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Chiral Replacement Criterion for Characterizing Holotopic and Hemitopic Relationships

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A chiral replacement criterion has been proposed to characterize stereochemical equivalence. This criterion is effective to determine holotopic and hemitopic relationships, which are sub-relationships of a homotopic relationship. The criterion has been shown to be complementary to the membership criterion based on the sphericity concept.

The suffix "topic" used in stereochemistry has two distinct connotations, which have given some inharmoniousness to the terminology of stereochemistry.

The first series of such terms ("enantiotopic", "diastereotopic", "homotopic", and "heterotopic") characterize a *relationship* between two object (e.g. atoms and sites). The terms, "enantiotopic", "diastereotopic", and "equivalent", have been introduced by Mislow and Raban to determine stereochemical equivalence and non-equivalence.[1] For the sake of consistent description, another term "equitopic" (Nakazaki[2—4]) and later an alternative term "homotopic" (by Hirschmann and Hanson[5]) have been proposed in place of the term "equivalent".[6,7] These topicity terms have been widely used by organic chemists and biochemists to characterize the symmetry (non) equivalence of nuclei or groups in NMR spectroscopy and in physicochemical determinations[8—10] as well as to specify the processes of asymmetric syntheses.[11—13] The concept of prochirality, which is closely related to enantiotopic nature, has also been used to specify the processes of asymmetric syntheses and biological transformations.[7,14—16] In order to characterize the topicity relationships (as for the first sense), a replacement criterion (substitution or addition criterion) and a symmetry criterion have been described by Mislow and Raban,[1] where the former criterion is essentially equivalent to the one described by Hanson[14] to test prochirality. Table 1 summarizes these criteria with brief explanations. A flow chart for the classification of topic relationships has been reported in the form of a decision tree, each decision step of which is based on a distinct symmetry criterion.[17,18]

On the other hand, the second series of terms ("chirotopic" and "achirotopic") deal with an *attribute* of a single object, not with any relationship between two objects. They have been proposed to specify local chirality in a molecule, where a new treatment of prochirality has been described.[17] By virtue of this terminology, for example, each of two atoms placed in an enantiotopic relationship is stated to be chirotopic in nature, each of two atoms placed in a homotopic relationship is explained to be chirotopic or achirotopic, and so on. The chirotopic nature appears in a homotopic relationship as well as in an enantiotopic relationship. In other words, the chirotopic nature in a homotopic relationship implies a chiral molecule, while the chirotopic nature in an enantiotopic relationship implicitly supposes an achiral (prochiral) molecule. Thus, such dual expressions may be a barrier to the understanding of organic chemists even if the topic terms of the two series have been carefully differentiated.

To overcome such difficulties that come from the usage of these two series of terms having the suffix "topic", there are two ways: (1) one of the two series is renamed to have another suffix than "topic"; or (2) one of the two series is discarded after the coinage of new terms. We have adopted the latter way after the proposal of the concept of chirality fittingness (sphericity),[19] which controls the chirality fittingness of an orbit consisting of equivalent ligands (or other objects) in a molecule. The key point of the concept is that such an orbit is assigned to a coset representation $\mathbf{G}(/\mathbf{G}_i)$, where $\mathbf{G}$ is the global symmetry of the molecule and $\mathbf{G}_i$ is the local symmetry of each ligand of the orbit. Note that $\mathbf{G}_i$ is a subgroup of $\mathbf{G}$ and that the $\mathbf{G}(/\mathbf{G}_i)$ is a kind of permutation representations.[20] Thereby, we have proposed the sphericity terms ("homospheric", "enantiospheric", and "hemispheric") by comparing the global symmetry $\mathbf{G}$ with the local one $\mathbf{G}_i$. The sphericity concept has been successfully used to redefine prochirality,[19] topicity,[20,21] stereogenecity,[21] and anisochrony.[22] In particular, a membership criterion for determining topic relationships have been derived from the concept of sphericity (Table 1),[19,23] where the homotopic relationship can further be divided into holotopic and hemitopic relationships.[20] Although the membership criterion has much merit in deriving such subdivided relationships smoothly, its apparant mathematical character would provide organic chemists with some difficulties. The symmetry criterion has more or less suffered from the same kind of apparent drawbacks, though it could be redefined by adding subsidiary conditions in order to characterize

Table 1. Criteria for Determining Topicities

Topicity	Replacement criterion[1,6)]	Symmetry criterion[1,6)]	Membership criterion[19,20)]
Homotopic	Pairwise replacement gives identical (homomeric) products	Pair interchanged by proper rotations	Holotopic: Homospheric orbit Hemitopic: Either half of enantiospheric orbit or hemispheric orbit
Enantiotopic	Pairwise replacement gives enantiomeric products	Pair interchanged by improper rotations but not by proper rotations	Two halves of an enantiospheric orbit
Diastereotopic	Pairwise replacement gives diastereomeric products	Pair not interchanged by improper rotations or by proper rotations	Two related orbits governed by the same kind of coset representations.

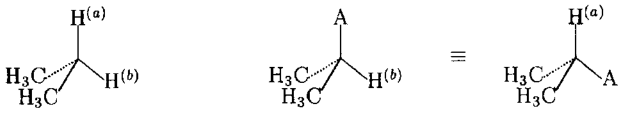
the holotopic (a pair of ligands interchanged by proper and *improper* rotations) and the hemitopic (a pair interchanged by proper rotations, *but not by improper rotations*). On the other hand, the replacement criterion is most familiar to organic chemists, since it can be easily correlated to the processes of asymmetric syntheses. However, the original definition cannot so easily be revised as to derive the holotopic and hemitopic relationships if the explanation given in Table 1 is maintained.

As clarified in the preceding paragraphs, the target of the present paper is to propose a chiral replacement criterion for characterizing the holotopic and hemitopic relationships. This proposal reveals chemical connotations of the membership criterion and shows how to apply the relationships to complex molecules.

Results

Chiral Replacement Criterion. The topicity terms are used here to deal with the *relationship* between two related atoms (or molecular environments) in a molecule, not to characterize local chirality. In other words, the topicity is concerned only with a pairwise relationship. More clearly speaking, the terms of the second series (chirotopic and achirotopic) are no longer to be used in the present approach, where the terms "holotopic" and "hemitopic"[20] are used, respectively, in place of such dual expressions as "homotopic and achirotopic" and "homotopic and chirotopic". As a result, all of the topic terms have been consistently coined in the present approach so as to characterize pairwise relationships

The term "homotopic" is used, for example, to describe the relationship between two methylene hydrogens $H^{(a)}$ and $H^{(b)}$ in propane (**1**). In light of the replacement criterion (Table 1), one of the two atoms in **1** is replaced by a ligand A to give a mono-substituted derivative **2**, which is homomeric to the other **3** derived otherwise (Fig. 1).[24]



1 **2** **3**

Fig. 1. Replacement criterion for characterizing homotopicity.

As found in the process of Fig. 1, the definition of the replacement criterion (Table 1) has an implicit assumption: i.e., the ligand A is achiral and structureless.[25] This implicit assumption can be revised to an explicit formulation by adopting the concept of proligands, which have been defined as structureless objects with chirality/achirality.[26,27] If the proligand concept is applied to the replacement criterion for determining a homotopic relationship (Table 1), we obtain a more strict definition of homotopicity, where a pairwise replacement with an *achiral proligand* gives identical (homomeric) products.

In order to define a holotopic relationship, we use a chiral replacement criterion in which a chiral proligand Q and its antipodal (enantiomeric) proligand $\overline{Q}$ are selected as probes. *A homotopic pair of ligands*[28] *is determined to be holotopic, if a pairwise replacement of the ligand pair with a pair of antipodal proligands* (Q *and* $\overline{Q}$) *gives enantiomeric products.* For example, the top row of Fig. 2 shows a set of two homomers (**4** and **5**) produced by replacing a pair of methylene hydrogens with a chiral proligand Q, while the bottom row shows a set of two homomers (**6** and **7**) with an antipodal proligand $\overline{Q}$. The two rows represent isomers enantiomeric to each other. Note that a pairwise replacement with Q and $\overline{Q}$ means the process of producing **4** and **7** (or **5** and **6**), which are enantiomeric. Hence, by virtue of the chiral replacement criterion, $H^{(a)}$ and $H^{(b)}$ in **1** are determined to be holotopic to each other (Fig. 1). This result is consistent with the one derived from the membership criterion (Table 1).[24]

The chiral replacement criterion is also applicable to more complex cases. Let us consider adamantane-2,6-dione (**8**) containing four bridgehead and eight bridge hydrogens (Fig. 3). The orbit of the four bridgehead hydrogens $H^{(A)}$

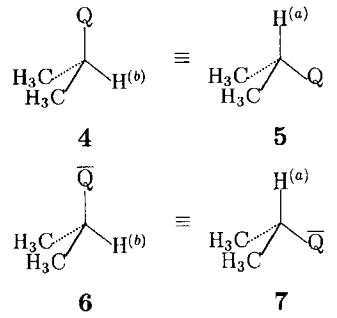


Fig. 2. Chiral replacement criterion for characterizing holotopicity.

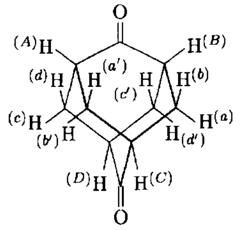


Fig. 3. Eight bridge hydrogens and four bridgehead hydrogens in adamantane-2,6-dione.

to $H^{(D)}$ is governed by the coset representation $\mathbf{D}_{2d}(/\mathbf{C}_s)$,[29] while the orbit of the eight bridgehead hydrogens $H^{(a)}$ to $H^{(d)}$ and $H^{(a')}$ to $H^{(d')}$ is governed by the coset representation $\mathbf{D}_{2d}(/\mathbf{C}_1)$.[30]

Any pairwise hydrogens selected from the four bridgehead hydrogens in adamantane-2,6-dione (**8**) are homotopic to each other by the original replacement criterion (Table 1).[31] Their relationship is further specifically determined to be holotopic by the chiral replacement criterion, as shown in Fig. 4, where the set of homomers with Q (**9** to **12**) are enantiomeric to the set of homomers with $\overline{\mathrm{Q}}$ (**13** to **16**). When we focus our attention on $H^{(A)}$ in **8**, for example, we have three pairs of holotopic relationship, i.e., $H^{(A)}$ and $H^{(B)}$; $H^{(A)}$ and $H^{(C)}$; and $H^{(A)}$ and $H^{(D)}$. It should be noted that the relationship between $H^{(A)}$ and $H^{(B)}$ is different from the relationship between $H^{(A)}$ and $H^{(C)}$ (or between $H^{(A)}$ and $H^{(D)}$).

A hemitopic relationship is another subclass of a homotopic relationship. A pair of a chiral proligand Q and its antipodal (enantiomeric) proligand $\overline{\mathrm{Q}}$ is used as probes to determine the hemitopic relationship in the light of the chiral replacement criterion. Thus, *a homotopic pair of ligands is determined to be hemitopic, if a pairwise replacement of the ligand pair with a pair of antipodal proligands* Q *and* $\overline{\mathrm{Q}}$ *gives diastereomeric products.* The hemitopic relationship are recognized clearly in the case of a four or more-membered enantiospheric orbit, where each of the two halves of the orbit is considered to be a homotopic part.

Let us examine the relationship between four hydrogen atoms ($H^{(a)}$, $H^{(b)}$, $H^{(c)}$, and $H^{(d)}$) on the bridge positions of adamantane-2,6-dione (**8**). These four hydrogen atoms construct a homotopic half of an eight-membered enantiospheric orbit. As a result, we have three homotopic pairs, i.e., $H^{(a)}$ and $H^{(b)}$; $H^{(a)}$ and $H^{(c)}$; and $H^{(a)}$ and $H^{(d)}$, when we focus our attention on $H^{(a)}$ as a pivot.[32] The top row of Fig. 5 shows a set of four homomers **17** to **20** produced by replacing each of methylene hydrogens with a chiral proligand Q, while the bottom row shows a set of four homomers **21** to **24** with an antipodal proligand $\overline{\mathrm{Q}}$. The two rows represent isomers diastereomeric to each other. Note that a pairwise replacement with Q and $\overline{\mathrm{Q}}$ means the process of producing **17** and **22** (or **17** and **23**; or **17** and **24**), which are diastereomeric. Hence, by virtue of the chiral replacement criterion, Fig. 5 shows that $H^{(a)}$ to $H^{(d)}$ in **1** are determined to be hemitopic to one another. This result is consistent with the one derived from the membership criterion (Table 1).

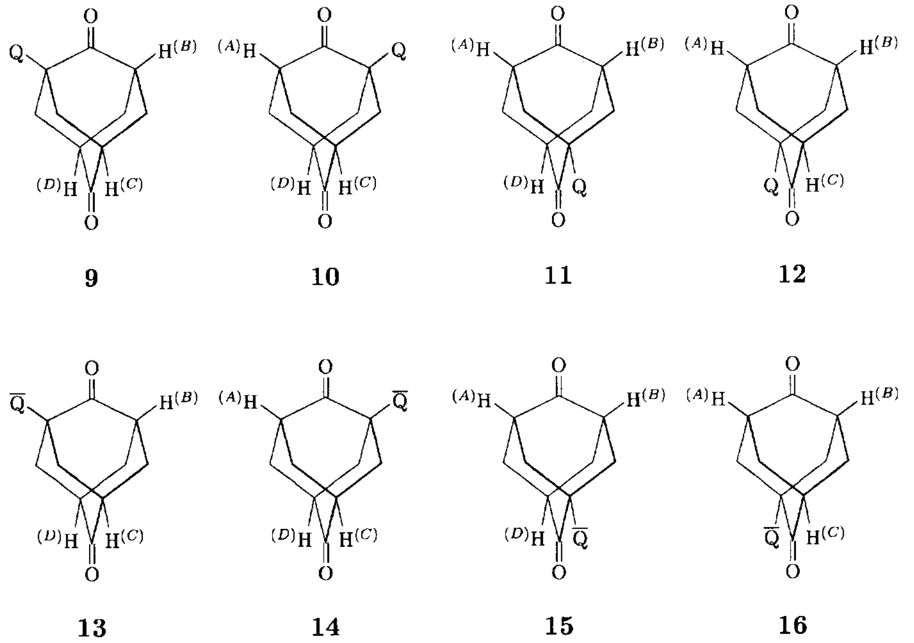


Fig. 4. Holotopic relationship for four bridgehead hydrogens of adamantane-2,6-dione.

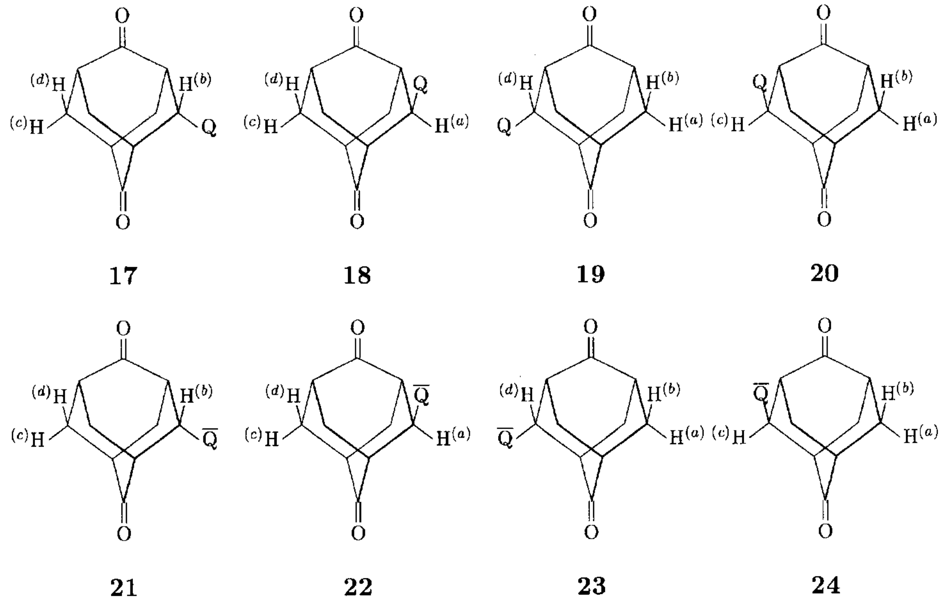


Fig. 5. Chiral replacement criterion for characterizing hemitopicity in adamantane-2,6-dione.

Since a hemitopic relationship is concerned with two or more proligands, it is not effective to a two-membered enantiospheric orbit.[33] Note that each half of such an orbit contains only one member. However, the one-membered half also gives diastereomeric products when it is replaced by a pair of antipodal proligands Q and $\overline{\mathrm{Q}}$. For example, let us consider the methylene hydrogens $\mathrm{H}^{(a)}$ and $\mathrm{H}^{(b)}$ of ethanol (**25**), which construct a two-membered enantiospheric orbit (Fig. 6). The one-membered half containing only $\mathrm{H}^{(a)}$ (or $\mathrm{H}^{(b)}$) gives **26** and **28** (or **27** and **29**), which are diastereomeric to each other. In this meaning, Fig. 6 is regarded to show a self-hemitopicity, i.e., a relationship between a ligand and itself.

Ligand- and Face-Differentiation. In the treatment of the preceding subsection, we have adopted the concept of proligands. Such a proligand can be conceptually transformed into a ligand containing faces, which cause further topic relationships. Since this type of transformation is related to the chiral replacement criterion proposed in the present paper, we shall consider acetyl groups introduced in place of proligands as a typical example (Fig. 7). The main target of this subsection is the comparison between the chiral replacement criterion and the membership criterion.

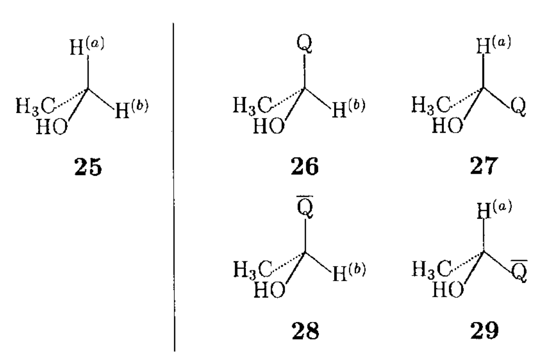


Fig. 6. Chiral replacement criterion for characterizing self-hemitopicity.

Let us first examine ligand-differentiation by using compounds **30** and **31** listed in Fig. 7. The two acetyl groups $\mathrm{COCH}_3^{(a)}$ and $\mathrm{COCH}_3^{(b)}$ in **30** construct an orbit governed by $\mathbf{C}_{2v}(/\mathbf{C}_s)$, when they are regarded as achiral proligands. The orbit is homospheric, since $\mathbf{C}_{2v}$ and $\mathbf{C}_s$ are achiral. Note that the acetyl groups in **30** are homotopic in terms of the conventional topicity and further holotopic in terms of the present method. It follows that the acetyl groups as proligands are not prochiral, so that no ligand-differentiating reactions occur.

On the other hand, the two acetyl groups of **31** as proligands construct an orbit governed by $\mathbf{C}_s(/\mathbf{C}_1)$. Since this orbit is enantiospheric, ligand-differentiating reactions (e.g. a conversion of one acetyl group into a carboxyl group) are possible to give enantiomers, where either enantiomer may be dominant under appropriate chiral conditions. Note that the resulting ligand (e.g. the carboxyl group) is achiral. This is an example of the original replacement criterion for an enantiotopic relationship (Table 1).

Let us next examine face-differentiation concerning **30** and **31**. The two faces (*re* and *si*) of every acetyl group in **30** construct an enantiospheric orbit of four faces, which is governed by $\mathbf{C}_{2v}(/\mathbf{C}_1)$.[34] As a result, the *re*-faces of the two acetyl groups in **30** are involved in one homotopic (hemitopic) half of the $\mathbf{C}_{2v}(/\mathbf{C}_1)$-orbit, while the *si*-faces are involved in the other homotopic (hemitopic) half. These halves are enantiotopic to each other. Hence, the orbit can undergo a face-

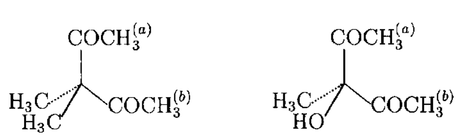


Fig. 7. Ligand- or face-differentiation.

differentiating reaction under chiral conditions. When the local symmetry $\mathbf{C}_s$ is taken into consideration, the two faces (*re* and *si*) of each acetyl group construct a local orbit which is governed by $\mathbf{C}_s(/\mathbf{C}_1)$.[35] Since the orbit is enantiospheric, we obtain the same conclusion as obtained above by considering $\mathbf{C}_{2v}(/\mathbf{C}_1)$.

On the other hand, a face of the one acetyl group ($\mathrm{COCH}_3^{(a)}$) and a face of the other acetyl group ($\mathrm{COCH}_3^{(b)}$) in **31** construct a two-membered enantiospheric orbit governed by $\mathbf{C}_s(/\mathbf{C}_1)$. The remaining two faces in **31** also construct a two-membered enantiospheric orbit governed by $\mathbf{C}_s(/\mathbf{C}_1)$. As a result, the one face of each acetyl group is diastereotopic to the other face of the same acetyl group.

Keeping these relationships in mind, let us consider the attack of a nucleophilic reagent to the carbonyl group of $\mathrm{COCH}_3^{(a)}$ in **31** to produce a chiral proligand Q. For example, ethylmagneseum bromide can be used to give a chiral group $\mathrm{C(OH)(CH_3)(CH_2CH_3)}$ as a proligand Q (or $\overline{\mathrm{Q}}$), though an experimental testing is necessary. By virtue of the chiral replacement criterion described in the preceding subsection, the attacks to the two faces of the carbonyl group produce a pair of products diastereomeric to each other even in achiral environments. The ratio of the diastereomeric products may vary according to the effect of the remaining part $\mathrm{C(OH)(CH_3)(COCH_3^{(b)})}$. The products are racemic, since the same kind of attacks occur in $\mathrm{COCH}_3^{(b)}$. Under chiral environments, either enantiomer of each diastereomeric product may be dominant to exhibit optical activity.

The diastereotopicity of the two faces of each acetyl group in **31** can also be deduced from the local symmetry $\mathbf{C}_1$ of the acetyl group, which is a half of the enantiospheric orbit governed by $\mathbf{C}_s(/\mathbf{C}_1)$. Hence, the two faces of one acetyl group, to which our attention is paid, are governed separately by the coset representation $\mathbf{C}_1(/\mathbf{C}_1)$. This means again that the one face of the acetyl group is diastereotopic to the other face of the same acetyl group.

The discussions in the preceding paragraphs are effective for more complex cases. For example, the four acetyl groups in **32** construct a homospheric orbit governed by $\mathbf{D}_{2d}(/\mathbf{C}_s)$, when they are regarded as achiral proligands. Hence, no ligand-differentiating chiral reactions take place.

On the other hand, the totally eight faces of the four acetyl groups in **32** construct an enantiospheric orbit governed by $\mathbf{D}_{2d}(/\mathbf{C}_1)$ (Fig. 8). Hence, the orbit can undergo a face-differentiating reaction, e.g., the transformation of one acetyl group into a chiral group $\mathrm{C(OH)(CH_3)(CH_2CH_3)}$ as a proligand Q (or $\overline{\mathrm{Q}}$). The same conclusion as above can be obtained by considering the local symmetry $\mathbf{C}_s$ of $\mathbf{D}_{2d}(/\mathbf{C}_s)$. Thus, the two faces of each acetyl group construct a local orbit, which is enantiospheric because of the coset representation $\mathbf{C}_s(/\mathbf{C}_1)$. It should be noted that the process of the face-differentiating reaction in **32** is regarded as an example of the chiral replacement criterion (see Fig. 3), by which the holotopic nature of the four acetyl groups in **32** is determined.

The four acetyl groups (A = $\mathrm{COCH_3}$) of **33** as proligands construct an enantiospheric orbit governed by $\mathbf{S}_4(/\mathbf{C}_1)$, where the set of $\mathrm{A}^{(a)}$ and $\mathrm{A}^{(c)}$ constructs one half of the orbit, while the set of $\mathrm{A}^{(a')}$ and $\mathrm{A}^{(c')}$ constructs the other half of the orbit. The two sets are enantiotopic so that ligand-differentiating reactions (e.g. a conversion of one acetyl group into a carboxyl group) are possible to give enantiomers. This is an example of the original replacement criterion for an enantiotopic relationship (Table 1).

Moreover, one face of every acetyl group ($\mathrm{A}^{(a)}$, $\mathrm{A}^{(a')}$, $\mathrm{A}^{(c)}$, or $\mathrm{A}^{(c')}$) in **33** is a member of a four-membered enantiospheric orbit governed by $\mathbf{S}_4(/\mathbf{C}_1)$.[36] The remaining face of every acetyl group is a member of another four-membered enantiospheric orbit governed by $\mathbf{S}_4(/\mathbf{C}_1)$. The two enantiospheric orbits are diastereotopic to each other. If we focus our attention on each acetyl group, we find that its one face is diastereotopic to its other face. As a result, the attacks to the two faces of each carbonyl group (e.g. $\mathrm{A}^{(a)}$) in **33** produce chiral proligands Q and $\overline{\mathrm{Q}}$. The resulting products are a pair of products diastereomeric to each other even in achiral conditions. This gives an embodiment of the chiral replacement criterion described in the preceding subsection (Fig. 5). The products are racemic under achiral reaction conditions, since the same kind of attacks occur in $\mathrm{A}^{(a')}$ or $\mathrm{A}^{(c')}$. Under chiral conditions, either enantiomer of each diastereomeric product may be dominant to exhibit optical activity.

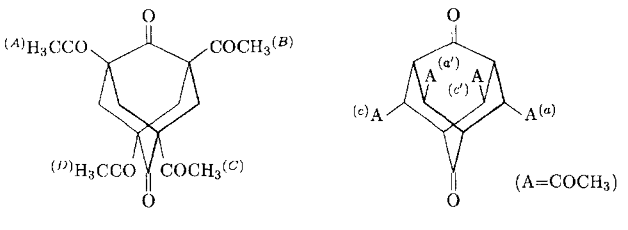
The local symmetry of the acetyl group in **33** is determined to be $\mathbf{C}_1$ from the coset representation $\mathbf{S}_4(/\mathbf{C}_1)$. This clarifies the diastereotopicity of the two faces of each acetyl group in **33** because of the subduction represented by $\mathbf{C}_s(/\mathbf{C}_1)\downarrow\mathbf{C}_1 = 2\mathbf{C}_1(/\mathbf{C}_1)$.[20]

Discussion

A scheme for classifying topic relationships by Hirschmann and Hanson[5,6] takes both stereochemical and constitutional standpoints at the top-level comparison so as to differentiate a homotopic relationship from a heterotopic one. A constitutionally heterotopic relationship and a stereochemical heterotopic one (enantiotopic and diastereotopic) are then differentiated:[6]

- heterotopic
  - constitutionally heterotopic
  - stereoheterotopic
    - diastereotopic
    - enantiotopic
- homotopic

Note that the enantiotopic relationship is classified into the heterotopic category in the above scheme. On the other hand,



32 **33**

Fig. 8. Ligand- and face-differentiation in derivatives of adamantane-2,6-dione.

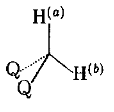
an enantiotopic relationship is classified into the symmetry equivalent category in a modified scheme by Mislow and Siegel:[17]

- Symmetry equivalent
  - homotopic
  - enantiotopic
- Symmetry nonequivalent
  - diastereotopic
  - constitutionally heterotopic

The comparison between the two schemes shows that equivalence and non-equivalence vary according to the standpoints. Moreover, a diastereotopic relationship can be regarded as an equivalent relationship, in contrast to the schemes shown above. This is because diastereomeric products due to the replacement criterion are regarded as a kind of stereoisomers, or more mathematically because diastereotopic ligands are exchangeable by virtue of permutation-group operations.

To remedy such involved situations, we have proposed the concept of sphericity (chirality fittingness), where a set of equivalent objects (ligands, faces, etc.) is regarded as an orbit governed by a coset representation and such an orbit is classified into homospheric, enantiospheric and hemispheric.[19] It should be noted that a sphericity is an attribute of the orbit. We have then redefined the topicity terms subsidiarily by starting from the sphericity terms (the membership criterion shown in Table 1).[19,20] The redefined topic relationships are used to characterize the relationship between orbits or between the parts of orbits (Table 2). Since symmetry equivalence and constitutional equivalence are distinct categories, such a tabular description as Table 2 is suitable to clarify the situations.

It is helpful here to compare between the chiral replacement criterion and the membership criterion by using rather simple compounds (Fig. 9), where Q (or R) represents a chiral ligand (e.g. –CH(OH)COOH) and $\overline{Q}$ (or $\overline{R}$) and represents its antipode; and A and B represent achiral ligands.



34

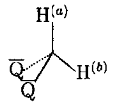
$C_2(/C_1)$

$|C_2|/|C_1| = 2/1 = 2$

hemispheric

homotopic

(hemitopic)



35

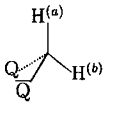
$C_2(/C_1)$

$|C_2|/|C_1| = 2/1 = 2$

hemispheric

homotopic

(hemitopic)



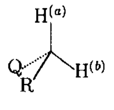
36

$2C_s(/C_s)$

$|C_s|/|C_s| = 2/2 = 1$

homospheric (two)

diastereotopic



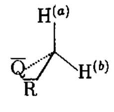
37

$2C_1(/C_1)$

$|C_1|/|C_1| = 1/1 = 1$

hemispheric (two)

diastereotopic



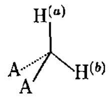
38

$2C_1(/C_1)$

$|C_1|/|C_1| = 1/1 = 1$

hemispheric (two)

diastereotopic



39

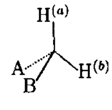
$C_{2v}(/C_s)$

$|C_{2v}|/|C_s| = 4/2 = 2$

homopheric

homotopic

(holotopic)



40

$C_s(/C_1)$

$|C_s|/|C_1| = 2/1 = 2$

enantiospheric

enantiotopic

Fig. 9. Chiral replacement criterion and membership criterion. The first line of each comment represents the coset representation(s) corresponding to H$^{(a)}$ and H$^{(b)}$; the 2nd line shows the size of the coset representation; the 3rd line indicates the sphericity; the 4th line the topicity; and the 5th line the subclass of homotopicity if applicable.

1. The two methylene hydrogens (H$^{(a)}$ and H$^{(b)}$) in a chiral molecule **34** belong to a two-membered hemispheric orbit governed by the coset representation $C_2(/C_1)$. In the light of the membership criterion (Table 1), they are determined to be homotopic/hemitopic. The original symmetry criterion shows that they are homotopic, since they are superimposed by the C_2-operation (a proper rotation). Since there exist no improper rotations by which they are superimposed, they are hemitopic by virtue of the revised symmetry criterion described in the introduction. In the light of the chiral replacement criterion, H$^{(a)}$ and H$^{(b)}$ are determined to be hemitopic, since the replacement of H$^{(a)}$ by a chiral proligand Q$'$ and the replacement of H$^{(b)}$ by its antipode $\overline{Q}'$ (or vice versa) gives diastereomeric products. Parallel results are obtained for **35**,

Table 2. Equivalence on Symmetry and Constitution

		Symmetry (Point-group)	
		Equivalence	Non-equivalence
	Equivalence	Homotopic	Diasterotopic
Constitution		holotopic hemitopic	
(Permutation-group)		Enantiotopic	
	Non-equivalence		Heterotopic

since this is chiral and enantiomeric to **34**. The hemitopicities in **34** and **35** are concerned with the hemispheric orbits, which are intermolecularly in an enantiomeric relationship. On the other hand, the hemitopicity described in Fig. 5 is concerned with each half of an enantiospheric orbit, which shows an enantiotopic relationship intramolecularly.

By virtue of a coset representation $\mathbf{G}(/\mathbf{G}_i)$, the size of each orbit can be calculated to be $|\mathbf{G}|/|\mathbf{G}_i|$ from the orders of the groups ($|\mathbf{G}|$ and $|\mathbf{G}_i|$) appearing in the coset representation. In this case, we have $|\mathbf{C}_2|/|\mathbf{C}_1| = 2/1 = 2$.

2. Each methylene hydrogen ($\mathrm{H}^{(a)}$ or $\mathrm{H}^{(b)}$) in an achiral molecule **36**, which is a so-called meso-compound, belongs to a one-membered homospheric orbit governed by the coset representation $\mathbf{C}_s(/\mathbf{C}_s)$. Note that the orbit of $\mathrm{H}^{(a)}$ and that of $\mathrm{H}^{(b)}$ are distinctly assigned to the same kind of coset representation $\mathbf{C}_s(/\mathbf{C}_s)$. Hence, the relationship beween $\mathrm{H}^{(a)}$ and $\mathrm{H}^{(b)}$ is diastereotopic in the light of the membership criterion (Table 1).

The original replacement criterion (with achiral proligands) and the symmetry criterion also give results parallel to the one coming from the membership criterion. On the other hand, an apparent pairwise replacement described for the chiral replacement criterion is not permitted because of the diastereotopic relationship between $\mathrm{H}^{(a)}$ and $\mathrm{H}^{(b)}$ in **36**, though the replacement of $\mathrm{H}^{(a)}$ by Q' and that of $\mathrm{H}^{(b)}$ by $\overline{\mathrm{Q}'}$ produce diastereomers. When we focus our attention on the one-membered homospheric orbit containing $\mathrm{H}^{(a)}$, the replacement of $\mathrm{H}^{(a)}$ by Q' and that of $\mathrm{H}^{(a)}$ by $\overline{\mathrm{Q}'}$ produce enantiomers. In this meaning, the orbit of $\mathrm{H}^{(a)}$ is regarded to show a self-holotopicity, i.e., a relationship between a ligand and itself. This case is akin to the self-hemitopicity described for Fig. 6.

3. Each methylene hydrogen ($\mathrm{H}^{(a)}$ or $\mathrm{H}^{(b)}$) in a chiral molecule **37** (or its enantiomer **38**) belongs to a one-membered hemispheric orbit, which is governed by the coset representation $\mathbf{C}_1(/\mathbf{C}_1)$. Since the two $\mathbf{C}_1(/\mathbf{C}_1)$-orbits are distinct, the relationship beween $\mathrm{H}^{(a)}$ and $\mathrm{H}^{(b)}$ is diastereotopic in the light of the membership criterion (Table 1). The original replacement and symmetry criteria give parallel results.

4. The relationship between $\mathrm{H}^{(a)}$ and $\mathrm{H}^{(b)}$ in **39** is the same as that discussed for **1**. Note that $\mathrm{H}^{(a)}$ and $\mathrm{H}^{(b)}$ construct a $\mathbf{C}_{2v}(/\mathbf{C}_s)$-orbit, which is homospheric.[24]

5. The two hydrogens $\mathrm{H}^{(a)}$ and $\mathrm{H}^{(b)}$ in **40** belong to a two-membered $\mathbf{C}_s(/\mathbf{C}_1)$-orbit, which is enantiospheric. Hence, the relationship between them is concluded to be enantiotopic. The chiral replacement criterion for this molecule is the same as that discussed for **25**.

The comparison indicates that the chiral replacement criterion gives intuitive ways for determining topicities to organic chemists, while the membership criterion is a straightforward method if they overcome the mathematical barriers of the latter criterion.

It should be noted again that the diastereotopic relationship of the present scheme is concerned with equivalence. For example, when the one face (*re*-face) of $\mathrm{A}^{(a)}$ is selected from **33**, the S_4-operation gives the *si*-face of $\mathrm{A}^{(b)}$, the *re*-face of $\mathrm{A}^{(c)}$, and *si*-face of $\mathrm{A}^{(d)}$, successively. These four faces construct a four-membered enantiospheric orbit governed by $\mathbf{S}_4(/\mathbf{C}_1)$. The remaining faces of the four acetyl groups produce another four-membered enantiospheric orbit governed by $\mathbf{S}_4(/\mathbf{C}_1)$. The two enantiospheric orbits are diastereotopic, since they are related to each other in terms of the alternation of the lobes of π-orbitals.

Conclusion

The replacement criterion described previously[1] has been shown to assume the replacement by atoms or by achiral ligands so that it is not effective for the detection of sub-relationships of a homotopic relationship. The criterion named "chiral replacement criterion", which adopts a pair of chiral enantiomeric proligands as probes, has been proposed to classify topicity relationships. Thereby, the term *homotopic* has been subdivided into *holotopic* and *hemitopic* so as to avoid such dual expressions as "homotopic and achirotopic" and "homotopic and chirotopic".

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4 The term "equitopic" did not obey a standard coinage rule, as Nakazaki himself commented, noting that "equi" had a Roman origin while "topic" came from the Greek *topos*. However, his proposal was the first one to point out that the term "equivalent" should be replaced by another appropriate topic term.

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24 The two hydrogens $\mathrm{H}^{(a)}$ and $\mathrm{H}^{(b)}$ in **1** construct an orbit governed by the coset representation $\mathbf{C}_{2v}/\mathbf{C}_s$. Since the global symmetry $\mathbf{C}_{2v}$ and the local symmetry $\mathbf{C}_s$ are both achiral, the orbit is determined to be homospheric. Hence, $\mathrm{H}^{(a)}$ and $\mathrm{H}^{(b)}$ are determined to be homotopic (and holotopic) in the light of the membership criterion.

25 The condition "structureless" is not always necessary to discuss the topicity relationships. However, it is important in examining more complex stereochemical relationships, as discussed previously for the symmetry of pentaerythritol $C(CH_2OH)_4$. See Ref. 26.

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28 Strictly speaking, a pair of ligands should be a pair of objects or sites in a molecule. For the sake of simplicity, we here use the word "ligands" as a representative.

29 The assignment of $\mathbf{D}_{2d}/\mathbf{C}_s$ to the orbit of the four bridgehead hydrogens ($\mathrm{H}^{(A)}$ to $\mathrm{H}^{(D)}$) is carried out by determining the local symmetry of each one of the hydrogens to be $\mathbf{C}_s$. An alternative algebraic method[20] can also be applied to this case. The number of hydrogens is equal to $|\mathbf{D}_{2d}|/|\mathbf{C}_s|$, which calculated to be 4, because the order $|\mathbf{D}_{2d}|$ is equal to 8 and the order $|\mathbf{C}_s|$ is equal to 2.

30 The assignment of $\mathbf{D}_{2d}(/\mathbf{C}_1)$ to the orbit of the eight bridge hydrogens ($\mathrm{H}^{(a)}$ to $\mathrm{H}^{(d')}$) is accomplished by determining the local symmetry of each one of the hydrogens to be $\mathbf{C}_1$. An alternative algebraic method[20] can also be applied to this case. Note that $|\mathbf{D}_{2d}|/|\mathbf{C}_1|$ is equal to 8, because the order $|\mathbf{D}_{2d}|$ is equal to 8 and the order $|\mathbf{C}_1|$ is equal to 1.

31 Since the orbit of the bridgehead hydrogens is governed by $\mathbf{D}_{2d}(/\mathbf{C}_s)$, it is homospheric. Hence, any pair of hydrogens selected from the orbit is ascribed to the homotopic relationship in the light of the membership criterion.

32 Since two objects in a pairwise relationship are not even, the word "pivot" is used to designate either one of the objects on which we focus our attention.

33 In the original replacement and symmetry criteria, the term "homotopic" mainly deals with homospheric orbits (Table 1). In contrast, the present treatment extends the term to determine relationships in a two- or more-membered hemispheric orbit and in each half of a four- or more-membered enantiospheric orbit. The former conventional cases are holotopic, while the latter cases are hemitopic in terms of the present proposal.

34 We postulate a conformer of the highest attainable symmetry $\mathbf{C}_{2v}$ in this discussion, though several conformers are possible to give lower symmetries. In such a conformer, the two carbonyl groups are considered to be involved in the plane that bisects the bond angle of CH_3–C–CH_3.

35 Strictly speaking, this treatment takes account of the local symmetry of a proligand in a promolecule. Hence, such a conformer of the highest attainable symmetry is not necessary to be postulated. The local symmetry shows that the average environment of the proligand belongs to $\mathbf{C}_s$ without considering the conformation of the acetyl group.

36 We postulate a conformer of the highest attainable symmetry $\mathbf{S}_4$ in this discussion, though conformers of lower symmetries may exist. In such a conformer, the carbonyl group $\mathrm{A}^{(a)}$ is fixed to give an arbitrary conformation, then the conformations of the other carboxyl groups are derived by one or more symmetry operations of $\mathbf{S}_4$ so as to maintain the global symmetry.