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Systematic Design of Chiral Molecules of High Symmetry. Achiral Skeletons Substituted with Chiral Ligands

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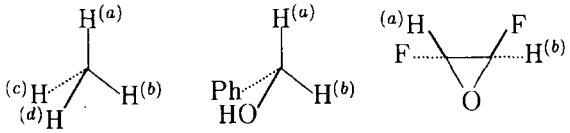
For the design of chiral molecules of high symmetry, a set of substitution positions in an achiral skeleton of G-symmetry are replaced by chiral ligands or proligands of the same kind so that there emerge three criteria of generating chiral molecules or promolecules. Thus, Criterion 1 controls the desymmetrization of a homospheric orbit in an achiral skeleton, where the resulting molecule or promolecule is determined to belong to the maximum chiral subgroup of G in agreement with a size-invariant subduction. Criterion 2 for the desymmetrization of an enantiospheric orbit shows that the resulting molecule or promolecule is determined to belong to the maximum chiral subgroup of G and that the original enantiospheric orbits are divided into two hemispheric orbits of equal size. Criterion 3 deals with a chiral skeleton, where subsitution by chiral ligands or proligands of the same kind is examined as the transformation of the hemispheric orbit in the skeleton. Although no change of symmetry occurs from a group-theoretical point of view, the transformation is shown to be important chemically, since relevant ligands or proligands alter the stereochemical properties.

Desymmetrization of an achiral skeleton with appropriate substituents is a potential methodology for designing chiral molecules.[1—3] This methodology dates from the beginning of organic stereochemisty founded by van't Hoff[4] and has been a guiding principle for designing chiral molecules with a so-called asymmetric carbon,[5,6] where an organic molecule was regarded as a tetrahedral structure modified by substituents. Farina and Morandi[7] have proposed principles for designing chiral molecules of high symmetry, where the chirality is determined in terms of the highest attainable symmetry of each molecule. They have recognized the existence of submolecular asymmetric units in order to determine the symmetry group to which the molecule actually belongs. This methodology has used the concept of symmetry number and has been implicitly based on the concept of local symmetry (or site symmetry). The latter concept has been used in the field of crystallography[8] and applied to the characterization of molecular symmetry[9] and prochirality.[10]

Although these treatments have clarified several important aspects of stereochemistry, a more logical approach based on group-theoretical foundations has been desired in order to design chiral molecules systematically as well as to reach further precise prospects about chirality phenomena. For this purpose, we have pointed out the importance of coset representations $G/(G_i)$, which are a kind of permutation representation. Thereby, we have proposed the concept of sphericity and coined sphericity terms (homospheric, enantiospheric, and hemispheric) on the basis of the chirality/achirality properties of the groups G and G_i.[11] This concept has been applied to the redefinition of prochirality,[11,12] topicity,[13,14] stereogenicity,[14] and anisochrony.[15] We have further proposed the subduction of coset representations as a new concept,[16] which has been applied to combinatorial enumeration,[16] to the classification of molecular symmetries,[17] and to the design of achiral and chiral molecules.[18] Although the last subject has been made more sophisticated by the proposal of the concept of promolecules,[19,20] further studies are necessary to provide an effective design of such molecules. As a continuation of our article on the design of prochiral molecules,[21] the present paper deals with a method for systematic design of chiral molecules, which is based on the concept of size-invariant chiral subductions.

Results

1 Systematic Design of Chiral Molecules. Throughout this paper, we adopt the sphericity terms (i.e. homospheric, enantiospheric, and hemispheric)[11] to determine symmetrical properties of moclecules (Fig. 1). For example, the four hydrogens of a methane molecule (CH_4, **1**) are equivalent so as to construct an orbit, which is assigned to a coset representation $T_d(/C_{3v})$. Then, the orbit is charac-



1	**2**	**3**
$T_d(/C_{3v})$	$C_s(/C_1)$	$C_2(/C_1)$
homospheric	enantiospheric	hemispheric
$\|T_d\|/\|C_{3v}\| = 4$	$\|C_s\|/\|C_1\| = 2$	$\|C_2\|/\|C_1\| = 2$

Fig. 1. Sphericities for orbits of hydrogens.

terized as being homospheric, since the global symmetry T_d and the local symmetry C_{3v} are both achiral groups. The two methylene hydrogens of benzyl alcohol ($PhCH_2OH$, **2**) construct an enantiospheric orbit assigned to $C_s(/C_1)$, where the enantiosphericity is determined because the global symmetry C_s is achiral and the local symmetry C_1 is chiral. The two methine hydgrogens of *trans*-2,3-difluorooxirane (**3**) are equivalent to form a $C_2(/C_1)$-orbit, which is determined to be hemispheric since the global symmetry C_2 and the local symmetry C_1 are both chiral groups.

Let us regard each set of hydrogens as a set of positions in order to be substituted by a set of chiral substituents (Q) of the same kind, as found in Fig. 2.[22] For a stricter point of view, the substituent Q may be a ligand or proligand according to the levels to which our discussions apply. Note that a ligand is defined as a three-dimensional object belonging to an appropriate point group, while a proligand is defined as an object with chirality/achirality but no structure.[19,23] The resulting molecules or promolecules (**4**,**5**, and **6**) are different in their behaviors toward the change of molecular symmetries. The homospheric $T_d(/C_{3v})$-orbit in methane (**1**) is converted into a hemispheric $T(/C_3)$-orbit filled with the chiral substituents (Q), as found in **4**. The size of $T_d(/C_{3v})$-orbit remains invariant during the desymmetrization process into a $T(/C_3)$-orbit. In other words, the four Qs in **4** are equivalent to each other, so that they construct a four-membered orbit.[24]

The enantiospheric $C_s(/C_1)$-orbit in benzyl alcohol (**2**) is converted into two one-membered $C_1(/C_1)$-orbits in **5**, where the original two-membered orbit is divided into two one-membered $C_1(/C_1)$-orbits. This means that the two Qs are non-equivalent to each other in **5**.[25]

The symmetrical property of the hemispheric $C_2(/C_1)$-orbit in **3** remains unchanged on replacing the hydrogens with two chiral substituents (Q) so that the global and local symmetries are unchanged during the conversion from **3** to **6**.[24] Hence, the two Qs remain equivalent to each other in **6**.

The desymmetrization processes described above can be extended into general cases, the rationalization of which is the target of the present article. Such extensions shall provide us with a deeper insight into the design of chiral molecules of high symmetry.

2 Chiral Molecules by Size-Invariant Subduction of Homospheric Orbits.

2.1 General Treatment. In general, a set of equivalent substituents (ligands or proligands)[22] constructs an orbit governed by a coset representation $G(/G_i)$,[11,13] which is a kind of permuation representation. The degree of the representation is calculated to be $|G|/|G_i|$ and is equal to the number of the equivalent substituents, where the symbols G and G_i represent the global and local symmetries respectively and the symbols $|G|$ and $|G_i|$ represent the orders of the groups G and G_i. The resulting orbit is called a $G(/G_i)$-orbit. Then, the sphericity of the $G(/G_i)$-orbit is determined by the following criteria:[11] If both G and G_i are achiral, the $G(/G_i)$-orbit is defined as being homospheric; if the G is achiral and G_i is chiral, the $G(/G_i)$-orbit is defined as being enantiospheric; and if both G and G_i are chiral, the $G(/G_i)$-orbit is defined as being hemispheric.[11,13]

Let us consider an achiral skeleton that has a set of positions to be substituted by a set of chiral substituents (Q) of the same kind, where the set of positions are governed by a coset representation $G(/G_i)$ of a homospheric property. This desymmetrization process is controlled by a size-invariant subduction of the coset representation, as represented by the following equation:

$$G(/G_i) \downarrow G^{max} = G^{max}(/G_i^{max}), \tag{1}$$

where G^{max} is the maximum chiral subgroup of the group G and G_i^{max} is the maximum chiral subgroup of G_i. See eq. 11.6 of Ref. 13. The resulting hemispheric $G^{max}(/G_i^{max})$-orbit has the same size as the original $G(/G_i)$-orbit, i.e. $|G^{max}|/|G_i^{max}| = |G|/|G_i|$.

The discussion of this subsection can be summarized as the following criterion. It should be noted that ligands to be selected should have a symmetry higher than the local symmetry G_i^{max}.

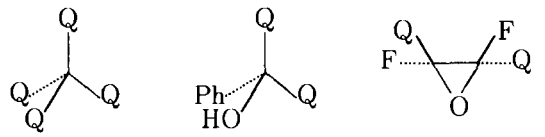
Criterion 1. All of the positions in a homospheric orbit of an achiral skeleton are replaced by chiral proligands (or ligands) of the same kind so as to produce a chiral promolecule (or molecule) of the maximum chiral subgroup of the original group of the skeleton, in agreement with Eq. 1.

2.2 Methane Derivatives. Let us consider a chiral desymmetrization of methane (**1**), where the $T_d(/C_{3v})$-orbit is taken into consideration. From the subduction table of T_d,[13] we select size-invariant subductions relevant to such chiral desymmetrizations:

$$T_d(/C_{3v}) \downarrow D_2 = D_2(/C_1) \tag{2}$$

$$T_d(/C_{3v}) \downarrow T = T(/C_3) \tag{3}$$

Equation 3 corresponds to the case of the conversion from **1** into **4**, where T is the maximum subgroup of T_d. When proligands (Qs) are selected as substituents, the resulting promolecule belongs to T-symmetry in agreement with Eq. 3.[26] To maintain the global symmetry T, four Qs as ligands should belong to the local symmetry of C_3 or higer. An example of such ligands is a 4-[2-(1*S*,3*S*,5*R*,6*S*,8*R*,10*R*)-trishomocubayl]buta-1,3-diyn-1-yl ligand of D_3-symmetry, which has been reported by Nakazaki et al.[27] Note that C_3 is a subgroup of D_3.



4	**5**	**6**
$\mathbf{T(/C_3)}$	$\mathbf{2C_1(/C_1)}$	$\mathbf{C_2(/C_1)}$
hemispheric	hemispheric	hemispheric
(size-invariant)	(divided)	(size-invariant)
$\mathbf{\lvert T\rvert/\lvert C_3\rvert = 4}$	$\mathbf{\lvert C_1\rvert/\lvert C_1\rvert = 1}$	$\mathbf{\lvert C_2\rvert/\lvert C_1\rvert = 2}$

Fig. 2. Size-invariant and size-variant subductions.

If we select ligands of a symmetry lower than C_3, the resulting molecule **4** no longer belongs to T. This type of phenomenon has been discussed by us in terms of mismatched molecules.[19] These are controlled by another size-invariant subduction (eq. 2) so as to give a D_2-molecule. For example, we obtain a molecule **7** by selecting Q = CXYZ as ligands of C_1-symmetry. The resulting molecule **7**, which is schematically represented by the diagram **8** (Fig. 3), belongs to D_2-symmetry, in agreement with Eq. 2. Note here that the diagram **8** indicates a conformer of D_2-symmetry as the highest attainable symmetry in a fixed condition. As a result, the sets of four X's, of four Y's, and of four Z's construct their respective four-membered $D_2(/C_1)$-orbits in the fixed conformation. If we select the corresponding enantiomeric ligand ($\overline{Q} = \overline{CXYZ}$), we can design the enantiomer of the molecule **8**. Pentaerythritol tetrakis[(−)-menthyloxyacetate] has been reported by McCasland et al.[28] as an example of this type of D_2-molecules.

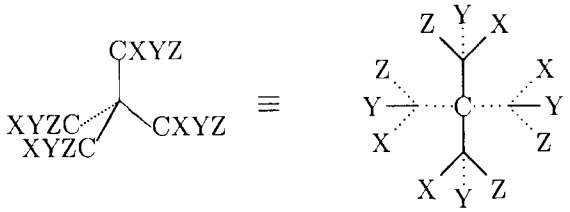
Let us next replace the methylene hydrogens of propane by two chiral substituents (Q), where the methylene hydrogens belong to a $C_{2v}(/C_s)$-orbit from the viewpoint of the promolecule concept.[19] The desymmetrization corresponds to a size-invariant subduction represented by

$$C_{2v}(/C_s) \downarrow C_2 = C_2(/C_1), \tag{4}$$

which is cited from the subduction table of C_{2v}.[13] By selecting trisubstituted methyl ligands as ligands of C_1-symmetry (i.e. Q = CXYZ), we obtain **9** (Fig. 4) as a C_2-molecule, in which the orbit of Qs is governed by $C_2(/C_1)$.

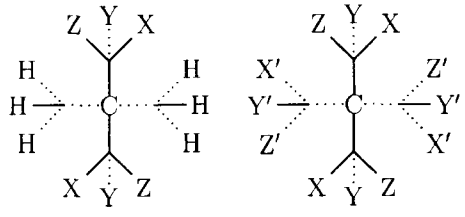
The desymmetrization represented by Eq. 4 is alternatively explained by a successive desymmetrization of the $T_d(/C_{3v})$-orbit as follows:

$$\begin{aligned} T_d(/C_{3v}) \downarrow C_2 &= [T_d(/C_{3v}) \downarrow C_{2v}] \downarrow C_2 = [C_{2v}(/C_s) + C_{2v}(/C_s')] \downarrow C_2 \\ &= 2C_2(/C_1) \end{aligned} \tag{5}$$



7 **8 (D_2)**

Fig. 3. Chiral methane derivative with chiral ligands of the same kind.



9 (C_2) **10 (C_2)**

Fig. 4. Chiral methane derivatives of C_2-symmetry.

For the alternative design of **9**, one of the resulting $C_2(/C_1)$-orbits accomodates two methyl ligands and the other accomodates two chiral ligands (Q = CXYZ). It should be noted that the methyl ligands are achiral in isolation but chiral after becoming involved in **9**. This means that the two methyls in **9** can be replaced by chiral ligands other than Qs. Hence, Eq. 5 indicates another C_2-molecule (**10**), in which Q = CXYZ and R = CX'Y'Z' are selected as ligands of C_1-symmetry.

2.3 Allene Derivatives. Let us consider the four hydrogens of allene as substitution positions; they construct a homospheric orbit governed by a coset representation $D_{2d}(/C_s)$. From the subduction table of D_{2d},[13] we can select a chiral size-invariant subduction as follows:

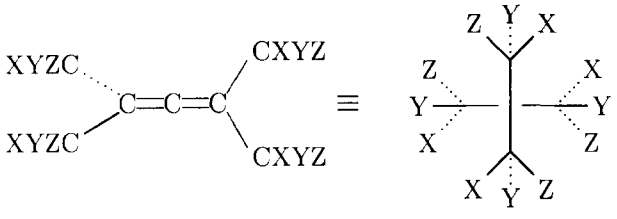
$$D_{2d}(/C_s) \downarrow D_2 = D_2(/C_1) \tag{6}$$

When we select Q = CXYZ as ligands of C_1-symmetry, we obtain **11** as a chiral molecule, which is schematically represented by the diagram **12** (Fig. 5).

When the two sets of methylene hydrogens in allene are replaced by AA and BB, we can obtain a promolecule of C_{2v}-symmetry (AA>C=C=C<BB), where the AA and the BB construct respective $C_{2v}(/C_s)$-orbits. By replacing BB by a set of chiral ligands (Q), an allene promolecule (AA>C=C=C<QQ) of C_2-symmetry can be obtained in agreement with Eq. 4. When we select Q = CXYZ as ligands of C_1-symmetry along with methyl ligands as ligands As, we obtain **13** as a chiral molecule (Fig. 6).

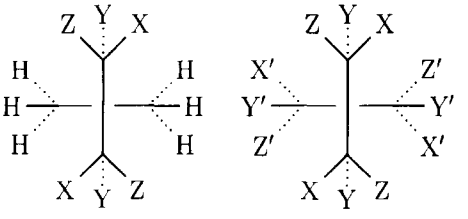
The desymmetrization represented by Eq. 4 is alternatively explained by a successive desymmetrization of the $D_{2d}(/C_{2v})$-orbit as follows:

$$\begin{aligned} D_{2d}(/C_{2v}) \downarrow C_2 &= [D_{2d}(/C_{2v}) \downarrow C_{2v}] \downarrow C_2 \\ &= [C_{2v}(/C_s) + C_{2v}(/C_s')] \downarrow C_2 \\ &= 2C_2(/C_1) \end{aligned} \tag{7}$$



11 **12 (D_2)**

Fig. 5. Chiral allene derivative with chiral ligands of the same kind.



13 (C_2) **14 (C_2)**

Fig. 6. Chiral allene derivatives of C_2-symmetry.

The symmetrical situation of the two methyls in the allene **13** is group-theoretically akin to that in the methane **9**. As a result, Eq. 7 indicates another C_2-molecule (**14**), in which Q = CXYZ and R = CX'Y'Z' are selected as ligands of C_1-symmetry. Compare this with the case of **10**. This alternative explanation can be ascertained by comparing Eq. 7 with Eq. 5, since D_{2d} is a subgroup of T_d and we have a size-invariant subduction represented by $T_d(/C_{3v})\downarrow D_{2d} = D_{2d}(/C_{2v})$.

2.4 Adamantane Derivatives. The four bridgehead hydrogens of adamantane belong to a $T_d(/C_{2v})$-orbit, while the counterparts of adamantane-2,6-dione belong to a $D_{2d}(/C_s)$-orbit. These orbits are both homospheric. To characterize the desymmetrization processes of adamantane derivatives, we can use Eqs. 3 and 6. In other words, these processes are considered to be group-theoretically equivalent to the methane case and the allene case, respectively. Thereby, we are able to design **15** and **16** as chiral molecules (Fig. 7). Equation 3 indicates that the four ligands Q in **15** should belong to the local symmetry of C_3 or higher in order to maintain the global symmetry T. The synthesis of such a $T(/C_3)$-molecule has been reported by Nakazaki et al.[27]

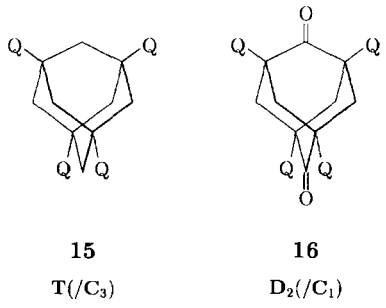
If we select ligands of a symmetry lower than C_3, the resulting molecule **15** no longer belongs to T. The global symmetry of the resulting molecule is lowered into D_2. The synthesis of such a $D_2(/C_1)$-molecule due to such further desymmetrization has also been reported by Nakazaki and Naemura.[3] On the other hand, any chiral ligands (Q) can be selected for **16**, since the local symmetry for the $D_2(/C_1)$-orbit of **16** is the lowest symmetry, i.e. C_1.

2.5 Biphenyl Derivatives. A biphenyl derivative in which achiral ortho-substituents (As) prohibit the rotation around the central single bond belongs to D_{2d}-symmetry in a conformation of the highest attainable symmetry. The terminal para-positions of such a non-rotatable biphenyl construct a two-membered $D_{2d}(/C_{2v})$-orbit. Suppose that such a $D_{2d}(/C_{2v})$-obrit accomodates chiral substituents (Qs) of the same kind, as found in **17**. Then, the orbit is desymmetrized by virtue of the following subduction:[13]

$$D_{2d}(C_{2v}) \downarrow D_2 = D_2(/C_2) \tag{8}$$

The resulting two-membered $D_2(/C_2)$-orbit is hemispheric so that it is packed with two proligands (Qs), giving a promolecule (**17**).

The local symmetry of the $D_2(/C_2)$-orbit in the promolecule (**17**) is C_2 so that the chiral proligand Q can be replaced by a three-membered cyclic ligand of C_2-symmetry without desymmetrization, giving a chiral molecule **18**. The resulting molecule (**18**) has D_2-symmetry. When chiral ligands of C_1-symmetry (e.g. Q = CXYZ) are substituted for the Qs of **17**, the resulting molecule no longer belongs to D_2, but is desymmetrized into C_1 (Fig. 8).



15 **16**

$T(/C_3)$ $D_2(/C_1)$

Fig. 7. Chiral derivatives of adamantane and adamantane-2, 6-dione.

3 Chiral Subduction of Enantiospheric Orbits. 3.1 General Treatment. Let us consider a case in which an enantiospheric $G(/G_i)$-orbit is filled with a set of chiral ligands (Q) of the same kind. This desymmetrization process is controlled by a subduction of the coset representation represented by either of the following equations:

$$G(/G_i) \downarrow G^{max} = 2G^{max}(/G_i) \tag{9}$$

$$G(/G_i) \downarrow G^{max} = G^{max}(/G_i) + G^{max}(/G_i'), \tag{10}$$

where G^{max} is the maximum chiral subgroup of the group G, and where G_i' and G_i are conjugate to each other within G but are non-conjugate within G^{max}. See Lemma 10.1 of Ref. 13. The resulting hemispheric $G^{max}(/G_i)$-orbit (or $G^{max}(/G_i')$-orbit) has half the size as compared with the original $G(/G_i)$-orbit, i.e. $2|G^{max}|/|G_i| = |G|/|G_i|$. The two halves are non-equivalent because they construct distinct orbits in agreement with Eq. 9 or Eq. 10.[29]

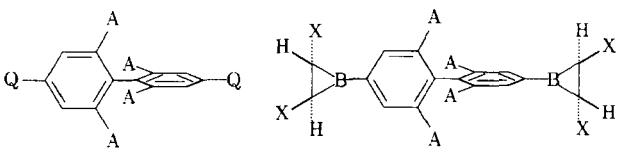
The discussion of this subsection can be summarized as the following criterion. It should be noted that ligands to be selected should have a symmetry higher than the local symmetry G_i^{max}.

Criterion 2. All of the positions in an enantiospheric orbit of an achiral skeleton are replaced by chiral proligands (or ligands) of the same kind so as to produce a chiral promolecule (or molecule) of the maximum chiral subgroup of the original group of the skeleton, in agreement with Eq. 9 or Eq. 10.

3.2 Methane Derivatives. The molecule **5** derived from **2** is an example of Eq. 9, which is represented by

$$C_s(/C_1) \downarrow C_1 = 2C_1(/C_1). \tag{11}$$

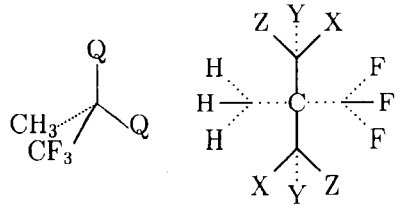
Figure 9 shows another example of this case, in which 1,1,1-trifluoropropane ($CH_3CH_2CF_3$) is selected as an achiral skeleton. The two methylene hydrogens on the methylene of the skeleton, which construct a two-membered $C_s(/C_1)$-orbit, are replaced by chiral substituents (Qs) to give **19** as a chiral promolecule of C_1-symmetry. When the Qs are further replaced by chiral ligands of the same chirality (Q = CXYZ), there emerges a chiral molecule (**19**). It should be noted



17 **18**

$D_2(/C_2)$ $D_2(/C_2)$

Fig. 8. Chiral biphenyl derivatives.



19 (C_1) **20** (C_1)

Fig. 9. Chiral methane derivatives.

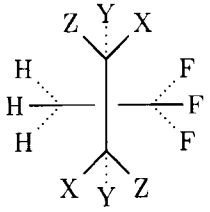
that the two Qs in **19** (or the two chiral ligands in **20**) are non-equivalent to each other; in other words, they belong to distinct one-membered $C_1(/C_1)$-orbits.

3.3 Allene Derivatives. Figure 10 shows a chiral allene with ABQQ, where we select CH_3 and CF_3 as achiral ligands (A and B), and Q = CXYZ as ligands of C_1-symmetry. The derivation of **21** agrees with Eq. 11.

3.4 Adamantane Derivatives. The eight bridge hydrogens in adamantane-2,6-dione (**22**) construct an enantiospheric orbit governed by $D_{2d}(/C_1)$ as shown in Fig. 11. The one half (H) and the other half (H′) are equivalent so as to be the members of the $D_{2d}(/C_1)$-orbit. When they are replaced by Qs, there emerges a D_2-molecule (**23**), in which the one half (Q) and the other half (Q′) are non-equivalent, even if Q and Q′ represent ligands of the same kind. Thus, four-membered $D_2(/C_1)$-orbits are distinctly constructed in agreement with the following subduction:

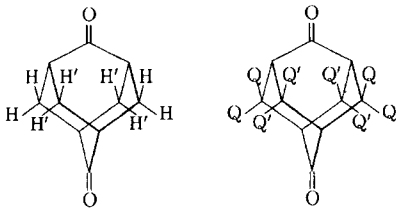
$$D_{2d}(/C_1) \downarrow D_2 = 2D_2(/C_1). \tag{12}$$

4 Transformation of Hemispheric Orbits. 4.1 General Treatment. Let us consider a chiral skeleton that has a set of positions to be substituted by a set of chiral ligands (Q) of the same kind, where the set of positions are governed by a coset representation $G(/G_i)$ of a hemispheric property. The



21 (C_1)

Fig. 10. Chiral allene derivative.



22 **23**

$D_{2d}(/C_1)$ $2D_2(/C_1)$

Fig. 11. Chiral adamantane-2,6-dione.

global symmetry G and the local symmetry G_i are unchanged during the substitution, because of the hemisphericity of the original $G(/G_i)$-orbit. This is formally represented by the following equation:

$$G(/G_i) \downarrow G = G(/G_i) \tag{13}$$

Group-theoretically speaking, Eq. 13 shows a trivial case in which no change of symmetry occurs. However, the case is important chemically, since relevant ligands or proligands alter the stereochemical properties.

The discussion described above can be summarized as the following criterion. It should be noted that ligands to be selected should have a symmetry higher than the local symmetry G_i^{max}.

Criterion 3. All of the positions in a hemispheric orbit of a chiral skeleton are replaced by chiral proligands (or ligands) of the same kind so as to produce a chiral promolecule (or molecule) of the same symmetry as the original the skeleton in agreement with Eq. 13.

4.2 Examples. The molecule **6** derived from **3** is an example of Eq. 13, which is represented by

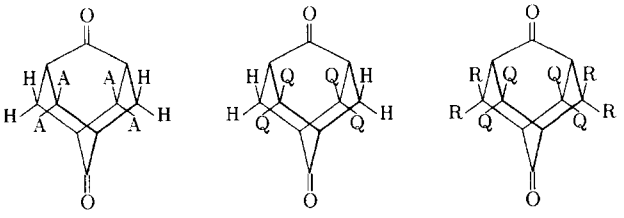
$$C_2(/C_1) \downarrow C_2 = C_2(/C_1). \tag{14}$$

The C_2-molecule (**10**) described above can be derived from the C_2-molecule (**9**). This derivation is an example of a hemispheric orbit. The two methyl ligands in **9** belong to a two-membered $C_2(/C_1)$-orbit. They are replaced by R = CX′Y′Z′, giving the C_2-molecule (**10**). Since the ligand symmetry of R in isolation satisfies the local symmetry (i.e. C_1), no desymmetrization occurs during the derivation.

The C_2-molecule (**14**) described above can be derived from the C_2-molecule (**13**). The two methyl ligands in **13** belonging to a two membered $C_2(/C_1)$ are replaced by R = CX′Y′Z′ so as to give the C_2-molecule (**14**). This is the same as the case of **10** with respect to a group-theoretical formulation.

Discussion

1 Selection of Skeletons. The present methodology permits us flexible selection of skeletons. Figure 12 indicates the essence of this idea. For the discussion of the process of **22** (D_{2d}) to **23** (D_2), all of the eight hydrogens are replaced by Qs, where **22** is regarded as a skeleton. When the half of the $D_{2d}(/C_1)$-orbit are replaced by a set of achiral proligands



24 **25** **26**

$2D_2(/C_1)$ $2D_2(/C_1)$ $2D_2(/C_1)$

Fig. 12. Various chiral adamantane-2,6-dione.

(As), we obtain a chiral promolecule **24**, which belongs to D_2-symmetry. The set of the four hydrogens in **24** and the other set of the four As construct distinct $D_2(/C_1)$-orbits in agreement with Eq. 12.

Then, the resulting promolecule (**24**) can be regarded as a new chiral skeleton for further transformations. Since the two relevant $D_2(/C_1)$-orbits are hemispheric in the skeleton **24**, Criterion 3 is effective to give another chiral promolecule **25**, where all of the As in one of the orbits are replaced by chiral proligands (Qs).

The resulting chiral promolecule (**25**) can be regarded as a further chiral skeleton to give another chiral promolecule **26**, where all of the Hs in the $D_2(/C_1)$-orbit are replaced by chiral proligands (Rs). This case is also an example of Criterion 3. The comparison between **23** and **26** clarifies that the non-equivalency of the two $D_2(/C_1)$-orbits in **23** is in the same situation as that of the counterparts in **26**.

2 Taxonomy of Chiral Molecules. By using the framework for the concept of promolecules,[19,20] we are able to obtain a simple and convenient method for the classification of chiral molecules.[30] Thus, a promolecule is considered to be a skeleton with a set of proligands (structureless objects with chirality/achirality); and a molecule is considered to be a skeleton with a set of ligands (three-dimensional objects). As a result, a molecule can be considered to be derived by substituting ligands for proligands in a promolecule. Then, we take account of achiral and chiral skeletons as well as achiral and chiral (pro)ligands. Thereby, chiral (pro)molecules are classified into four cases:

1. a chiral skeleton with achiral (pro)ligands [case 1],
2. a chiral skeleton with chiral (pro)ligands [case 2],
3. an achiral skeleton with achiral (pro)ligands [case 3], and
4. an achiral skeleton with chiral (pro)ligands [case 4].

Case 1 contains intrinsically chiral molecules or promolecules, e.g. twistane[31,32] and a bridged 1,8-diphenylnaphthalenetwistane.[33] Case 2 has been discussed in the present article as chiral skeletons with hemispheric orbits, where Criterion 3 has been derived for the design of chiral molecules. Case 3 contains molecules or promolecules in which a three-dimensional distribution of substituents generates chirality, e.g. a distribution around an asymmetric carbon and the cases of **3** and **24** described above.

It should be noted here that such a skeleton may be derived from another primary skeleton. For example, *trans*-2,3-difluorooxirane (**3**) can be designed by regarding oxirane (an achiral skeleton) as a skeleton (case 3). On the other hand, the latter is regarded as a further skeleton (a chiral skeleton for case 1 or case 2), when *trans*-2,3-difluoro-2,3-dimethyloxirane is designed.[34] From an alternative point of view, *trans*-2,3-difluoro-2,3-dimethyloxirane can be considered to be a derivative of oxirane, where oxirane is regarded as an achiral skeleton (case 3). For another example found in Fig. 1, methane (**1**) is regarded as a tetrahedral skeleton with four hydrogens (an achiral skeleton for case 3 or case 4).[35] Benzyl alcohol (**2**), which is regarded as a derivative of the methane skeleton, can be in turn regarded as a skeleton of C_s-symmetry (for case 3 or case 4).

In the present paper, we have taken account of chiral (pro)-ligands only. In other words, we have examined case 2 and case 4, where the latter (case 4) has been the main subject of the present article. Thus, achiral skeletons with a homospheric orbit (Criterion 1) have been shown to behave differently from those with an enantiospheric orbit (Criterion 2).

Finally, it is worthy to mention the superiority of the present sphericity terms (homospheric, enantiospheric, and hemispheric)[11,13] over the conventional topicity terms (homotopic, enantiotopic, diastereotopic, and heterotopic;[36] and chirotopic and achirotopic[10]). Each of the sphericity terms represents the nature of an orbit (an equivalent class) assigned to a coset representation. In other words, the sphericity is an *attribute* of an orbit, where the local symmetry and the global symmetry of a molecule can be discussed on a common and integrated basis.

On the other hand, the topicity terms have two distinct connotations. The first type of topicity terms (homotopic, enantiotopic, diastereotopic, and heterotopic) represents equivalent or non-equivalent *relationships* between two sites, while the second type (chirotopic and achirotopic) represents the nature of each site. This means that the local symmetry of a molecule is discussed distinctly apart from the global symmetry. As a result, a chirotopic site may be homotopic, enantiotopic, and diastereotopic to another site, where each case should be described by such a combination as "chirotopic and homotopic". This feature indicates that the topicity terms are not suitable to discussions on such complicated cases as examined in the present article. Moreover, the sphericity terms are capable of redefining the topicity terms easily as subsidiary ones,[11] while the converse is not such a straightforward task with the result that combinations of two types of topicity terms are inevitable. It should be added here the sphericity terms are closely linked with symmetry-based combinatorial enumeration of isomers, whereas the topicity terms have been incapable of illuminating such enumeration problems.

Conclusion

A systematic method for the design of chiral molecules of high symmetry is described, where three criteria have been derived: Criterion 1 for the desymmetrization of a homospheric orbit, Criterion 2 for the desymmetrization of an enantiospheric orbit, and Criterion 3 for the transformation of a hemispheric orbit.

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22 In this paper, we specifically use the terms "substituent", "ligand", and "proligand". Thus, the term *proligand* is used to designate an object with chirality/achirality but no structure.[19,23] The term *ligand* represents a three-dimensional object with an appropriate symmetry (assigned to a point group). The term *substituent* is used to indicate a concept superior to ligands and proligands. We do not use the term "group" for the purpose of representing such a chemical meaning as "functional group".
23 This treatment means that methane is regarded as a skeleton instead of a hypothetical tetrahedral skeleton. This type of conventions provide us with a convenient viewpoint that links the concept of promolecules with the conventional approach of stereochemistry.
24 In terms of the conventional approach, the four hydrogens in **1** are homotopic, and the four Qs in **4** are also homotopic.
25 In terms of the conventional approach, the two hydrogens in **2** are enantiotopic, while the two Qs in **5** are diastereotopic.
26 Each of the proligands (Qs) in the T-promolecule is controlled by the coset representation $T(/C_3)$. Hence, each Q belongs to the C_3-symmetry in the promolecule, though it is only chiral in an isolation.
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30 Farina and Morandi (Ref. 7) adopted another type of classification, where chiral molecules are categorized into four classes: (type 1) rigid molecules with intrinsically chiral structure; (type 2) molecules having a rigid non-chiral basic framework, in which chirality derives from the presence of non-chiral substituents in convenient positions; (type 3) flexible molecules containing equivalent chiral groups, provided that at least one conformer (possibly the stablest) exhibits high rotational symmetry; and (type 4) flexible molecules that do not contain chiral groups, in which at least one conformer that is stable and isolable under accessible experimental conditions is chiral and shows high rotational symmetry. Type 1 corresponds to cases 1 and 2 of the preset paper; type 2 corresponds to case 3; and type 3 corresponds to case 4. The present paper omits Type 4, since Type 4 is a special case of Type 1. By considering skeletons and (pro)ligands distinctly, the definitions of the present paper become more concise than those of Farina and Morandi.
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