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Group-Theoretical Framework for Characterizing the Ring Flipping and *N*-Inversion of Piperidine Derivatives. Extended Pseudo-Point Groups and Subsymmetry-Itemized Enumeration

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The ring flipping (F) and the N-inversion (I) of piperidine are discussed by presuming a quadruplet of conformers as a model. After an extended pseudo-point group $\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}$ is defined, the concept of *FI*-energeticity is proposed. The flexible piperidine derivatives are enumerated on the basis of the model by the unit-subduced-cycle-index approach. The enumerated derivatives are classified into *FI*-isoenergetic (Types I, I′, and II) and *FI*-anisoenergetic (Types III and IV) by means of their extended pseudo-point groups.

Nitrogen-containing six-membered rings have given significant stereochemical problems to organic chemists, since two factors of the conformational changes have to be considered, i.e., the flippings of the rings and the inversions on the nitrogen atoms.[1—3] For example, the number of isomers of 2, 5-dimethylpiperidine varies with the standpoints of organic chemists, as Eliel[4] has once discussed in terms of *residual isomers*. Although the number of isomers should be equal to 8 under fixed conditions, four isomers have been seen in low-temperature ^{13}C NMR,[5] and only two isomers (i.e. residual isomers) have been discerned at room temperature, if enantiomers are not distinguished. Eliel[4] has given the temperature-dependent definition for characterizing such residual isomers. The temperature-dependent definitions may cause some fluctuation of conclusions. Suppose, for example, that the isomerism phenomenon of one compound and at an appropriate temperature is essentially equivalent to that of the other compound at another temperature. For discussing these two phenomenons from the general point of view, it is rational to give temperature-independent definitions at the first step, where their temperature-dependent effects are characterized afterwards. In other words, the development of a temperature-independent theoretical framework is desirable so as to comprehend both temperature-independence and temperature-dependence.

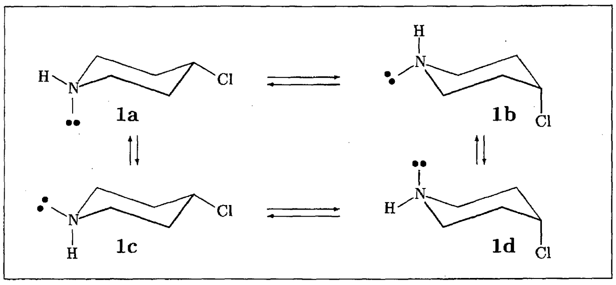
We have recently proposed pseudo-point groups, $\hat{\mathbf{D}}_{6h}$, $\hat{\mathbf{D}}_{2h}$, and $\hat{\mathbf{C}}_{2v}$, for discussing the flippings of a cyclohexane ring[6,7] and of six-membered oxygen-containing rings.[8,9] Such pseudo-point groups were originally aimed at treating the flippings of rings and are by themselves incapable of characterizing nitrogen-containing six-membered rings. Hence, the purpose of this paper is the extension of the pseudo-point groups so they can be applied to the inversions on nitrogen atoms in addition to the flippings of rings.

Theoretical Foundations and Results

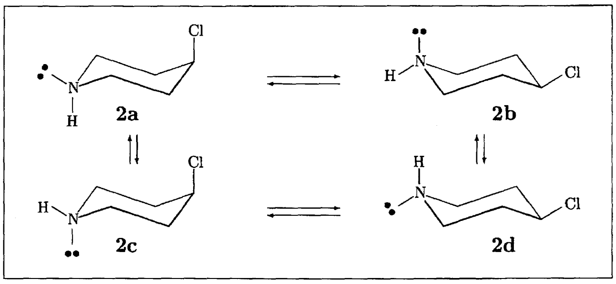
1 Ergo-Enantiomeric Quadruplets of Conformers. In order to manipulate both the flipping of a piperidine ring[10,11] and the inversion on the nitrogen atom (*N*-inversion),[12—14] we consider a standard quadruplet that consists of four conformers concerning the two processes. We then regard the quadruplet of conformers as an isomer. Figure 1(a) shows a standard quadruplet (**1**) of conformers (**1a**—**1d**) for 4-chloropiperidine as an example. The quadruplet of conformers undergoes confomational changes to generate the following four cases:

Case 1. When both the flipping and the *N*-inversion are fixed, the conformers (**1a**—**1d**) of the quadruplet (**1**) should be considered to be non-equivalent. This case is represented by the conversion of the quadruplet (**1**) into itself.

Case 2. Suppose that the flipping is unfixed while the *N*-inversion is fixed, i.e. only the flipping of the piperidine ring is taken into consideration. Then, the pair of the equivalent conformers on the top row (**1a** and **1b**) should be regarded to be non-equivalent to the pair of the equivalent conformers on the bottom row (**1c** and **1d**). For the consistency of our theoretical framework, we consider another quadruplet (**2**) shown in Fig. 1(b). Then the relationship between the standard quadruplet (**1**) and the flipped one (**2**) is defined as being *F-ergo-enantiomeric*, where "*F*" denotes the flipping of the ring.[15] It should be noted that the *F*-ergo-enantiomeric relationship is concerned with the equivalence between two quadruplets (e.g., **1** and **2**) under the one condition as well as with the non-equivalence under the other condition. Since each quadruplet is regarded as an isomer, the quadruplets shown in Figs. 1(a) and 1(b) illustrate a set of *F*-ergo-enantiomeric isomers (*F*-ergo-enantiomers). The *F*-ergo-enantiomerism between **1** and **2** means that every pair of corresponding conformers (**1a** and **2a**; **1b** and **2b**; **1c** and



(a) Standard quadruplet of 4-chloropiperidine



(b) Flipped quadruplet of 4-chloropiperidine

Fig. 1. A set of *F*-ergo-enantiomeric quadruplets (*F*-ergo-enantiomers).

2c; and **1d** and **2d**) is *F*-ergo-enantiomeric.

Case 3. Suppose on the other hand that the flipping is fixed while the *N*-inversion is unfixed. In other words, only the *N*-inversion on the nitrogen atom is taken into consideration. Then, the pair of the equivalent conformers in the left-hand column (**1a** and **1c**) should be regarded to be non-equivalent to the pair of the equivalent conformers in the right-hand column (**1b** and **1d**). For characterizing this case, we consider an additional quadruplet (**3**) shown in Fig. 2. Then the relationship between the standard quadruplet (**1**) and the inverted one (**3**) is defined as being *I-ergo-enantiomeric*, where "*I*" denotes the *N*-inversion.

Case 4. When both the flipping and the *N*-inversion are unfixed, these conformers (**1a**—**1d**) should be considered to be equivalent. For characterizing this case, we consider an additional quadruplet (**4**) shown in Fig. 3. Then the relationship between the standard quadruplet (**1**) and the inverted one (**4**) is defined as being *FI-ergo-enantiomeric* where "*FI*" denotes the flipping and *N*-inversion.

It should be noted that the term "equivalent" does not mean that the conformers at issue are energetically identical with each other, but means that they are interconvertible with an appropriate operation.

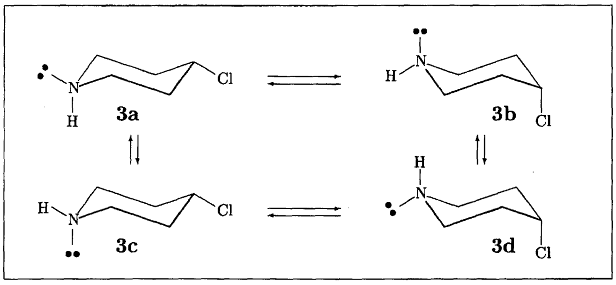


Fig. 2. A quadruplet *I*-ergo-enantiomeric to **1**.

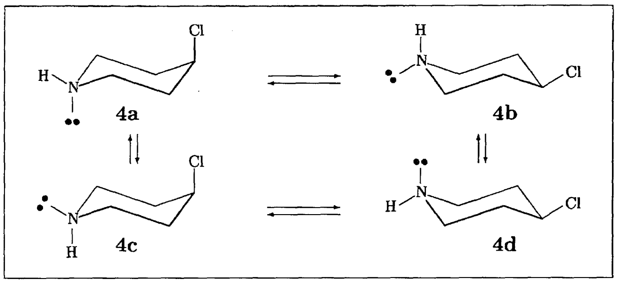


Fig. 3. A quadruplet *FI*-ergo-enantiomeric to **1**.

2 Pseudo-Rotations for Characterizing the Flipping of Rings. As illustrated in the preceding section, the four quadruplets (**1** to **4**) shown in Figs. 1 to 3 are to be counted as one isomer, since the equivalency is concerned with the interchangeability during the ring flipping and the *N*-inversion. Obviously, piperidine with no substituents belongs to the usual point group $\mathbf{C}_s$ (= $\{I, \sigma_v\}$) under fully fixed conditions (Case 1). In order to discuss the flipping of the ring and the inversion on the nitrogen atom, this case as well as the remaining cases (Cases 2 to 4) should be formulated within an integrated mathematical framework.

For the purpose of characterizing Case 2, we define a pseudo-rotation $\hat{C}_2$ as depicted in Fig. 4. This operation is essentially equivalent to the one that has been introduced for characterizing the flipping of tetrahydropyran,[8] except that a quadruplet of conformers is taken into consideration in place of a pair of conformers. Thus, the $\hat{C}_2$ operation is a combination of a rotation (the quadruplet of **5a** to **5d** into the quadruplet of **6a** to **6d**) and the subsequent column exchange (the quadruplet of **6a** to **6b** into the quadruplet of **7a** to **7d**). The total effect of the $\hat{C}_2$ operation is to exchange the axial and equatorial positions of the piperidine ring.

The operation $\hat{C}_2$ is assigned to a permutation,

$$\hat{C}_2 \sim \begin{pmatrix} 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & 11 & 12 \\ 7 & 12 & 11 & 10 & 9 & 8 & 1 & 6 & 5 & 4 & 3 & 2 \end{pmatrix}$$
$$= (1\ 7)(2\ 12)(3\ 11)(4\ 10)(5\ 9)(6\ 8), \qquad (1)$$

by numbering the positions to be considered as shown in Fig. 4. This permutation is obtained by comparing the locant numbers appearing in a starting conformer (e.g., **5a**) and the resulting one (e.g., **7a**). It should be noted that the same permutation as represented by Eq. 1 can be obtained by comparing between **5b** and **7b**, between **5c** and **7c**, or between **5d** and **7d**. We refer to this fact by saying that *the four conformers of the quadruplet* **5** *behave concurrently* on the action of $\hat{C}_2$.

Let us consider two consecutive operations (the $\hat{C}_2$ operation and the operation σ_v of the group $\mathbf{C}_s$) so that we place $\sigma_v\hat{C}_2 = \hat{\sigma}_v$. Thereby we can construct a group

$$\hat{\mathbf{C}}_{2v} = \mathbf{C}_s + \mathbf{C}_s\hat{C}_2 = \{I, \sigma_v, \hat{C}_2, \hat{\sigma}_v\}, \qquad (2)$$

which characterizes Case 2. Obviously, the pseudo-point group $\hat{\mathbf{C}}_{2v}$ is isomorphic to the usual point group $\mathbf{C}_{2v}$. Note that the operations denoted by a symbol with a hat represent

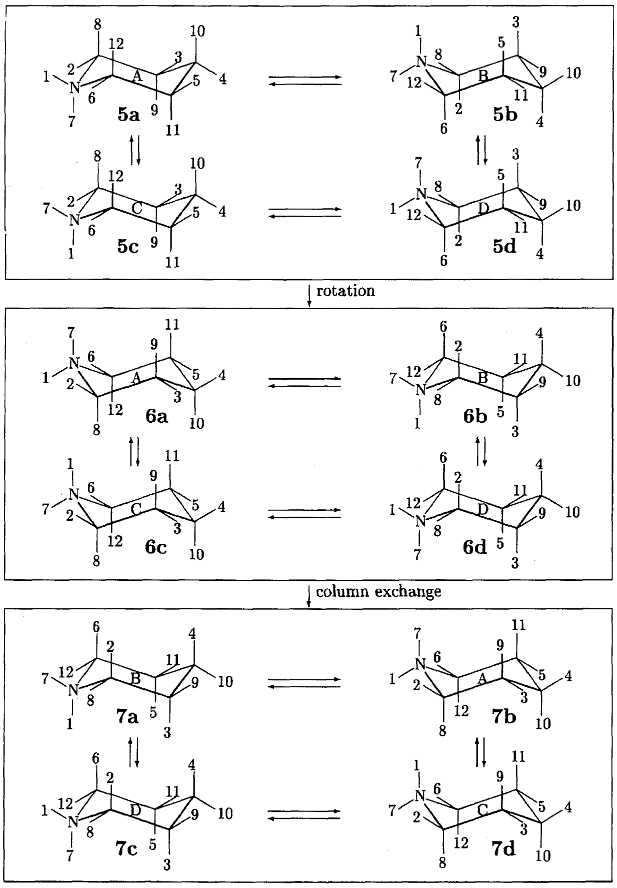


Fig. 4. The definition of the operation $\hat{C}_2$.

the behaviors concerning the flipping of the ring. Among the operations of $\hat{\mathbf{C}}_{2v}$, the two operations with a hat symbol, $\hat{C}_2$ and $\hat{\sigma}_v$, are called improper pseudo-rotations.

3 *N*-Inversion Operation. On the other hand, we define another operation $\tilde{I}$ as depicted in Fig. 5 for the purpose of characterizing Case 3. Thus, the *N*-inversion operation ($\tilde{I}$) corresponds to the row exchange (the quadruplet of **5a** to **5d** into the quadruplet of **8a** to **8d**). It should be noted that we consider two equivalent positions (1 and 7) on the nitrogen atom for the purpose of consistent mathematical manipulation, though the neutral nitrogen atom by no means presents such equivalent positions. Chemically speaking, the two positions can be considered to be two lone pairs of a hypothetical nitrogen anion, which are capable of accomodating a proton to give a neutral nitrogen with a lone pair and a hydrogen atom.

The $\tilde{I}$ operation describes the *N*-inversion and corresponds to the following permutation:

$$\tilde{I} \sim \begin{pmatrix} 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & 11 & 12 \\ 7 & 2 & 3 & 4 & 5 & 6 & 1 & 8 & 9 & 10 & 11 & 12 \end{pmatrix}$$
$$= (1\ 7)(2)(3)(4)(5)(6)(8)(9)(10)(11)(12) \tag{3}$$

It should be noted again that the permutation represented by Eq. 3 can be obtained by comparing between **5a** and **8a**, between **5b** and **8b**, between **5c** and **8c**, or between **5d** and **8d**. Thus, the four conformers of the quadruplet **5** behave concurrently under the action of $\tilde{I}$.

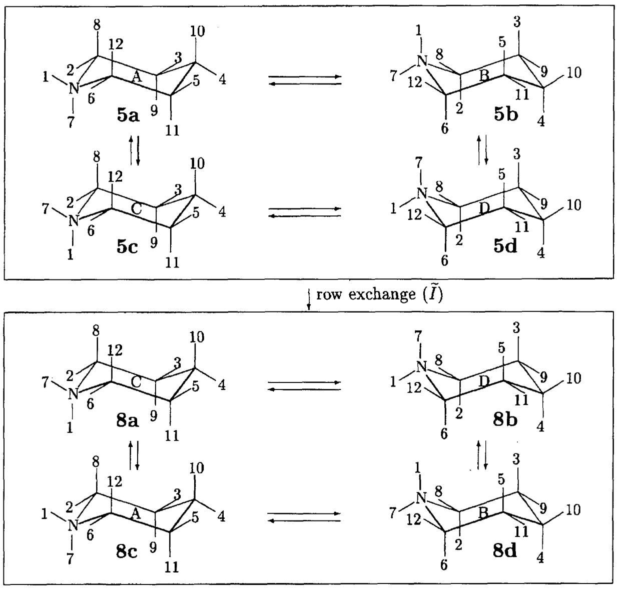


Fig. 5. The definition of the operation $\tilde{I}$.

The consecutive action of the $\tilde{I}$ operation and the σ_v operation generates a new operation, $\sigma_v\tilde{I} = \tilde{\sigma}_v$. Thereby we can construct another type of pseudo-point group,

$$\tilde{\mathbf{C}}_{\tilde{I}v} = \mathbf{C}_s + \mathbf{C}_s\tilde{I} = \{I, \sigma_v, \tilde{I}, \tilde{\sigma}_v\}. \tag{4}$$

The pseudo-point group $\tilde{\mathbf{C}}_{\tilde{I}v}$ is isomorphic to the usual point group $\mathbf{C}_{2v}$. Note that the operations denoted by the symbol with a tilde represent the behaviors concerning the *N*-inversion.

Among the operations of $\tilde{\mathbf{C}}_{\tilde{I}v}$, the two operations with a tilde symbol, $\tilde{I}$ and $\tilde{\sigma}_v$, are called *improper N-inversions*. For holding the consistency of terminology, the operations without a tilde symbol are sometimes called *proper N-inversions* or referred to as being *proper with respect to N-inversion*, although they by no means involve *N*-inversions.

4 Extended Pseudo-Point Group $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$. For the purpose of manipulating Case 4, we should take accout of both the operations, $\hat{C}_2$ and $\tilde{I}$. As a result, there appear two operations, i.e., $\hat{C}_2\tilde{I} = \hat{\tilde{C}}_2$ and $\hat{\sigma}_v\tilde{I} = \hat{\tilde{\sigma}}_v$, where the resulting operations are denoted by a symbol with a hat and tilde so as to be related to both the flipping and the *N*-inversion. These operations are called *rotoinversions* in this paper. Since the behavior of the four conformers of the quadruplet **5** is concurrent, we are able to select either one of the conformers as a representative to show the effect of each operation. Figure 6 shows the effects of the resulting operations by using **5a** as a representative. For example, the effect of the $\hat{C}_2$ operation (Fig. 4) is simply represented by the scheme **5a**→**7a** in Fig. 6, while that of the $\tilde{I}$ operation (Fig. 5) is expressed by the scheme **5a**→**8a**.

The operations listed in Fig. 6 construct a set $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$ in accord with the equation,

$$\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v} = \hat{\mathbf{C}}_{2v} + \hat{\mathbf{C}}_{2v}\tilde{I} = \{I, \sigma_v, \hat{C}_2, \hat{\sigma}_v, \tilde{I}, \tilde{\sigma}_v, \hat{\tilde{C}}_2, \hat{\tilde{\sigma}}_v\} \tag{5}$$

or alternatively the equation,

$$\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v} = \tilde{\mathbf{C}}_{\tilde{I}v} + \tilde{\mathbf{C}}_{\tilde{I}v}\hat{C}_2 = \{I, \sigma_v, \tilde{I}, \tilde{\sigma}_v, \hat{C}_2, \hat{\sigma}_v, \hat{\tilde{C}}_2, \hat{\tilde{\sigma}}_v\}. \tag{6}$$

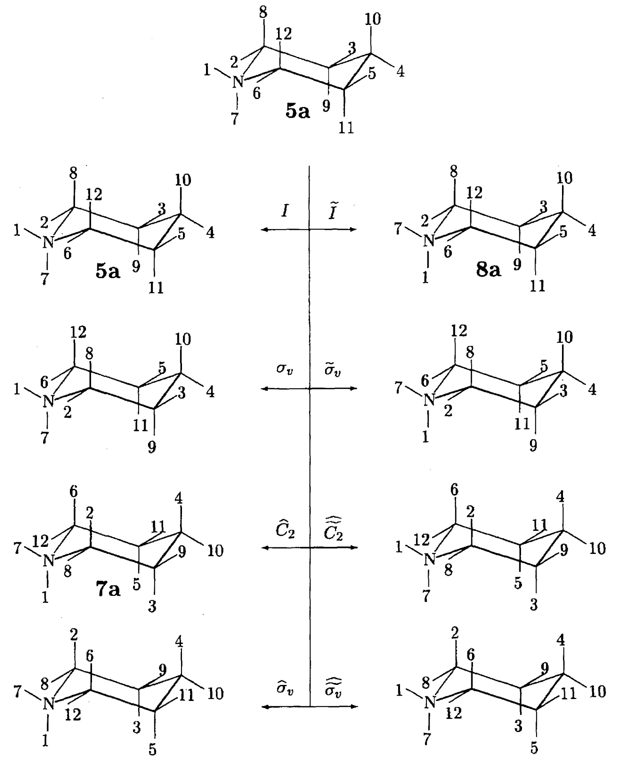


Fig. 6. The operations of $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$.

Since the resulting set $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$ satisfies the multiplication table shown in Table 1, it is concluded to be a group. Such a group is called an *extended pseudo-point group* because of the presence of pseudo-rotations and the N-inversion operation ($\tilde{I}$). Examination of Table 1 reveals that the group $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$ is isomorphic to the usual point group $\mathbf{D}_{2h}$.

The elements of the extended pseudo-point group $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$ are categorized in terms of three criteria to be proper or improper, as shown in Table 2. The "rotation" column of Table 2 is based on a geometrical criterion. Thus, an improper rotation changes one conformer into the antipodal conformer. The "pseude-rotation" column of Table 2 is concerned with the second criterion, where an improper pseudo-rotation indicates that the flipping of a ring changes one conformer into the other conformer of equal energy level. The "N-inversion operation" column of Table 2 indicates that an (improper) N-inversion causes an axial-equatorial interconversion of an N-substituent.

Table 1. Multiplication Table of $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$

	I	σ_v	$\hat{C}_2$	$\hat{\sigma}_v$	$\tilde{I}$	$\tilde{\sigma}_v$	$\hat{\tilde{C}}_2$	$\hat{\tilde{\sigma}}_v$
I	I	σ_v	$\hat{C}_2$	$\hat{\sigma}_v$	$\tilde{I}$	$\tilde{\sigma}_v$	$\hat{\tilde{C}}_2$	$\hat{\tilde{\sigma}}_v$
σ_v	σ_v	I	$\hat{\sigma}_v$	$\hat{C}_2$	$\tilde{\sigma}_v$	$\tilde{I}$	$\hat{\tilde{\sigma}}_v$	$\hat{\tilde{C}}_2$
$\hat{C}_2$	$\hat{C}_2$	$\hat{\sigma}_v$	I	σ_v	$\hat{\tilde{C}}_2$	$\hat{\tilde{\sigma}}_v$	$\tilde{I}$	$\tilde{\sigma}_v$
$\hat{\sigma}_v$	$\hat{\sigma}_v$	$\hat{C}_2$	σ_v	I	$\hat{\tilde{\sigma}}_v$	$\hat{\tilde{C}}_2$	$\tilde{\sigma}_v$	$\tilde{I}$
$\tilde{I}$	$\tilde{I}$	$\tilde{\sigma}_v$	$\hat{\tilde{C}}_2$	$\hat{\tilde{\sigma}}_v$	I	σ_v	$\hat{C}_2$	$\hat{\sigma}_v$
$\tilde{\sigma}_v$	$\tilde{\sigma}_v$	$\tilde{I}$	$\hat{\tilde{\sigma}}_v$	$\hat{\tilde{C}}_2$	σ_v	I	$\hat{\sigma}_v$	$\hat{C}_2$
$\hat{\tilde{C}}_2$	$\hat{\tilde{C}}_2$	$\hat{\tilde{\sigma}}_v$	$\tilde{I}$	$\tilde{\sigma}_v$	$\hat{C}_2$	$\hat{\sigma}_v$	I	σ_v
$\hat{\tilde{\sigma}}_v$	$\hat{\tilde{\sigma}}_v$	$\tilde{\sigma}_v$	$\hat{\tilde{C}}_2$	$\tilde{I}$	$\hat{\sigma}_v$	$\hat{C}_2$	σ_v	I

Table 2. Extended Symmetry Operations of $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$

Extended symmetry operation	Rotation (Geometry)	Pseudo-rotation (Flipping)	N-Inversion operation (N-Inversion)
I	Proper	Proper	Proper
σ_v	Improper	Proper	Proper
$\hat{C}_2$	Proper	Improper	Proper
$\hat{\sigma}_v$	Improper	Improper	Proper
$\tilde{I}$	Proper	Proper	Improper
$\tilde{\sigma}_v$	Improper	Proper	Improper
$\hat{\tilde{C}}_2$	Proper	Improper	Improper
$\hat{\tilde{\sigma}}_v$	Improper	Improper	Improper

The subgroups of $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$ are collected in Table 3. Each substitution for the twelve positions of a quadruplet gives a derivative of piperidine, the symmetry of which is ascribed to a subgroup of $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$.

It is worthwhile to mention the procedure of equalizing the standard quadruplet (**1**) for 4-chloropiperidine to the equivalent quadruplets (**2**, **3**, and **4**). The procedure of each derivation is accomplished by placing a hydrogen on the position 1 and a chlorine on the position 4 of the representative which resulted from each operation shown in Fig. 6.

1. Thus, the representatives which resulted from I and σ_v in Fig. 6 give the standard quadruplet (**1**) itself. This means that 4-chloropiperidine is invariant under these operations.
2. The representatives which resulted from $\hat{C}_2$ and $\hat{\sigma}_v$ (Fig. 6) give the F-ergo-enantiomeric quadruplet (**2** or the representative **2a**).
3. The representatives from $\tilde{I}$ and $\tilde{\sigma}_v$ operations (Fig. 6) give the I-ergo-enantiomeric quadruplet **3** (or the representative **3a**).
4. The representatives from $\hat{\tilde{C}}_2$ and $\hat{\tilde{\sigma}}_v$ operations (Fig. 6) give the FI-ergo-enantiomeric quadruplet (**4** or the representative **4a**) by placing a hydrogen on the position 1 and a chlorine on the position 4.

These four steps exemplify the methodology of the symmetry characterization employed in this paper. Thus, 4-chloropiperidine is concluded to belong to the $\mathbf{C}_s$-group in the first step. The remaining three steps show the ergo-enantiomers that are counted once as one isomer.

5 Combinatorial Enumeration. The set of positions numbered from 1 to 12 are classified into several sets of equivalent positions, which are assigned to the corresponding coset representations.[16] The fixed-point vector (FPV) is obtained by counting fixed points corresponding to the restriction to each subgroup listed in Table 3.

$$FPV = (12,0,10,2,4,0,2,2,0,2,0,0,0,2,0,0). \qquad (7)$$

Since the group $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$ is isomorphic to $\mathbf{D}_{2h}$, the inverse $M^{-1}_{\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}}$ is equal to $M^{-1}_{\hat{\tilde{\mathbf{D}}}_{2h}}$, which was reported previously.[16] The FPV is multiplied by the inverse to give a row vector,

Table 3. Subgroups of $\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}$ [a)]

Subgroup	Elements	Chirality	*F*-Energeticity	*I*-Energeticity	*FI*-Energeticity
$\mathbf{C}_1$	$=\{I\}$	Chiral	*F*-anisoenergetic	*I*-anisoenergetic	*FI*-anisoenergetic
$\hat{\mathbf{C}}_2$	$=\{I,\hat{C}_2\}$	Chiral	*F*-isoenergetic	*I*-anisoenergetic	*FI*-anisoenergetic
$\tilde{\mathbf{C}}_{\tilde{I}}$	$=\{I,\tilde{I}\}$	Chiral	*F*-anisoenergetic	*I*-isoenergetic	*FI*-anisoenergetic
$\hat{\hat{\mathbf{C}}}_2$	$=\{I,\hat{\hat{C}}_2\}$	Chiral	*F*-anisoenergetic	*I*-anisoenergetic	*FI*-isoenergetic
$\mathbf{C}_s$	$=\{I,\sigma_v\}$	Achiral	*F*-anisoenergetic	*I*-anisoenergetic	*FI*-anisoenergetic
$\hat{\mathbf{C}}_s$	$=\{I,\hat{\sigma}_v\}$	Achiral	*F*-isoenergetic	*I*-anisoenergetic	*FI*-anisoenergetic
$\tilde{\mathbf{C}}_s$	$=\{I,\tilde{\sigma}_v\}$	Achiral	*F*-anisoenergetic	*I*-isoenergetic	*FI*-anisoenergetic
$\hat{\hat{\mathbf{C}}}_s$	$=\{I,\hat{\hat{\sigma}}_v\}$	Achiral	*F*-anisoenergetic	*I*-anisoenergetic	*FI*-isoenergetic
$\hat{\mathbf{C}}_{2v}$	$=\{I,\hat{C}_2,\sigma_v,\hat{\sigma}_v\}$	Achiral	*F*-isoenergetic	*I*-anisoenergetic	*FI*-anisoenergetic
$\tilde{\mathbf{C}}_{\tilde{I}v}$	$=\{I,\tilde{I},\tilde{\sigma}_v,\sigma_v\}$	Achiral	*F*-anisoenergetic	*I*-isoenergetic	*FI*-anisoenergetic
$\hat{\hat{\mathbf{C}}}_{2v}$	$=\{I,\hat{\hat{C}}_2,\tilde{\sigma}_v,\hat{\sigma}_v\}$	Achiral	*F*-isoenergetic	*I*-isoenergetic	*FI*-isoenergetic
$\hat{\hat{\mathbf{C}}}'_{2v}$	$=\{I,\hat{C}_2,\tilde{\sigma}_v,\hat{\hat{\sigma}}_v\}$	Achiral	*F*-isoenergetic	*I*-isoenergetic	*FI*-isoenergetic
$\hat{\hat{\mathbf{C}}}_{\tilde{I}v}$	$=\{I,\tilde{I},\hat{\sigma}_v,\hat{\hat{\sigma}}_v\}$	Achiral	*F*-isoenergetic	*I*-isoenergetic	*FI*-isoenergetic
$\hat{\hat{\mathbf{C}}}''_{2v}$	$=\{I,\hat{\hat{C}}_2,\sigma_v,\hat{\hat{\sigma}}_v\}$	Achiral	*F*-anisoenergetic	*I*-anisoenergetic	*FI*-isoenergetic
$\hat{\hat{\mathbf{C}}}_{2\tilde{I}}$	$=\{I,\hat{C}_2,\tilde{I},\hat{\hat{C}}_2\}$	Chiral	*F*-isoenergetic	*I*-isoenergetic	*FI*-isoenergetic
$\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}$	$=\{$All operations$\}$	Chiral	*F*-isoenergetic	*I*-isoenergetic	*FI*-isoenergetic

a) The group is isomorphic to the point group $\mathbf{D}_{2h}$. The subgroups listed correspond to the subgroups of $\mathbf{D}_{2h}$ in the following order: $\mathbf{C}_1$, $\mathbf{C}_2$, $\mathbf{C}'_2$, $\mathbf{C}''_2$, $\mathbf{C}_s$, $\mathbf{C}'_s$, $\mathbf{C}''_s$, $\mathbf{C}_i$, $\mathbf{C}_{2v}$, $\mathbf{C}'_{2v}$, $\mathbf{C}''_{2v}$, $\mathbf{C}_{2h}$, $\mathbf{C}'_{2h}$, $\mathbf{C}''_{2h}$, $\mathbf{D}_2$, and $\mathbf{D}_{2h}$. The inverse mark table and the USCI table reported for $\mathbf{D}_{2h}$[16] can be used by paying attention to this correspondence.

$$FPV \times M^{-1}_{\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}} = (0,0,2,0,0,0,0,0,0,1,0,0,0,1,0,0), \tag{8}$$

which corresponds to

$$\mathbf{P} = 2\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}}) + \hat{\hat{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}v}) + \hat{\hat{\mathbf{C}}}_{2\tilde{I}v}(/\hat{\hat{\mathbf{C}}}''_{2v}). \tag{9}$$

This equation means that the 2,6-positions (2, 6, 8, and 12) and the 3,5-positions (3, 5, 9, and 11) are assigned respectively to the coset representation $\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}})$, the 4-positions (4 and 10) to $\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}v})$ and the 1-positions (1 and 7 for a lone pair) to $\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}(/\hat{\hat{\mathbf{C}}}''_{2v})$.

We take account of the correspondence of the following coset representations,

$$\begin{gathered}
\tilde{\mathbf{C}}_{2\tilde{I}v}(/\hat{\hat{C}}_{\tilde{I}}) \Leftrightarrow \mathbf{D}_{2h}(/\mathbf{C}'_2) \\
\tilde{\mathbf{C}}_{2\tilde{I}v}(/\hat{\hat{\mathbf{C}}}_{\tilde{I}v}) \Leftrightarrow \mathbf{D}_{2h}(/\mathbf{C}'_{2v}) \\
\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}(/\hat{\hat{\mathbf{C}}}''_{2v}) \Leftrightarrow \mathbf{D}_{2h}(/\mathbf{C}''_{2h}),
\end{gathered}$$

where the coset representations appearing on the right-hand sides are those of the point group $\mathbf{D}_{2h}$ reported previously.[16] Thereby, the use of the corresponding rows in the USCI table for $\mathbf{D}_{2h}$[17] gives the subduced cycle indices (SCIs) as a formal row vector,

$$\begin{aligned}
&((a_1^2)(s_1^{10}),(a_2)(s_2^5),(a_2)(s_1^{10}),(a_1^2)(s_2^5),(a_1^2)(s_1^2s_2^4),(a_2)(s_2^5),\\
&(a_2)(s_1^2s_2^4),(a_1^2)(s_2^5),(a_2)(s_2s_4^2),(a_2)(s_1^2s_2^4),(a_2)(s_2s_4^2),\\
&(a_2)(s_2s_4^2),(a_2)(s_2^5),(a_1^2)(s_2s_4^2),(a_2)(s_2^5),(a_2)(s_2s_4^2)) \times M^{-1}_{\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}},
\end{aligned} \tag{10}$$

where the row vector is multiplied by the inverse $M^{-1}_{\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}}$. Note that the dummy variables for the lone pair (the $\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}(/\hat{\hat{\mathbf{C}}}''_{2v})$-orbit) are represented on the basis of *a* in place of *s*. The formal matrix calculation of Eq. 10 gives a set of partial subduced indices (PCIs)[18,19] of the respective subgroups. Thereby, we have

$$PCI(\mathbf{C}_1;a_d,s_d) = (a_1^2 - a_2)\left(\frac{1}{8}s_1^{10} - \frac{1}{4}s_2^5 - \frac{1}{8}s_1^2s_2^4 + \frac{1}{4}s_2s_4^2\right) \tag{11}$$

$$PCI(\hat{\mathbf{C}}_2;a_d,s_d) = 0 \tag{12}$$

$$PCI(\tilde{\mathbf{C}}_{\tilde{I}};a_d,s_d) = (a_2)\left(\frac{1}{4}s_1^{10} - \frac{1}{2}s_2^5 - \frac{1}{4}s_1^2s_2^4 + \frac{1}{2}s_2s_4^2\right) \tag{13}$$

$$PCI(\hat{\hat{\mathbf{C}}}_2;a_d,s_d) = (a_1^2 - a_2)\left(\frac{1}{4}s_2^5 - \frac{1}{4}s_2s_4^2\right) \tag{14}$$

$$PCI(\mathbf{C}_s;a_d,s_d) = (a_1^2 - a_2)\left(\frac{1}{4}s_1^2s_2^4 - \frac{1}{4}s_2s_4^2\right) \tag{15}$$

$$PCI(\hat{\mathbf{C}}_s;a_d,s_d) = 0 \tag{16}$$

$$PCI(\tilde{\mathbf{C}}_s;a_d,s_d) = 0 \tag{17}$$

$$PCI(\hat{\hat{\mathbf{C}}}_s;a_d,s_d) = (a_1^2 - a_2)\left(\frac{1}{4}s_2^5 - \frac{1}{4}s_2s_4^2\right) \tag{18}$$

$$PCI(\hat{\mathbf{C}}_{2v};a_d,s_d) = 0 \tag{19}$$

$$PCI(\tilde{\mathbf{C}}_{\tilde{I}v};a_d,s_d) = (a_2)\left(\frac{1}{2}s_1^2s_2^4 - \frac{1}{2}s_2s_4^2\right) \tag{20}$$

$$PCI(\hat{\hat{\mathbf{C}}}_{2v};a_d,s_d) = 0 \tag{21}$$

$$PCI(\hat{\hat{\mathbf{C}}}'_{2v};a_d,s_d) = 0 \tag{22}$$

$$PCI(\hat{\hat{\mathbf{C}}}_{\tilde{I}v};a_d,s_d) = (a_2)\left(\frac{1}{2}s_2^5 - \frac{1}{2}s_2s_4^2\right) \tag{23}$$

$$PCI(\hat{\mathbf{C}}''_{2v};a_d,s_d) = (a_1^2 - a_2)\left(\frac{1}{2}s_2s_4^2\right) \tag{24}$$

$$PCI(\hat{\hat{\mathbf{C}}}_{2\tilde{I}};a_d,s_d) = (a_2)\left(\frac{1}{2}s_2^5 - \frac{1}{2}s_2s_4^2\right) \tag{25}$$

$$PCI(\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}; a_d, s_d) = (a_2)(s_2 s_4^2) \tag{26}$$

The PCIs with the term a_2 (not with the term $a_1^2 - a_2$) show that the corresponding orbits such as the $\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}(/\hat{\hat{\mathbf{C}}}_{\tilde{I}})$-orbit accomodate two objects of the same kind. These situations should not be permitted on the basis of the present presumption that the orbit concerning the piperidine nitrogen should accomodate one lone pair and one other object (e.g., one hydrogen atom) so as to give a neutral nitrogen atom. Hence, the PCIs with the term $a_1^2 - a_2$ (Eqs. 11, 14, 15, 18, and 24) are concluded to be chemically possible for our purpose of enumeration.

Suppose that two kinds of substituents (X and Y) are substituted for the 10 positions on the five carbon atoms and a hydrogen atom is placed on either one of the two positions (1 and 7) on the nitrogen. Then, we use the ligand inventory represented by

$$s_d = 1 + x^d + y^d \tag{27}$$

for the former 10 positions and the one represented by

$$a_d = 1 + z^d \tag{28}$$

for the latter two positions. These inventories (Eqs. 27 and 28) are introduced into Eq. 11 to Eq. 26. The expansion of these equations produces the generating functions for giving the numbers of isomers of the respective subgroups. The coefficient of the term $1^k x^l y^m z^n$ of each equation indicates the number of isomers with $X^l Y^m H^n$ and with the symmetry at issue, where H represents a hydrogen atom on the nitrogen.

As mentioned above, we focus our attention on the five PCIs (Eqs. 11, 14, 15, 18, and 24). In these equations, the power n is calculated to 1, since we have

$$a_1^2 - a_2 = (1+z)^2 - (1+z^2) = 2z. \tag{29}$$

For example, the PCI for $\hat{\mathbf{C}}''_{2v}$ gives the result:

$$\begin{aligned} & PCI(\hat{\mathbf{C}}''_{2v}; 1 + z^d, 1 + x^d + y^d) \\ & = \frac{1}{2} \times \{(1+z)^2 - (1+z^2)\}\{(1+x^2+y^2)(1+x^4+y^4)^2\} \\ & = \{1 + (x^2+y^2+\cdots) + 2(x^4+y^4+\cdots) \\ & +2(x^4y^2+x^2y^4+\cdots)\}z. \end{aligned} \tag{30}$$

The result is collected in the $\hat{\mathbf{C}}''_{2v}$-column of Table 4. The results for the other symmetries are also collected in Table 4. For simplicity's sake, the set of powers $[k,l,m,n]$ is adopted for representing the terms $1^k x^l y^m z^n$, $1^l x^m y^k z^n$, etc., since these terms have the same coefficient. For example, the index [9, 1,0,1] corresponds to the terms, xz, x^9z, x^9yz, yz, y^9z, and xy^9z, where the power of z is equal to 1.

To obtain the total number of isomers with each formula, we use the CI calculated by summing up the five PCIs at issue (Eqs. 11, 14, 15, 18, and 24).

$$CI(\hat{\mathbf{C}}_{2\tilde{I}v}; a_d, s_d) = (a_1^2 - a_2)\left(\frac{1}{4}s_1^{10} + \frac{1}{4}s_2^5 + \frac{1}{4}s_1^2 s_2^4 + \frac{1}{4}s_2^5\right) \tag{31}$$

The inventories (Eqs. 27 and 28) are introduced into Eq. 31 to produce the generating function for giving the total numbers of isomers. They are collected in the rightmost column of Table 4. The values are equal to the sums for the respective rows of Table 4.

Table 4. Numbers of Piperidine Isomers

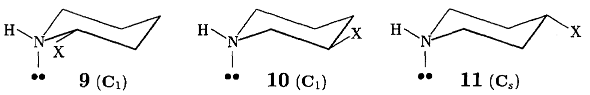
	$\mathbf{C}_1$	$\hat{\hat{\mathbf{C}}}_2$	$\mathbf{C}_s$	$\hat{\hat{\mathbf{C}}}_s$	$\hat{\hat{\mathbf{C}}}''_{2v}$	Total
[10,0,0,1]	0	0	0	0	1	1
[9,1,0,1]	2	0	1	0	0	3
[8,2,0,1]	8	2	2	2	1	15
[8,1,1,1]	22	0	1	0	0	23
[7,3,0,1]	28	0	4	0	0	32
[7,2,1,1]	88	0	4	0	0	92
[6,4,0,1]	46	4	4	4	2	60
[6,3,1,1]	208	0	4	0	0	212
[6,2,2,1]	300	10	10	10	0	330
[5,5,0,1]	60	0	6	0	0	66
[5,4,1,1]	312	0	6	0	0	318
[5,3,2,1]	624	0	12	0	0	636
[4,4,2,1]	766	14	14	14	2	810
[4,3,3,1]	1044	0	12	0	0	1056

The results collected in Table 4 are apparently the same as those reported for tetrahydropyran in the previous paper.[8] However, the PCIs (Eqs. 11—26) for the group $\hat{\hat{\mathbf{C}}}_{2\tilde{I}v}$ in this paper are different from the counterparts for the group $\hat{\mathbf{C}}_{2v}$. Thus, the close relationship between piperidine and tetrahydropyran has been revealed, whereas these two require different types of treatment.

6 Enumerated Piperidines. The inspection of the [9, 1,0,1] row of Table 4 reveals that these are three mono-substituted isomers (quadruplets), where two of these belong to $\mathbf{C}_1$ and one of these belongs to $\mathbf{C}_s$. They are illustrated in Fig. 7, where an arbitrary conformer of each quadruplet is depicted as a representative. It should be emphasized again that each representative conformer represents the corresponding quadruplet, which is in turn regarded to be equivalent to an *F*-, *I*-, or *FI*-ergo-enatiomeric quadruplet if present. For example, the 4-monosubstituted isomer (**11**) is a representative of the quadruplet (**1**, Cl = X), which is in turn selected as a standard quadruplet from the four quadruplets (**1**, **2**, **3**, and **4**; Cl = X). Moreover, a chiral quadruplet has the corresponding antipodal quadruplet.

The number of disubstituted isomers with C_1-symmetry is 8, as shown at the intersection between the [8,2,0,1] row and the C_1-column of Table 4. Figure 8 depicts these eight isomers. Since each of the $\mathbf{C}_1$-isomers is chiral, it is represented by an arbitrary antipodal quadruplet. Each of the pairs of the isomers (**12** and **13**; **14** and **15**; **16** and **17**; and **18** and **19**) shows an example of *cis–trans* isomerism.

The [8,2,0,1]-isomers of higher symmetries are depicted in Fig. 9. Since the $\hat{\hat{\mathbf{C}}}_2$, [8,2,0,1]-isomers (20 and 21) are chiral, Fig. 9 contains an arbitrary antipodal isomer (quadruplet).



9 ($\mathbf{C}_1$) **10** ($\mathbf{C}_1$) **11** ($\mathbf{C}_s$)

Fig. 7. Monosubstituted isomers of piperidine.

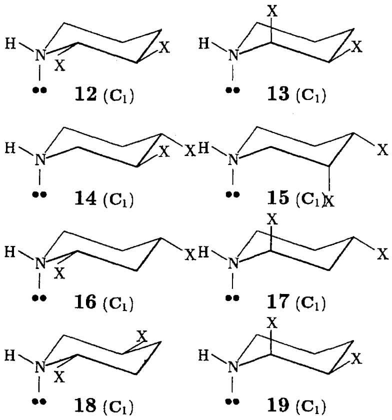


Fig. 8. $\mathbf{C}_1$-Disubstituted isomers of piperidine.

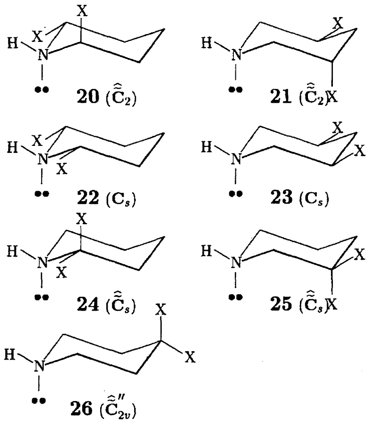


Fig. 9. Disubstituted isomers of higher symmetries.

Discussion

1 Iso- and Anisoenergetic Groups. The subgroups of $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$ are classified in terms of four criteria, as shown in Table 3.

1. Chirality (chiral and achiral). A group with no improper operations is called a chiral group.

2. *F*-Energeticity according to the procedure described in the previous paper.[7] In this paper, the energeticity concerning the flipping of the ring is referred to as *F*-energeticity in order to differentiate it from *I*-energeticity. A group that has at least one operation with a hat symbol and no operations with a tilde-containing symbol is called an *F*-isoenergetic group.

3. *I*-Energeticity. Moreover, another type of energeticity (*I*-energeticity) comes from the *N*-inversion operation. A group that has at least one operation with a tilde symbol and no operations with a hat-containing symbol is called an *I*-isoenergetic group.

4. *FI*-Energeticity. This is the combination of *F*-energeticity and *I*-energeticity. A group that has at least one operation with a tilde-hat symbol and no operations with a hat or tilde symbol is called an *FI*-isoenergetic group.

Since we presume the presence of the lone pair of the piperidine nitrogen, each of the possible cases is ascribed to be *F*-anisoenergetic and *I*-anisoenergetic without losing generality. The *F*-energeticity does not appear independent of the *I*-energeticity and vice versa, so as to produce *FI*-isoenergetic cases such as $\hat{\tilde{\mathbf{C}}}''_{2v}$ and $\hat{\tilde{\mathbf{C}}}_2$. This is the reason why there have appeared the group $\hat{\tilde{\mathbf{C}}}''_{2v}$ and its subgroups in the enumeration described above, though we have defined the extended point group $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$.

We have reported type I, I′, and II for *F*-isoenergetic groups as well as type III and IV for *F*-anisoenergetic groups.[7] This classification can be extended to characterize the *FI*-energeticity of piperidine derivatives. Note that the symmetry of piperidine itself is $\hat{\tilde{\mathbf{C}}}''_{2v} = \{I, \hat{\tilde{\mathbf{C}}}_2, \sigma_v, \hat{\tilde{\sigma}}_v\}$, the elements of which show that only *FI*-energeticity is to be examined (Table 3).

As summarized in Table 5, *FI*-isoenergetic groups are classified into three types (Types I, I′, and II), while *FI*-anisoenergetic ones are divided into two types (Types III and IV). The symbols A, B, A′, and B′ represent achiral conformers; Q, R, Q′, and R′ represent chiral conformers; and $\overline{\mathrm{Q}}$, $\overline{\mathrm{R}}$ $\overline{\mathrm{Q}}'$, and $\overline{\mathrm{R}}'$ represent the corresponding antipodal conformers. It should be noted that an extended pseudo-point group can be classified into either one of the types if only *FI*-energeticity is presumed to be considered. The results for the subgroups of $\hat{\tilde{\mathbf{C}}}''_{2v}$ are shown in the rightmost column of Table 5.

Type I is assigned to an extended pseudo-point group (e.g. $\hat{\tilde{\mathbf{C}}}''_{2v}$) that is achiral so as to involve at least an improper pseudo-rotoinversion (e.g. $\hat{\tilde{\sigma}}_v$) and an improper (usual) rotation (e.g. σ_v). The two conformers at the diagonal positions in a quadruplet of Type I are homomeric and achiral in themselves, as denoted by the symbol A (or B) (Table 5).

Type I′ corresponds to an extended pseudo-point group that shows another type of achirality (e.g. $\hat{\mathbf{C}}_s$). The *FI*-isoenergetic group of Type I′ involves at least an improper pseudo-rotoinvertion (e.g. $\hat{\tilde{\sigma}}_v$) but no improper rotation. As a result, one conformer of a quadruplet of Type I′ is enantiomeric to the other conformer at the diagonal place, as denoted by the symbols Q (or R) and $\overline{\mathrm{Q}}$ (or $\overline{\mathrm{R}}$) in Table 5. In other words, the chiral conformer (Q) undergoes racemization to give its

Table 5. Types of Flexible Isomers

	Type	Mode	Subgroup of $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$
FI-Isoenergetic	I	$\begin{array}{ccc} \mathrm{A} & \rightleftarrows & \mathrm{B} \\ \updownarrow & & \updownarrow \\ \mathrm{B} & \rightleftarrows & \mathrm{A} \end{array}$	$\hat{\tilde{\mathbf{C}}}''_{2v}$
	I′	$\begin{array}{ccc} \mathrm{Q} & \rightleftarrows & \mathrm{R} \\ \updownarrow & & \updownarrow \\ \overline{\mathrm{R}} & \rightleftarrows & \overline{\mathrm{Q}} \end{array}$	$\hat{\tilde{\mathbf{C}}}_s$
	II	$\begin{array}{ccc} \mathrm{Q} & \rightleftarrows & \mathrm{R} \\ \updownarrow & & \updownarrow \\ \mathrm{R} & \rightleftarrows & \mathrm{Q} \end{array}$ or $\begin{array}{ccc} \overline{\mathrm{Q}} & \rightleftarrows & \overline{\mathrm{R}} \\ \updownarrow & & \updownarrow \\ \overline{\mathrm{R}} & \rightleftarrows & \overline{\mathrm{Q}} \end{array}$	$\hat{\tilde{\mathbf{C}}}_2$
FI-Anisoenergetic	III	$\begin{array}{ccc} \mathrm{A} & \rightleftarrows & \mathrm{B} \\ \updownarrow & & \updownarrow \\ \mathrm{B}' & \rightleftarrows & \mathrm{A}' \end{array}$	$\mathbf{C}_s$
	IV	$\begin{array}{ccc} \mathrm{Q} & \rightleftarrows & \mathrm{R} \\ \updownarrow & & \updownarrow \\ \mathrm{R}' & \rightleftarrows & \mathrm{Q}' \end{array}$ or $\begin{array}{ccc} \overline{\mathrm{Q}}' & \rightleftarrows & \overline{\mathrm{R}}' \\ \updownarrow & & \updownarrow \\ \overline{\mathrm{R}} & \rightleftarrows & \overline{\mathrm{Q}} \end{array}$	$\mathbf{C}_1$

enantiomer ($\overline{\mathrm{Q}}$) in the quadruplet of Type I′.

Type II results from a chiral extended pseudo-point group (e.g. $\hat{\tilde{\mathbf{C}}}_2$) that involves at least a proper pseudo-rotoinvertion (e.g. $\hat{\tilde{C}}_2$) but contains no improper pseudo-rotation, improper rotation or improper pseudo-rotoinversion. There exists the corresponding enantiomeric quadruplet.

Type III is assigned to an achiral (extended pseudo-) point group (e.g. $\mathbf{C}_s$) that involves at least an improper rotation but contains neither pseudo-rotations nor pseudo-rotoinversions.

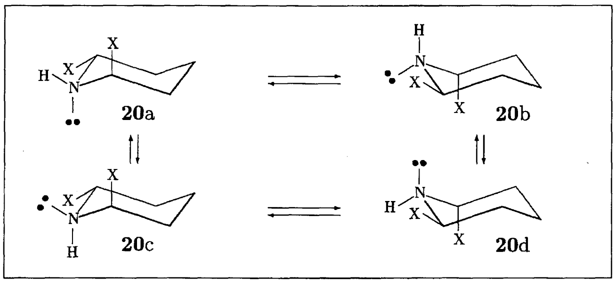
Type IV is ascribed to a chiral (extended pseudo-)point group (e.g. $\mathbf{C}_1$) that involves at least a proper rotation but contains no improper rotations and no pseudo-rotations or pseudo-rotoinverions.

2 Symmetry Characterization of $\hat{\tilde{\mathbf{C}}}_2$-Isomers. Figure 10(a) depicts a quadruplet for the isomer **20** of $\hat{\tilde{\mathbf{C}}}_2$-symmetry. The *FI*-isoenergetic nature of **20** (Type II) is deduced by the comparison between a set of homomers (**20a** and **20d**) or between another set of homomers (**20b** and **20c**).

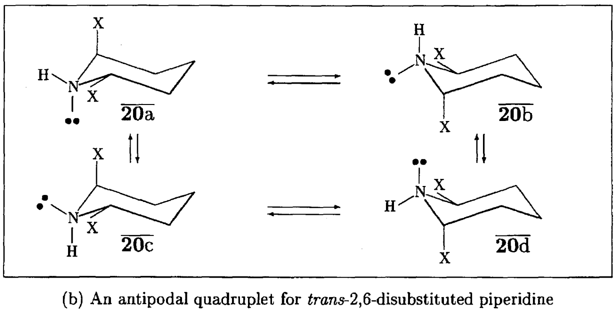
Since the extended pseudo-point group $\hat{\tilde{\mathbf{C}}}_2$ is chiral, there exists the corresponding antipodal quadruplet ($\overline{\mathbf{20}}$) as shown in Fig. 10(b). The derivation of the antipodal set, **20** and $\overline{\mathbf{20}}$, can be explained by the following subduction of the coset representation $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}})$:

$$\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}}) \downarrow \hat{\tilde{\mathbf{C}}}_2 = 2\hat{\tilde{\mathbf{C}}}_2(/\mathbf{C}_1) \tag{32}$$

In agreement with this equation, the orbit of positions no. 2, 6, 8, and 12 governed by $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}})$ is divided into two sets (2 and 12) and (6 and 8), both of which are governed by $\hat{\tilde{\mathbf{C}}}_2(/\mathbf{C}_1)$. When we place two Xs on the one set of positions (2 and 12), we obtain the isomer **20** of $\hat{\tilde{\mathbf{C}}}_2$-symmetry. When we place two Xs on the other set of positions (6 and 8), we obtain the antipodal isomer $\overline{\mathbf{20}}$.



(a) A quadruplet for *trans*-2,6-disubstituted piperidine



(b) An antipodal quadruplet for *trans*-2,6-disubstituted piperidine

Fig. 10. A set of antipodal quadruplets.

The positions 2 and 12 in **20** are equivalent though they are axial and equatorial under fixed conditions. The equivalency under unfixed conditions is established by the fact that they construct an orbit governed by $\hat{\tilde{\mathbf{C}}}_2(/\mathbf{C}_1)$. We here define the term *FI-enantiochronal* if the global symmetry is *FI*-isoenergetic and the local symmetry is *FI*-anisoenergetic. According to this definition, the coset representation $\hat{\tilde{\mathbf{C}}}_2(/\mathbf{C}_1)$ is *FI*-enantiochronal. The *FI*-enantiochronality causes the splitting of the orbit to the axial and equatorial halves under fixed conditions. Hence, the positions 2 and 12 (or Xs) governed by the *FI*-enantiochronal $\hat{\tilde{\mathbf{C}}}_2(/\mathbf{C}_1)$ behave in the predicted way to produce the axial and equatorial halves under fixed conditions.

The four hydrogens on the positions 3, 5, 9, and 11 are governed by $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}})$ in piperidine. They are divided into two orbits (5 and 9) and (3 and 11) in **20** according to the subduction represented by Eq. 32. Each of the resulting orbits is governed by $\hat{\tilde{\mathbf{C}}}_2(/\mathbf{C}_1)$. This means that the interchangeable set of hydrogens at positions 5 and 9 do not coincide with the other interchangeable set of hydrogens at positions 3 and 11 under unfixed conditions. To indicate this situation, we say that the former set (5 and 9) is *FI-ergo-diastereomeric* to the latter one (3 and 11).

3 Symmetry Characterization of $\mathbf{C}_s$-Isomers. Figure 11 depicts a quadruplet (**22**) for the *cis*-2,6-disubstituted isomer of $\mathbf{C}_s$-symmetry. The *FI*-anisoenergetic nature of **22** (Type III) is established by the inspection of the four conformers.

The extended pseudo-point group $\mathbf{C}_s$ (the same as the usual point group) is achiral. The derivation of **22** can be explained by the following subduction of the coset representation $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}})$:

$$\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}}) \downarrow \mathbf{C}_s = 2\mathbf{C}_s(/\mathbf{C}_1) \tag{33}$$

As a result, the orbit of positions no. 2, 6, 8, and 12 governed by $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}})$ is divided into two sets (2 and 6) and (8 and 12), both of which are governed by $\mathbf{C}_s(/\mathbf{C}_1)$. The substitution of two Xs for the one set of positions (2 and 6) gives the isomer **22** of $\mathbf{C}_s$-symmetry. When we place two Xs on the other set of positions (8 and 12), we obtain an *FI*-ergo-enantiomeric quadruplet, the representative of which is identical with the conformer **22d**. In our formulation, *FI*-ergo-enantiomeric quadruplets are regarded as being equivalent.

The X atoms on the positions 2 and 6 of **22a** are equa-

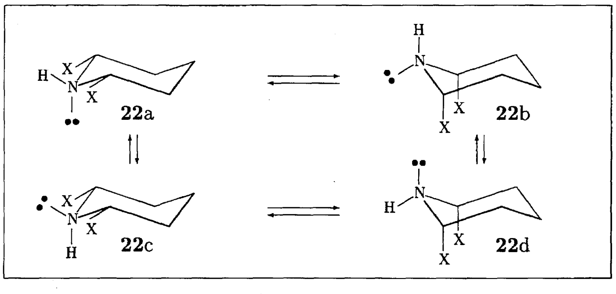


Fig. 11. *cis*-2,6-Disubstituted piperidine.

torial, while the counterparts of **22d** are axial. We here define the term *FI-hemichronal* if the global symmetry is *FI*-anisoenergetic and the local symmetry is *FI*-anisoenergetic. According to this definition, the coset representation $\mathbf{C}_s(/\mathbf{C}_1)$ is *FI*-hemichronal. The *FI*-hemichronality causes the splitting to give unequal amounts of axial and equatorial atoms under fixed conditions.

The four hydrogens on the positions 3, 5, 9, and 11 are governed by $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\hat{\tilde{\mathbf{C}}}_{\tilde{I}})$ in piperidine. They are divided into two orbits (3 and 5) and (9 and 11) in **22**. This division agrees with the subduction represented by Eq. 33. Each of the resulting orbits is governed by the *FI*-hemichronal $\mathbf{C}_s(/\mathbf{C}_1)$. The interchangeable set of hydrogens at positions 3 and 5 do not coincide with the other interchangeable set of hydrogens at positions 9 and 11 under unfixed conditions. Thus, the set (3 and 5) is *FI*-ergo-diastereomeric to the other set (9 and 11).

4 Symmetry Characterization of $\hat{\tilde{\mathbf{C}}}_s$-Isomers. Figure 12 depicts the quadruplet for the isomer **24** of $\hat{\tilde{\mathbf{C}}}_s$-symmetry. The conformers **24a** and **24d** are enantiomeric to each other, while **24b** and **24c** construct another set of enantiomers. Hence, **24** is concluded to be *FI*-isoenergetic (Type I′).

The derivation of **24** is in accord with the following subduction of coset representation $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}})$:

$$\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}}) \downarrow \hat{\tilde{\mathbf{C}}}_s = 2\hat{\tilde{\mathbf{C}}}_s(/\mathbf{C}_1) \qquad (34)$$

According to this equation, the orbit of positions no. 2, 6, 8, and 12 governed by $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}})$ is divided into two sets (2 and 8) and (6 and 12), both of which are governed by $\hat{\tilde{\mathbf{C}}}_s(/\mathbf{C}_1)$. When we place two Xs on the one set of positions (6 and 12), we obtain the isomer **24** of $\hat{\tilde{\mathbf{C}}}_s$-symmetry.

The positions 6 and 12 in **24** are equivalent, though they are axial and equatorial under fixed conditions. The equivalency under unfixed conditions is concluded by the fact that they construct an orbit governed by $\hat{\tilde{\mathbf{C}}}_s(/\mathbf{C}_1)$, since $\hat{\tilde{\mathbf{C}}}_s(/\mathbf{C}_1)$ is *FI*-enantiochronal as defined above. The *FI*-enantiochronality causes the splitting of the orbit to the axial and equatorial halves under fixed conditions.

5 Symmetry Characterization of $\hat{\tilde{\mathbf{C}}}''_{2v}$-Isomers. Figure 13 depicts a quadruplet for the isomer **25** of $\hat{\tilde{\mathbf{C}}}''_{2v}$-symmetry. By the comparison between a set of homomers (**25a** and **25d**) or between another set of homomers (**25b** and **25c**), the isomer **24** is concluded to be *FI*-isoenergetic (Type I).

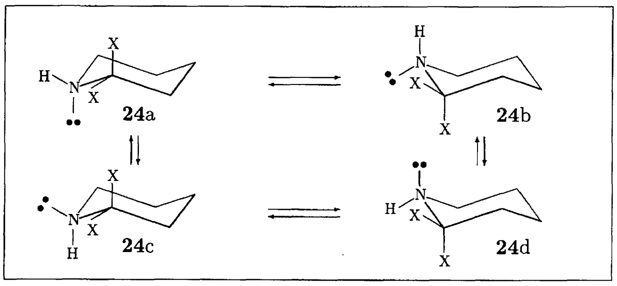


Fig. 12. 2,2-Disubstituted piperidine.

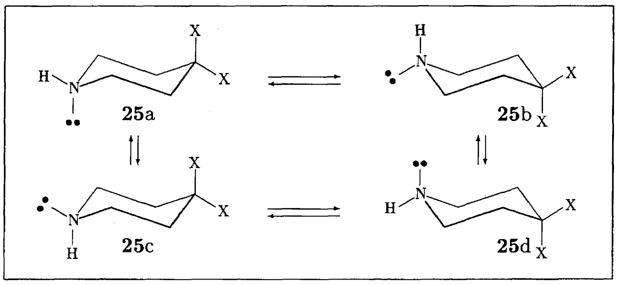


Fig. 13. 4,4-Disubstituted piperidine.

The coset representations appearing in the right-hand side of Eq. 9 are not divided during the subduction to $\hat{\tilde{\mathbf{C}}}''_{2v}$. For example, the coset representation $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}v})$ for the orbit {4, 10} undergoes the subduction represented by

$$\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\tilde{\mathbf{C}}_{\tilde{I}v}) \downarrow \hat{\tilde{\mathbf{C}}}''_{2v} = \hat{\tilde{\mathbf{C}}}''_{2v}(/\mathbf{C}_s). \qquad (35)$$

As a result, the orbit of position no. 4 an 10 governed by $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}(/\hat{\tilde{\mathbf{C}}}_{\tilde{I}v})$ remains a single orbit, which is governed by $\hat{\tilde{\mathbf{C}}}''_{2v}(/\mathbf{C}_s)$. When we place two Xs on the one set of positions (4 and 10), we obtain the isomer **25** of $\hat{\tilde{\mathbf{C}}}''_{2v}$-symmetry.

The positions 4 and 10 in **25** are equivalent under unfixed conditions, since they construct an orbit governed by the *FI*-enantiochronal $\hat{\tilde{\mathbf{C}}}''_{2v}(/\mathbf{C}_s)$. Hence, they are fixed to give the axial and equatorial halves.

Conclusion

An extended pseudo-point group $\hat{\tilde{\mathbf{C}}}_{2\tilde{I}v}$ is defined for characterizing the symmetries of flexible piperidine derivatives, which are enumerated by the unit-subduced-cycle-index approach. The enumerated derivatives are classified into *FI*-isoenergetic (Types I, I′, and II) and *FI*-anisoenergetic (Types III and IV) by means of their extended pseudo-point groups.

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15 The term "enantiomeric" is used to designate the relationship between two isomers with opposite chiralities (e.g., *R* vs. *S*). The term "ergo-enantiomeric" is coined here by analogy with the chirality phenomena, since it aims at designating the relationship between two isomers (quadruplets) with opposite energeticities (e.g. axial vs. equatorial). The prefix "ergo" comes from the Greek word "ergon" (work).

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