, which is determined to be homospheric in the light of Table 2. Along the same line, the proligand A (hydroxyl group) in the promolecule **7** (or **8**) belongs to another one-membered homospheric orbit governed by $C_s(/C_s)$. Moreover, the central atom C(3) in **7** (or **8**) belongs to a further one-membered homospheric orbit governed by $C_s(/C_s)$. As a result, the plane containing H, A and C(3) belongs to a one-membered orbit governed by $C_s(/C_s)$, where all points in the place are governed by $C_s(/C_s)$(Fig. 2).

By consulting the assignment for the promolecule **7** (or **8**), we can clarify the orbits appearing in the molecule **4** (or **5**). Since the highest attainable symmetry of **4** (or **5**) is C_s, we have a $C_s(/C_1)$-orbit of 2-OH (O and H) and 4-OH (O and H); a $C_s(/C_1)$-orbit of 1-COOH (C, O, O, and H) and 4-COOH (C, O, O, and H); a $C_s(/C_1)$-orbit of C(2) and C(4); a $C_s(/C_1)$-orbit of 2-H and 4-H; a $C_s(/C_s)$-orbit of 3-H; a $C_s(/C_s)$-orbit of C(3); and a $C_s(/C_s)$-orbit of 3-OH (O and H). The symmetry environment around the C(3) can also be deduced by virtue of this method.

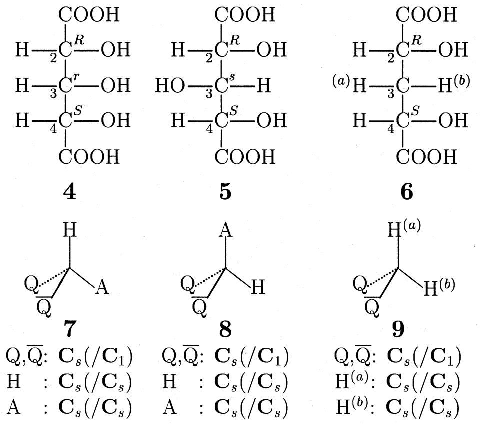


Figure 2. Orbits in achiral 2,3,4-trihydroxyglutaric acids and achiral 2,4-dihydroxyglutaric acid.

The proligand H on the C(3) of **4** (or **7**) (belonging to the homospheric $C_s(/C_s)$-orbit) and the proligand A on the C(3) (belonging to the other $C_s(/C_s)$-orbit) are placed in a diastereotopic relationship according to the membership criterion (Table 3). This relationship holds true for the counterparts in **5** (or **8**). In other words, they are transformed into one another by exchanging these ligands (H and OH). This means that the C(3) of **4** (or **7**) and the C(3) of **5** (or **8**) are stereogenic centers.

Rule C is an alternative recognition of stereogenic centers. This is based on recognition of the corresponding prostereogenic centers. The deletion of the hydroxyl group on C(3) gives an achiral 2,4-dihydroxyglutaric acid (**6**). The corresponding promolecule **9** belongs to C_s, where Q and $\bar{Q}$ construct a two-membered $C_s(/C_1)$-orbit; $H^{(a)}$ belongs to a one-membered $C_s(/C_s)$-orbit; and $H^{(b)}$ belongs to a distinct one-membered $C_s(/C_s)$-orbit. In terms of the membership criterion for a diastereotopic relationship (Table 3), $H^{(a)}$ and $H^{(b)}$ are determined to be diastereotopic, because they (the two related orbits of one member) are governed by the same kind of coset representations, i.e. the two representations $C_s(/C_s)$. It follows that the C(3) attached by $H^{(a)}$ and $H^{(b)}$ is a prostereogenic center (Rule B) so as to give **4** and **5**.[13] This result in turn indicates that the C(3) in **7** (or **8**) is a stereogenic center (Rule C).

By considering the highest attainable symmetry C_s, we find that **6** contains a $C_s(/C_1)$-orbit of 2-OH (O and H) and 4-OH (O and H); a $C_s(/C_1)$-orbit of 1-COOH (C, O, O, and H) and 4-COOH (C, O, O, and H); a $C_s(/C_1)$-orbit of 2-C and 4-C; a $C_s(/C_1)$-orbit of 2-H and 4-H; a $C_s(/C_s)$-orbit of 3-H; a $C_s(/C_s)$-orbit of C(3); and a $C_s(/C_s)$-orbit of 3-$H^{(b)}$. As a result, the diastereotopic/prostereogenic relationship between $H^{(a)}$ and $H^{(b)}$ is also deduced from the direct inspection of the molecular model **6**.

Prostereogenicity in chiral molecules

An enantiomeric pair of chiral 2,3,4-trihydroxyglutaric acid (**10** and **11**) is another set of troublesome examples for stereochemistry, since the original IUPAC Rule E-4.12(b) regards each central carbon C(3) as a 'prochiral center', whereas each of the acids is chiral. The C(3) in **10** (or **11**) is now regarded as a prostereogenic center in terms of Rule B as will be discussed in detail (Fig. 3).

When Q is substituted for R-CH(OH)COOH and $\bar{Q}$ for S-CH(OH)COOH, **10** and **11** can be transformed into **14** and **15**. The resulting promolecules **14** and **15** belong to C_1 (asymmetric). The orbit of each Q in **14** (or each $\bar{Q}$ in **15**) is assigned to the coset representation $C_1(/C_1)$ (hemispheric) so that the two Qs in **14** (or the two $\bar{Q}$s in **15**) are diastereotopic to each other (Table 3). It follows that the C(3) attached by Qs (or $\bar{Q}$s) is determined to be a prostereogenic center by virtue of Rule B.

A related enantiomeric pair of chiral 2,4-dihydroxyglutaric acid (**12** and **13**) belong to C_2 (chiral). The corresponding

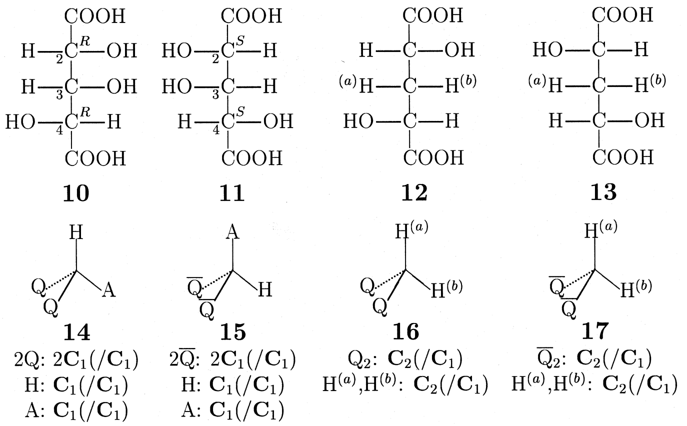


Figure 3. Orbits in enantiomers of chiral 2,3,4-trihydroxyglutaric acid and chiral 2,4-dihydroxyglutaric acid.

promolecules **16** and **17** also belong to C_2 (chiral). The orbit of Qs in **16** (or $\bar{Q}$s in **15**) is assigned to the coset representation $C_2(/C_1)$ (hemispheric). Hence, the two Qs in **14** (or the two $\bar{Q}$s in **15**) are homotopic (hemitopic) to each other (Table 3).

Nested proligands

For illustrating the usefulness of proligands used in place of actual ligands, let us reexamine **18** and **19** (Fig. 4), which have once been examined by Hirschmann and Hanson. Since the ligands rooted on C(2) and C(4) in **18** and **19** are achiral in isolation, they can be replaced by a proligand A or B to produce promolecules **20** and **21**. Note that the resulting promolecules contain achiral ligands only.

As for the achiral promolecule **20** belonging to C_s, two ligands (A) construct a two-membered enantiospheric orbit governed by $C_s(/C_1)$, while H and OH, respectively, construct a one-membered homospheric orbit governed by $C_s(/C_s)$. Hence, **20** is prochiral by virtue of the $C_s(/C_1)$-orbit (Rule A). Rule B indicates that the central carbon C(3) in **20** is a prostereogenic center because the two ligands (A) belong to an enantiospheric $C_s(/C_1)$-orbit.

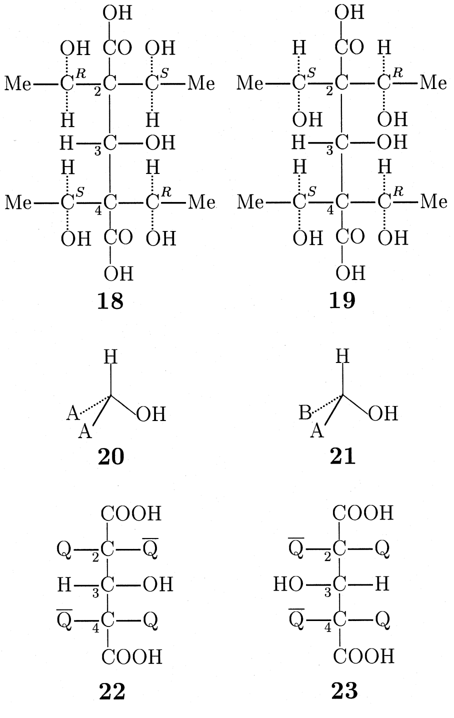


Figure 4. Orbits in promolecules of different levels.

On the other hand, **21** is chiral and belongs to C_1 (asymmetric). Each of the four proligands (A, B, H and OH) in **21** constructs a one-membered hemispheric orbit governed by $C_1(/C_1)$. Rule C indicates that C(3) in **21** is a stereogenic center.

When Q is substituted for R-CH(OH)Me and $\bar{Q}$ for S-CH(OH)Me, **18** and **19** are alternatively transformed into **22** and **23**. Since **22** belongs to C_s, we can deal in detail with the orbits appearing in the intermediate promolecule **22**. Thus, we have a $C_s(/C_1)$-orbit of 2-$\bar{Q}$ and 4-Q; a $C_s(/C_1)$-orbit of 1-COOH and 4-COOH; a $C_s(/C_1)$-orbit of C(2) and C(4); a $C_s(/C_1)$-orbit of 2-Q and 4-$\bar{Q}$; a $C_s(/C_s)$-orbit of 3-H; a $C_s(/C_s)$-orbit of C(3); and a $C_s(/C_s)$-orbit of 3-OH. All of the enantiospheric $C_s(/C_1)$-orbits indicate that **22** is prochiral. They correspond to the $C_s(/C_1)$-orbit assigned to the proligands (A) in **20** described above. It should be emphasized here that we can avoid the use of such terms as 'prochiral center' (abandoned) and 'prostereogenic' (adopted) in the process of assigning the prochirality to the promolecules **20** and **22**. What should be done is the detection of any enantiospheric orbit in a molecule or promolecule. Rule B indicates that the C(3) of **22** is a prostereogenic center. Since **23** belongs to C_1 (asymmetric), any of the proligands in **23** belong to a one-membered $C_1(/C_1)$-orbit. Rule C indicates that the C(3) of **23** is a stereogenic center.

Conclusion

A method for characterizing prochirality, prostereogenicity, and stereogenicity is described. A molecule containing at least one enantiospheric orbit is defined to be prochiral (Rule A). If a center or atom has two ligands that are indistinguishable in isolation and not homotopic (i.e. either enantiotopic, diastereotopic or heterotopic) in a molecule, it is called a prostereogenic center (Rule B). If a center or atom has two distinguishable-in-isolation ligands that can be transformed (even if virtually) into the two indistinguishable-in-isolation ligands at the resulting prostereogenic center, it is called a stereogenic center (Rule C). All of these definitions are based on the sphericity concept.

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17. The term 'prochiral center' defined by Hanson[5] is replaced by the term prostereogenic center. The terms 'prochiral centers' and 'propseudoasymmetric centers'[7] are replaced by the term prostereogenic center.
18. The term 'chiral center' by Hirschmann and Hanson[9] is replaced by the term stereogenic center. The terms 'chiral center' and 'pseudoasymmetric center'[7] are replaced by the term stereogenic center. The revision of Cahn–Ingold–Prelog (CIP) system[23] has adopted the term 'stereogenic' in the form of 'chirality elements as stereogenic units of the CIP-system'.
19. McCasland, G.E., *A New General System for the Naming of Stereoisomers*; Chemical Astracts: Columbus, 1953.
20. A promolecule is defined as a derivative of an appropriate skeleton with a set of proligands, which are in turn defined as structureless objects with chirality/achirality. See Ref. 21.
21. Fujita, S. *Tetrahedron* **1991**, *47*, 31.
22. The relationship between the two hydrogens of chlorofluoromethane is determined to be enantiotopic in the light of Mislow–Raban's criterion.[24] It should be emphasized that the present method of characterization takes a different process but gives an equivalent result: the orbit of the two hydrogens $\rightarrow C_s(/C_1)\rightarrow$ enantiospheric (Table 2) → enantiotopic (Table 3). The difference between Mislow–Raban's criterion and our membership criterion (Table 3) is further clarified by examining the eight bridge hydrogens of adamantane-2,6-dione. In the light of Mislow–Raban's criterion, there are four kinds of enantiotopic relationships and three kinds of homotopic relations with respect to each hydrogen. On the other hand, the present method shows that the eight hydrogens are equivalent and belong to an eight-membered orbit governed by $D_{2d}(/C_1)$, where the orbit is determined to be enantiospheric (Table 2). Then the orbit is divided into two halves, which are characterized in terms of hemitopic and enantiotopic (Table 3). The four bridgehead hydrogens of adamantane-2,6-dione belong to a four-membered $D_{2d}(/C_s)$-orbit, which is determined to be homospheric (Table 2). The relationships between the members of the homospheric orbit are determined to be holotopic by virtue of our membership criterion described in Table 3.
23. Prelog, V.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 567.
24. Mislow, K.; Raban, M. *Top. Stereochem.* **1967**, *1*, 1.