

# Organic and Biological Chemistry

## Properties and Maps of Stereochemical Reaction Cycles That Involve Compounds with Four Ligands Attached to a Tetrahedral Chiral Center<sup>1</sup>

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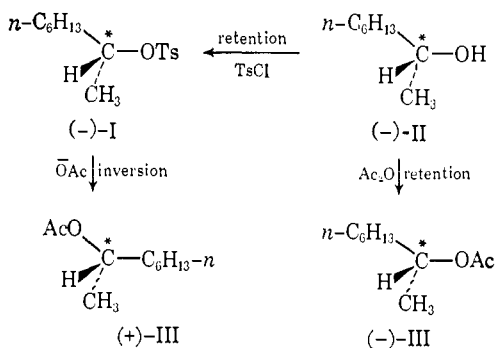
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**Abstract:** Principles, properties, and graphic representations are described for stereochemical reaction cycles which involve interconversions of compounds with four ligands tetrahedrally attached to a chiral center. Geometric figures are developed that allow all possible two-, three-, and four-reaction stereochemical reaction cycles to be classified and mapped. One class of a five-reaction cycle is also covered. General methods are reported that permit higher order stereochemical reaction cycles to be treated. Examples that illustrate types of reaction cycles are cited.

The concept and many examples of the stereochemical reaction cycle were introduced to organic chemistry by Walden<sup>3,4</sup> in connection with his discovery of the Walden or optical inversion. In the following 40 years many new examples of stereochemical reaction cycles came to hand, and much effort was devoted to establishment of the relative configurations of the compounds involved in the cycles. Of these the most quoted involves the stereochemical reaction cycle of Phillips and Kenyon<sup>5</sup> (Chart I), which served to

Chart I



demonstrate that the reaction of tosylate (-)-I with acetate ion to give acetate (+)-III occurred with inversion of configuration. Since this early work, stereochemical reaction cycles have been used both to determine the configuration of compounds and to establish the stereochemical course of substitution reactions at

carbon,<sup>6</sup> silicon,<sup>7</sup> phosphorus,<sup>8</sup> and sulfur.<sup>9</sup> Implicit in the evolution of the use of reaction cycles for correlating configurations and steric courses of reactions is the generalization that *in ligand replacement at chiral carbon, an odd number of inversions in a stereochemical reaction cycle must include two enantiomerically related compounds in that cycle.*

In the investigation of stereochemical reaction cycles that involved ligand replacement at chiral sulfur, it became clear that this generalization and others like it applied only to the important case in which all of the compounds of the cycle had three identical ligands.<sup>9a</sup> This paper develops a general analysis of stereochemical reaction cycles that involve four ligands attached to a tetrahedral chiral center. The topology of stereochemical isomerizations<sup>10a,b</sup> and of a blend of isomerizations and stereochemical reaction cycles in phosphonium salts and cognate systems<sup>10c</sup> has been treated previously.<sup>10c</sup> This paper is the first that presents a general analysis of the properties of stereochemical reaction cycles of the nonisomerization variety.

**Principles of Stereochemical Reaction Cycles.** Chiral compounds which possess four different ligands attached tetrahedrally to a central atom<sup>11</sup> can be repre-

(6) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(7) L. H. Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill Book Co., Inc., New York, N. Y., 1965.

(8) (a) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier Publishing Co., New York, N. Y., 1967; (b) G. Kamai and G. M. Usacheva, *Russ. Chem. Rev.*, **35**, 601 (1966); (c) W. E. McEwen in "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, New York, N. Y., 1965, pp 1-41.

(9) (a) D. R. Rayner, D. M. von Schrittz, J. Day, and D. J. Cram, *J. Amer. Chem. Soc.*, **90**, 2721 (1968); (b) M. Axelrod, P. Bickart, J. Jacobus, M. M. Greene, and K. Mislow, *ibid.*, **90**, 4835 (1968); (c) E. Ciuffarin and A. Fava in "Progress in Physical Organic Chemistry," Vol. 6, A. Streitwieser, Jr., and R. W. Taft, Ed., Interscience Publishers, New York, N. Y., 1968, pp 81-109.

(10) (a) E. L. Muetterties, *J. Amer. Chem. Soc.*, **91**, 1636 (1969); (b) E. L. Muetterties, *ibid.*, **91**, 4115 (1969); (c) K. E. DeBruin, K. Naumann, G. Zon, and K. Mislow, *ibid.*, **91**, 7031 (1969).

(11) The scheme may be extended to reactions of other classes of chiral compounds such as five-coordinate and six-coordinate (octahedral) compounds. The present scheme is also applicable to inter-

(1) This investigation was supported by the U. S. Public Health Service Research Grant No. GM12640-05 from the Department of Health, Education, and Welfare.

(2) National Institutes of Health Special Research Fellow, 1969-1970.

(3) (a) P. Walden, *Ber.*, **28**, 1287 2766 (1895); (b) P. Walden, *ibid.*, **29**, 133 (1896); (c) P. Walden, *ibid.*, **30**, 3146 (1897); (c) P. Walden, "Optische Umkehrerscheinungen," Vieweg, Braunschweig, 1919.

(4) (a) F. D. Chattaway and S. Smiles, *Annu. Rept. Progr. Chem.*, **8**, 60 (1911); (b) P. Franklin, *J. Chem. Soc.*, 103, 713 (1913).

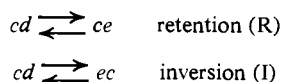
(5) (a) H. Phillips, *ibid.*, **123**, 44 (1923); (b) H. Phillips, *ibid.*, **127**, 2552 (1925); (c) J. Kenyon, H. Phillips, and H. G. Turley, *ibid.*, **127**, 399 (1925).

sented by the four symbols for the ligands. For example, *abcd* represents a compound possessing the four ligands *a*, *b*, *c*, and *d*.<sup>12</sup> The configuration of the compound is also represented in such a listing of ligands by the order of occurrence of the ligands, *i.e.*, *abcd* and *abdc* are enantiomers.<sup>13</sup> It is not always necessary to list all four ligands when reaction cycles are considered, since one or more ligands may remain unchanged upon reaction. Thus, *cd* and *dc* are enantiomers of a tetrahedral compound.<sup>14</sup>

To avoid complications of reaction mechanisms, an operational definition of a reaction is given. A reaction converts one compound into another by a stereospecific process consisting of an experimental step in which a ligand is modified or replaced and for which stereochemistry can be experimentally ascertained. Thus, a reaction can be represented by a single ligand substitution,<sup>15</sup> *i.e.*, *abcd* → *abce* or *cd* → *ce*. Any chemical modification of any part of a ligand is considered a ligand substitution in the scheme.

There are two possible stereochemical outcomes for a ligand substitution reaction, inversion or retention of configuration (Chart II). The terms retention and

Chart II



inversion apply only to the stereochemical outcome of individual reactions. For reasons which will become apparent later, these terms are not used in reference to the "outcome" of a stereochemical cycle.

Reactions may be coupled in sequence to produce reaction chains. A cycle is a closed chain of single ligand substitution reactions which connect compounds such that the number of different compounds is equal to the number of reactions. In this usage, compound does not distinguish enantiomers. Furthermore, the direction of a reaction as indicated by an arrow has no

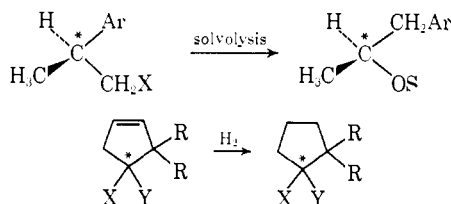
conversions of diastereomers consisting of two or more tetrahedral chiral or prochiral centers since reactions at each center can be treated separately. In this case, epimeric compounds replace enantiomeric compounds in the reaction cycles.

(12) The electron pair of tricoordinate compounds chiral at sulfur or phosphorus is considered to be a "ligand" to render the scheme applicable to this class of compounds. For example, electrophilic substitutions (*e.g.*, oxidations) at tricoordinate sulfur convert the electron pair to another ligand, and reductions of tetracoordinate sulfur generate the electron pair "ligands" from other ligands such as =O and =NH.<sup>9a</sup>

(13) The convention for representation of configuration possesses degeneracy, since a single configuration is represented by twelve equivalent letter sequences. The enantiomeric configuration is represented by another set of twelve equivalent sequences. Thus, *abcd* and *badc* describe the same configuration. In general, an *odd* number of interchanges of the positions of *two* ligands in a sequence generates the opposite configuration, whereas an *even* interchange gives the same configuration. Further restrictions of the convention in practical applications remove some or all of the degeneracy.

(14) A minimum of two ligands must be used to specify relative configuration. Positions of unnamed ligands are assumed identical in each representation, *i.e.*, *cd* and *dc* may correspond to *abcd* and *abdc*, respectively.

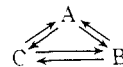
(15) Simultaneous double ligand substitutions do exist, *e.g.*



The scheme can be readily adjusted to accommodate such cases.

special significance in this treatment. Forward or reverse directions are equivalent. Usage of the term reaction is restricted to conversions in either direction ( $\rightleftharpoons$  in this context signifies only one reaction) of compounds adjacent to one another (*e.g.*, in a chain). Chart III illustrates a generalized reaction cycle com-

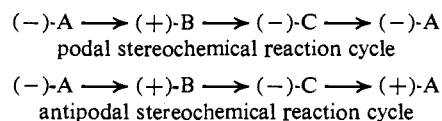
Chart III



posed of three compounds and three reactions.

A stereochemical reaction cycle is a cycle in the above sense in which all compounds are chiral and all reactions are stereospecific. There are two classes of stereochemical reaction cycles. Although the number of compounds and reactions are always equal for all cycles, the number of chiomers<sup>16</sup> may either equal the number of reactions or may exceed the number of reactions by one. The first class of cycle, in which only one enantiomer of each compound is included, is termed podal.<sup>17</sup> The other class of cycle is termed antipodal, in which both enantiomers (or both antipodes) of one of the compounds occur in the cycle. Chart IV illus-

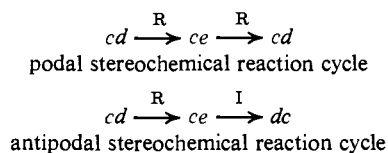
Chart IV



trates both cases for hypothetical stereochemical reaction cycles corresponding to the simple reaction cycle of Chart III. As depicted, the podal cycle begins and ends upon the same chiomer, whereas the beginning and ending chiomers of the antipodal cycle are enantiomers.

Chart V illustrates podal and antipodal stereochemical cycles of two reactions in terms of the ligand notation developed above.

Chart V



There are four general types of reaction cycles which are distinguished by the number of static ligands within the cycle. A static ligand is one which is common to all compounds of a cycle. Thus, in Chart V, *c* is a static ligand (so also are the two implied ligands, *a* and *b*). A reaction cycle in which three ligands are static is termed a triligostat. Triligostatic cycles are most often encountered in the literature. The other three types of cycles are diligostatic (two static ligands common to all compounds), moniligostatic (one static ligand), and aligostatic (no static ligands). In these latter types of cycles, in which less than three ligands are static, appar-

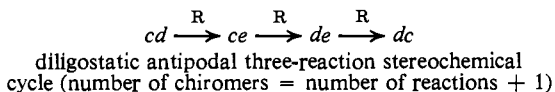
(16) The term enantiomer names one of a pair of substances configurationally related as mirror images. Chiomer here denotes any member of a set of chiral compounds related to one another by chemical interconversions. Both chiomers of an enantiomeric pair may be included in such a set. When prochiral compounds are involved in stereochemical reaction cycles, the term prochiromer might be used in place of chiomer.

(17) From the Greek *podos* meaning foot and applied in analogy to the term chiral derived from the Greek *cheir* meaning hand.

ent violations are found of the classical rule that an even number of inversions in a reaction chain gives product of overall retained configuration, whereas an odd number gives product of the enantiomeric configuration.

The simplest ligostat in which an even number (zero) of inversions for individual reactions produces an antipodal stereochemical reaction cycle is that of Chart VI.

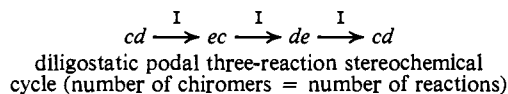
Chart VI



An essential feature of such a cycle is that in the overall conversion of  $cd$  to  $dc$ , the positions on the tetrahedron of ligands  $c$  and  $d$  have been interchanged although none of the reactions occur with inversion of configuration. Thus, a ligand originally present in the initial compound but replaced in the first reaction ( $d$ ), in the second reaction replaces another original ligand ( $c$ ). The freed ligand ( $c$ ) subsequently substitutes at the position on the tetrahedron originally occupied by the first ligand ( $d$ ). Thus, the reactions of Chart VI go with retention of configuration, and yet the final product possesses a configuration enantiomeric to that of the starting material.

The simplest ligostat in which an odd number of inversions (three) for individual reactions produces a podal stereochemical reaction cycle is that of Chart VII. In this cycle three reactions that occur with in-

Chart VII



version allow starting material of the same configuration to be regenerated. Thus, an odd number of inversions reproduces the starting chiomer.

The cycles of Charts VI and VII have the property in common that in the first reaction of each cycle,  $e$  replaces  $d$ ; in the second,  $d$  replaces  $c$ ; in the third,  $c$  replaces  $e$ . This overall interchange of ligands ( $c$  and  $d$ ) is independent of the stereochemical course (R or I) of the particular reactions that participate in the interchange. In both reaction cycles the ligands  $c$  and  $d$  are both replaced at one stage or another, and are absent from certain chiomers. When a pair of ligands interchange at a pair of bonds attached to a chiral tetrahedron by a series of ligand substitution reactions that involve each ligand leaving the molecule at some stage, that process will be called a ligand metathesis, or an LM. Clearly, an LM must be a property of a reaction cycle rather than of a particular reaction, and the minimum-sized cycle that can contain an LM involves three reactions.<sup>18</sup>

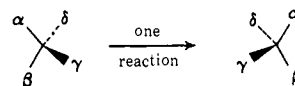
Both stereochemical cycles of Charts VI and VII contain one LM. The inclusion of an LM in a stereochemical reaction cycle has the same effect on the number of chiomers of the cycle as does the reversal of the stereochemical course of any single reaction. For example, if a stereochemical cycle involves two I's

(18) The condition that each of the two ligands must leave the molecule at some stage is necessary to the definition. Otherwise, the cycle,  $cd \rightarrow ce \rightarrow dc$ , would involve an LM, an R, and an I, and yet be antipodal. Modification of a ligand (e.g., acetylation of a hydroxyl group) is the equivalent of the ligand (e.g., the hydroxyl) leaving the molecule.

and no LM, the cycle is podal. If a cycle contains an LM and one I, it is also podal; but a cycle with two I's and one LM or three I's and no LM is antipodal.

The difference between a direct tetrahedral inversion and a ligand metathesis, as well as the characteristics of each, are illustrated as follows. In a tetrahedral inversion, attention is directed to the changes in relative positions of the bonds as a consequence of a single stereospecific reaction. Only a single ligand need be replaced (or modified) in a direct tetrahedral inversion.

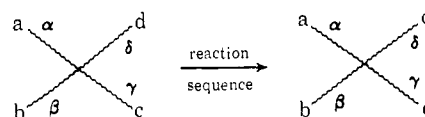
tetrahedral inversion



( $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  are labeled bonds (not ligands) arranged tetrahedrally around a chiral center)

On the other hand, in a ligand metathesis attention is directed to the interchange of two ligands between two bonds, irrespective of the movement of the bonds themselves. The ligand metathesis is caused by a minimum

ligand metathesis



( $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  are bond labels;  $a$ ,  $b$ ,  $c$ , and  $d$  are ligand labels; note that  $c$  and  $d$  exchange bonds,  $\gamma$  and  $\delta$ )

of three consecutive reactions, each of which may occur with either retention or inversion. At least two ligands must be removed and replaced during the reaction sequence.

The above principles may now be applied to establish the symmetry properties of a stereochemical reaction cycle of any length or type. In our definition of a stereochemical reaction cycle, only one set of enantiomers could be included among the chiomers. This fact in itself limits the number of LM's in a cycle to either 0 or 1, the former being an even and the latter an odd number. *When the sum of the number of I's and LM's in a cycle is even, the cycle is podal. The cycle is antipodal if the sum is odd.*

More complex closed reaction chains that contain more than one set of enantiomers can be imagined. These reducible cycles can always be divided into two or more ordinary reaction cycles that satisfy the condition that the number of reactions equals the number of compounds. For example, the reducible cycle  $cd \rightarrow ce \rightarrow cf \rightarrow ec \rightarrow dc$  contains the ordinary cycle  $ce \rightarrow cf \rightarrow ec$  with the reactions  $cd \rightarrow ce$  and  $ec \rightarrow dc$  left over. The existence of reaction  $ec \rightarrow dc$  makes the reaction  $ce \rightarrow cd$  predictable, and the combination of  $cd \rightarrow ce$  and  $ce \rightarrow cd$  provides the second full reaction cycle,  $cd \rightarrow ce \rightarrow cd$ .

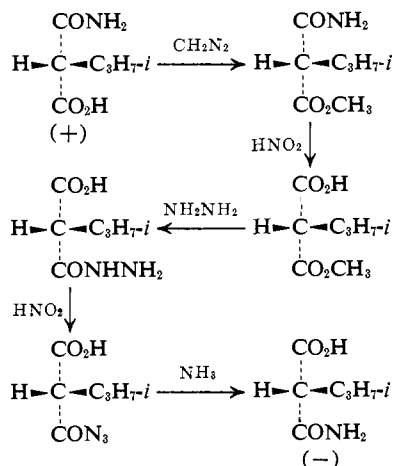
A special significance is attached to those podal cycles that contain an even number of I's, and those antipodal cycles that contain an odd number of I's. Such cycles are consistent with the classical concept that in a stereochemical reaction cycle, an even number of I's does not involve enantiomers, but an odd number of I's does involve enantiomers somewhere in the cycle. Podal cycles that contain an odd number of I's and antipodal cycles that contain an even number of I's

Table I. General Properties of Full Complements of Stereochemical Reaction Cycles of Different Sizes<sup>a</sup> and Types

Property	Trilogostat	Dilogostat	Monologostat	Aligostat
Minimum cycle size	2	3	4	5
Substitutable ligand positions	1	2	3	4
Maximum number of substitutable ligands <sup>b</sup>	$x$	$x$	$x$	$x$
Maximum number of chiomers	$2x$	$x(x - 1)$	$1/3x(x - 1)(x - 2)$	$1/12x(x - 1)(x - 2)(x - 3)$
Number of allowed reactions <sup>c</sup>	$2x(x - 1)$	$2x(x - 1)(x - 2)$	$x(x - 1)(x - 2)(x - 3)$	$1/8x(x - 1)(x - 2)(x - 3)(x - 4)$

<sup>a</sup> The cycle size in terms of number of reactions in a single cycle is  $x$ . <sup>b</sup> All ligands involved in substitutions. <sup>c</sup> Direct enantiomer interconversions and simultaneous multiple ligand substitutions are excluded (see text).

involve one LM. These types of cycles usually were not taken into account in the classical concepts.<sup>19</sup>



**Properties of Stereochemical Reaction Cycles.** An examination of the properties of stereochemical reaction cycles requires that a systematic procedure be established for generation of all different cycles of possible interest. Certain characteristics of the cycles, which are employed in the generation procedure, will be described first.

A stereochemical reaction cycle is characterized according to *size* by the number of reactions (equals compounds) involved in its generation. Also each type of cycle (tri-, di-, mono-, and aligostats) has a characteristic minimum size, and cannot exist with fewer reactions. Substitutions at the requisite number of tetrahedral positions (e.g., two positions for the dilogostat) can be accomplished with a specific minimum or a greater number of reactions. For example, a dilogostat of minimum size (three reactions) is found in Chart VI.

Another characteristic of a stereochemical reaction cycle is the number ( $l$ ) of all replaceable ligands entering or leaving the compounds of the cycle. This number of replaceable ligands differs for subcategories of cycle types, and serves as a further way of classifying cycle types.

To describe exhaustively a given size and type of cycle, the maximum number of usable chiomers ( $c$ )

(19) However, the principle of a ligand metathesis was illustrated by E. Fischer and F. Brauns [*Ber.*, 47, 3181 (1914)] and noted by H. Wheland, "Advanced Organic Chemistry," 3rd ed, John Wiley & Sons, New York, N. Y., p 305. Thus, in the stereochemical reaction cycle formulated, no bonds were made or broken to the chiral center, and therefore the ligand replacements all occurred with R. The cycle contains five reactions and six chiomers, and hence is antipodal. Since two ligands are common to all chiomers, the cycle is dilogostatic, and the cycle contains one LM.

and maximum number of allowed reactions connecting the chiomers ( $r$ ) must be determined. The maximum number of different compounds usable in a cycle of given size and type is the number of combinations of these replaceable ligands (such as  $a, b, c$ , etc.) with the substitutable tetrahedral positions (such as  $\alpha, \beta, \gamma$ , etc.). The number of substitutable tetrahedral positions  $s$  is, for example, 1 for trilogostats, 2 for dilogostats, etc. The maximum number of chiomers  $c$  is twice the maximum number of compounds. Equation 1 indi-

$$c = 2({}_lC_s) = \frac{2!}{(l-s)!s!} \quad (1)$$

cates these relationships where  ${}_lC_s$  is the symbol for the combination of  $l$  things taken  $s$  at a time. Application of this equation to four-reaction monologostats provides an exhaustive complement of  $2({}_1C_3) = 8$  chiomers (four pairs of enantiomers).

The maximum number of different replaceable ligands ( $l$ ) cannot exceed the number of reactions ( $x$ ) of the cycle. One subcategory of interest for each type of cycle involves a different entering ligand for each reaction. Thus, if all types of cycles are to be represented,  $l = x$ , and  $c = 2x!/[x-s]!s!$ .

The other information required to obtain a full complement of cycles of a given size and type is the total number of allowed reactions usable for connecting the different chiomers. Certain reactions are forbidden. A direct interconversion of enantiomers is forbidden because the reaction involves the stereospecific substitution of one ligand by itself. A stereochemical cycle of only one compound and one reaction does not exist in practice. The entering and leaving ligands are indistinguishable and complete racemization would result.<sup>20</sup>

Another forbidden reaction is the simultaneous substitution of more than one ligand ( $abcd \rightarrow abef$  is disallowed). Such reactions are factored into a sequence of single ligand substitutions. The maximum number of allowed reactions for a particular chiomer for the cycle type having  $s$  substitutable positions and cycle size  $x$  is  $2s(x-s)$ .<sup>21</sup> Multiplication of  $2s(x-s)$  by  $c$ , the number of chiomers, and division of this product by two to eliminate reactions which are counted twice give the maximum number of allowed reactions,

(20) A ligand labeled so as to be distinguishable from its substitutional partner is considered a different ligand in the scheme.

(21) For example, for  $s = 3$  and  $x = 4$  ( $b, c, d$ , and  $e$  are replaceable ligands), chiomer  $bcd$  may go to  $bce, bed, ecd$ , or their mirror images for a total of six reactions. In the general case, only substitutions of any one of the  $s$  substitutable positions by the remaining  $(x-s)$  ligands are allowed. The resulting configuration may be retained or inverted, so that the number of allowed reactions for one chiomer is  $2s(x-s)$ .

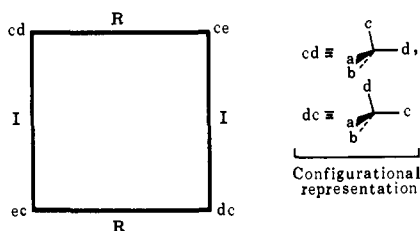


Figure 1. Graphical representations of two-reaction stereochemical cycles involving compounds with four different ligands attached to a tetrahedral chiral center.

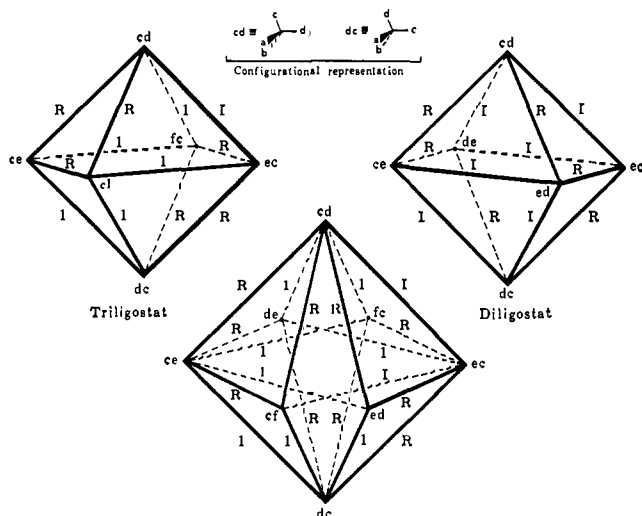


Figure 2. Graphical representations of three-reaction stereochemical cycles involving compounds with four different ligands attached to a tetrahedral chiral center.

$r$ , as is indicated in eq 2. Thus, eq 1 (with  $l = x$ )

$$r = cs(x - s) = 2s(x - s)_x C_s = \frac{2s(x - s)x!}{(x - s)!s!} \quad (2)$$

specifies the number of points (each representing a chiomer) which are connected by the number of lines (reactions) given by eq 2 for a specified cycle size  $x$  and cycle type  $s$ . Table I summarizes the properties of full complements of cycles of the four types.

Table II summarizes generalizations regarding the possible presence or absence of a ligand metathesis

Table II. Ligand Metatheses Present in Full Cycles

Cycle size	Cycle type			
	Triligostat	Diligostat	Monoligostat	Aligostat
2	Zero LM	$a$	$a$	$a$
3	Zero LM	One LM	$a$	$a$
4	Zero LM	Zero LM and one LM	Zero LM	$a$
5	Zero LM	Zero LM and one LM	Zero LM and one LM	One LM
6	Zero LM	Zero LM and one LM	Zero LM and one LM	Zero LM and one LM

<sup>a</sup> The number of reactions is below the minimum required for the cycle type.

(LM) for full cycles of different types and sizes. For triligostats of any size no LM process is possible, and an odd number of inversion reactions gives an antipodal

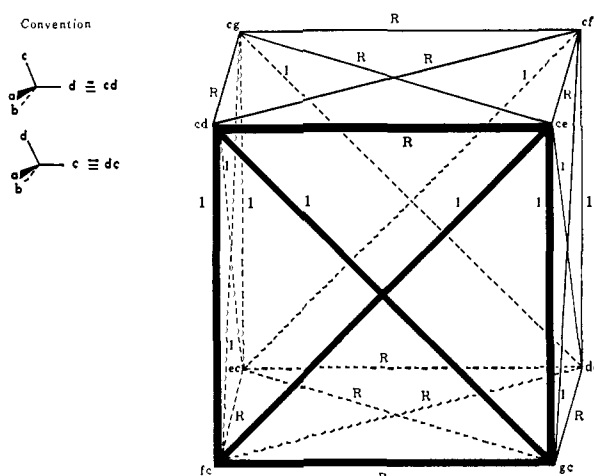


Figure 3. Four-reaction triligostatic cycles.

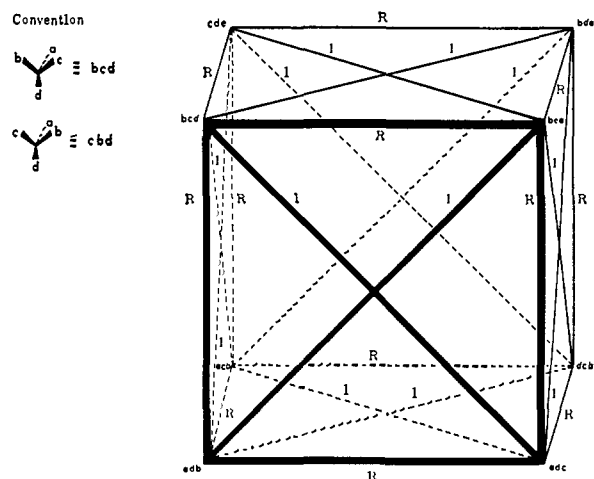


Figure 4. Four-reaction monoligostatic cycles.

cycle. The three-reaction diligostats and five-reaction aligostats each must possess an LM except for the four-reaction monoligostat which can be closed only without an LM; the remaining cycles can either contain zero or one LM, depending on which reactions are used.

Full complements for stereochemical reaction cycles of a given size may contain reaction chains corresponding to particular cycles of larger size, but are not exhaustive of any cycle of size larger than  $x$ . However, full complement for cycles of  $x$  size may be exhaustive for cycles of size smaller than  $x$ .

**Graphic Representations.** The ligostats with their full complements of reactions are best visualized with the aid of maps of alternate reaction pathways for each cycle size and type. Simple graphic representations are found to correlate all two- and three-reaction cycles (Figures 1 and 2). In these polyhedra the apexes represent the chiomers ( $c$  in number) and the reactions the edges ( $r$  in number). The number of edges leading from each apex is equal to  $2s(x - s)$  ( $x$  is the cycle size and  $s$  the substitutable positions). Four-reaction cycles are too complex to handle on a strictly similar basis. However, nonplanar graphs in the form of cubes (the three-dimensional graphs could be distorted so that lines connecting the apexes would not intersect) are used in Figures 3 and 4 to depict four-reaction cycles.

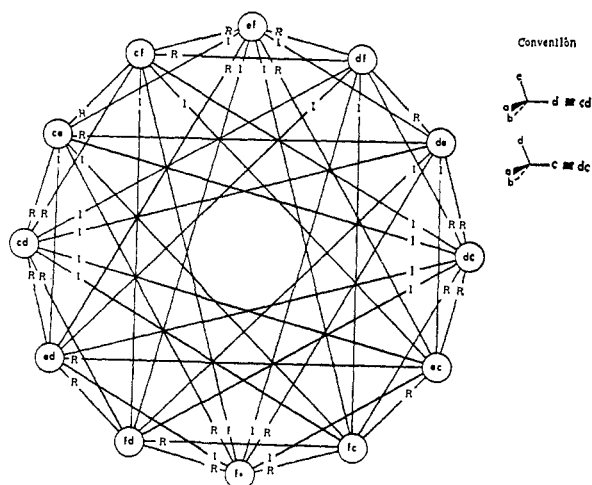


Figure 5. Stereochemical cycles, exhaustive for two- and three-reaction triglostic and for three- and four-reaction diligostic cases, and illustrative for five- and six-reaction diligostic cases.

Here apexes represent chiromers ( $c$  in number), lines connecting the apexes are reactions ( $r$  in number), and the number of connecting lines converging on one apex is  $2s(x - s)$ . In Figures 5 and 6, nonplanar graphs projected onto a plane were found to be clearer than polygons. In these figures the circles represent chiromers ( $c$  in number), the lines connecting the circles represent reactions ( $r$  in number), and the number of connecting lines converging on one circle is equal to  $2s(x - s)$ . The fact that many of the connecting lines of Figures 3-6 intersect in these planar projections has no significance.

Figure 1 contains a generalized polygonal representation of all combinations of two-reaction stereochemical cycles. The chiromers are named in terms of the ligands ( $a, b, c, d$ , or  $e$ ) attached to the chiral center. In the reactions of the cycle, ligand  $d$  is exchanged for  $e$ , or  $e$  for  $d$ , and  $a, b$ , and  $c$  remain the same. In the polygon the chiromers are specified as  $cd, dc, ce$ , or  $ec$ , depending on which ligands they contain and on their configuration. The figure indicates the convention used to indicate configuration. Each reaction occurs with either retention or inversion of configuration, which is indicated by placing an  $R$  or an  $I$  beside the lines that represent reactions in the polygon.

Only two types of three-reaction stereochemical cycles can be closed, and are generalized in the polyhedra of Figure 2. In the triglostic cycle only one ligand in any compound is substitutable (e.g.,  $d, e$ , or  $f$ ), and the other three ( $a, b$ , and  $c$ ) are common to all compounds of the cycle. For example, in the cycle,  $cd \rightarrow ce \rightarrow cf \rightarrow cd$ ,  $d$  is substituted by  $e$  in the first reaction,  $e$  by  $f$  in the second, and  $f$  by  $d$  in the third. In the diligostic cycle, two ligands ( $c$  and  $d$ , or  $d$  and  $e$ , or  $c$  and  $e$ ) of the four are substitutable, and two ligands ( $a$  and  $b$ ) are common to all compounds of the cycle. The substitutable ligands (e.g.,  $c$  and  $d$ ) must be substituted in the following order if the cycle is to be closed,  $cd \rightarrow ce \rightarrow de \rightarrow cd$  (no configuration implied). In the first reaction,  $e$  replaces  $d$ ; in the second,  $d$  replaces  $c$ ; and in the third,  $c$  replaces  $e$ . The order in which the two last letters appear now will be used to denote configuration as with the two-reaction cycle. The convention used is illustrated in Figure 2.

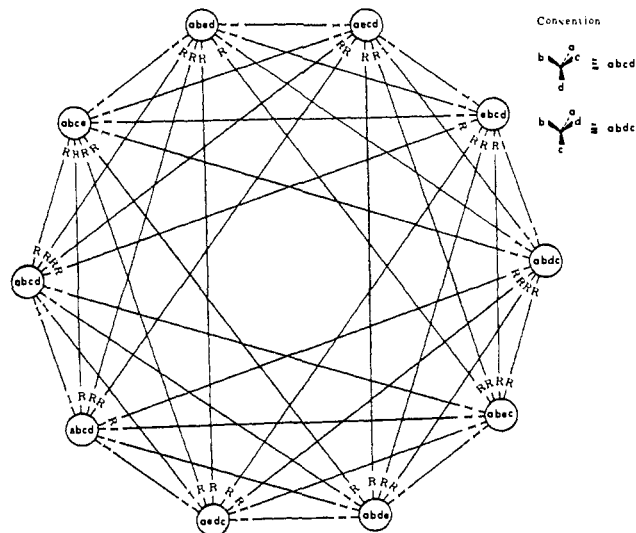
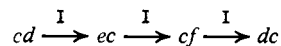


Figure 6. Five-reaction diligostic case.

All possible three-reaction cycles of the triglostic type can be concisely visualized (see Figure 2) through use of a square bipyramid. Again, the letters  $R$  and  $I$  are used to label each reaction. Enantiomers occupy apexes opposite one another in the square bipyramid. The three reactions denoted by any face of the polyhedron only involve three of the six possible chiromers. These triangles of reactions all involve three retentions ( $RRR$ ), or one retention and two inversions ( $RII$ ), and are podal.

To close a three-reaction triglostic cycle that includes enantiomers (antipodal), the path must involve three edges, two of which are not common to the same triangle and one of which is common to two triangles. These cycles all involve four chiromers and three reactions that go with three inversions ( $III$ ), or one inversion and two retentions ( $RRI$ ). A generalized example of the former is the sequence



All possible three-reaction cycles of a diligostic variety are summarized in the second square bipyramid of Figure 2. Enantiomers occupy apexes opposite one another on the polyhedron. The three reactions denoted by any face of this bipyramid only involve three of the six possible chiromers, and denote podal cycles. These triangles of reactions involve three inversions ( $III$ ), or one inversion and two retentions ( $IRR$ ). A generalized example of  $III$  is  $cd \rightarrow ec \rightarrow de \rightarrow cd$ . A generalized example of  $IRR$  is  $cd \rightarrow ec \rightarrow ed \rightarrow cd$ . Specific examples of many of these cycles are illustrated in the next section.

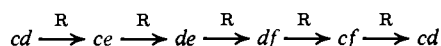
To close a stereochemical three-reaction antipodal diligostic cycle, the path must involve three edges, two of which are not common to the same triangle and one of which is common to two triangles. These cycles all involve either three retentions ( $RRR$ ), or two inversions and one retention ( $IIR$ ). A generalized example of the former is  $cd \rightarrow ce \rightarrow de \rightarrow dc$ , and of the latter is  $cd \rightarrow ec \rightarrow de \rightarrow dc$ . All such cycles involve four of the six apexes of the polyhedron.

The two square pyramids of Figure 2 have four of their six chiromers in common, and have been merged

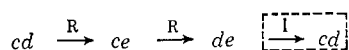
to form a hexagonal bipyramid, which is also included in Figure 2. This polyhedron has eight possible chiroomers at the eight apexes, and again opposite apexes are occupied by enantiomers. This hexagonal bipyramid can be used for the same purposes as the two square bipyramids taken together, since each square bipyramid is included in the hexagonal bipyramid. In all the polyhedra of Figure 2, enantiomers cannot be interconverted by a single reaction. To prevent any of the reaction lines from crossing, the hexagonal bipyramid could be slightly distorted.

Cycles of larger size are less easily represented. Table I indicates that for four-reaction cycles the full complements for triligostatic and moniligostatic types require 8 chiromers and 24 reactions each, and the full diligostat requires 12 chiromers and 48 reactions. It is not possible to build an aligostat with only four reactions (Table II). Figures 3 and 4 are nonplanar graphs in the form of cubes that represent four-reaction cycles of the tri- and moniligostatic varieties, respectively. Each figure possesses a center of inversion of symmetry with respect to both the figure geometry and the configurations of the chiromers.

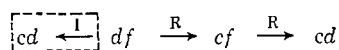
The planar projection of a nonplanar graph in Figure 5 maps the four-reaction diligostatic cycles, and also possesses a center of inversion symmetry with respect to both the figure geometry and the configuration of the chiromers. Figure 5 also contains cycles of smaller size, and is exhaustive for all types of stereochemical reaction cycles up to three reactions. It also contains examples of five- and six-reaction diligostats, but is exhaustive only for the four-reaction diligostats. An interesting example of a five-reaction diligostat of the podal type found in Figure 5 is



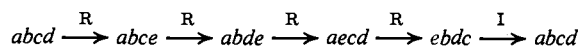
The central chiromers, *de* and *df*, can be visualized as convertible by phantom reactions to *cd* with inversions and this would break the cycle into two podal, three-reaction diligostats, each of which contains one LM and one I, respectively. Finally, Figure 6 provides a planar



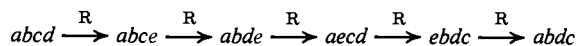
and



projection of a nonplanar graph representing the five-reaction aligostat. Five reactions are the smallest number needed to construct an aligostat. This figure also contains a center of inversion, both with respect to figure geometry and the chiromers that occupy the circles. An example of a podal cycle is



This cycle contains an LM and one I. An antipodal cycle that contains only an LM is



A general answer can be given to the question of what other cycles are included in an exhaustive representation of a cycle of given size and type.<sup>22</sup> An exhaustive

(22) The authors wish to thank A. J. Robson and K. Mislow for this treatment.

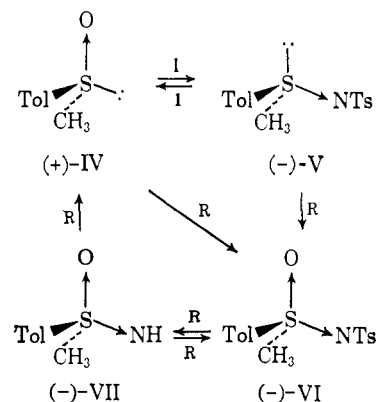
graphic representation for a given cycle of size  $x$  and type  $s$  will be exhaustive for all cycles of size  $x'$  and type  $s'$  when  $s' \geq s$  and  $x' \leq (x + s' - s)$ . This expression is derived as follows. All chiromers of the given cycle contain  $(4 - s)$  static ligands. Therefore, the representation could not be exhaustive for a cycle type with less than  $(4 - s)$  static ligands. Thus,  $s'$  must be less than or equal to  $s$ . The total number of available ligands in an included cycle must not be greater than those for the given cycle. In any cycle the maximum number of substitutable ligands is equal to the number of reactions. Therefore, the number of available ligands in any cycle is equal to the number of reactions plus the number of static ligands (*i.e.*,  $x + 4 - s$ ). In order for a cycle of another size and type to be completely included,  $(x' + 4 - s') \leq (x + 4 - s)$  or  $x' \leq (x + s' - s)$ . Application of this generalization to the five-reaction aligostat representation of Figure 6 indicates the following cycles also are included: two-reaction triligostats, three-reaction diligostats, and four-reaction moniligostats.

**Applications.** Stereochemical reaction cycles sometimes aid in assignment of relative configurations to compounds and in determination of the stereochemistry of substitution reactions. For example, if for reasons of mechanistic analogy all reactions of a three-reaction stereochemical cycle are thought to involve the same steric course, then that course (I or R) is determined alone by the knowledge of whether three or four chiromers are included in the cycle (podal or antipodal cycle) and by whether the cycle is a tri- or diligostat.

In general, knowledge of the number of stereospecific reactions and chiromers and of the number of tetrahedral positions affected by the reactions establishes the cycle size and type. Then, if the number of chiromers equals the size, the cycle is podal; otherwise it is antipodal. This information determines whether an even or odd number of individual reactions goes with inversion. If other knowledge is available concerning the stereochemistry of some of the reactions, the possibilities are narrowed for the steric courses of the remaining reactions. Thus, if the steric courses of all but one reaction are known, then the steric course of that one reaction becomes established, and all configurations are unambiguously related.

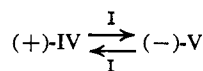
Examples of several stereochemical reaction cycles with sulfur as the chiral center have been reported.<sup>9</sup> Chart VIII<sup>a</sup> provides examples (the electron pair is

Chart VIII<sup>a</sup>

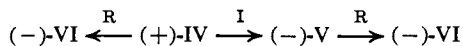


<sup>a</sup> Tol = *p*-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>; Ts = *p*-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>.

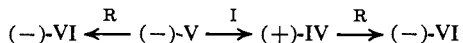
treated as a ligand). The two-reaction cycle



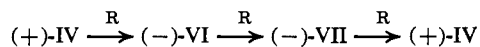
is trilogostatic, podal, and involves two I's. The cycles



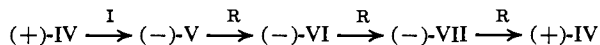
and



are three-reaction diligostats (O, NTs, and : are substitutable ligands) that are podal (one I and one LM). The cycle



is three-reaction, trilogostatic, and podal and involves no LM. The cycle

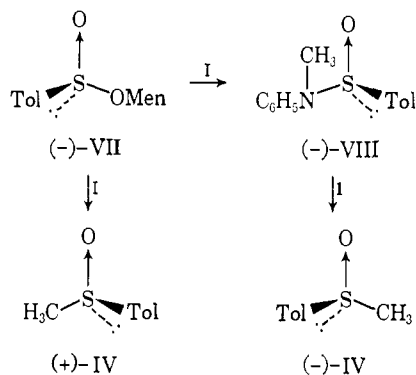


is four-reaction, diligostatic, and podal and contains one LM and one I.

In some cases the field of possible relative configurations and steric courses can be considerably reduced by simply counting the number of chiomers in each cycle. For example, since the two-reaction cycle of Chart VIII involves only two chiomers, the two reactions must either both proceed with retention or both with inversion. The three-reaction cycles of Chart VIII (two in number) that include (+)-IV and (-)-V involve only three chiomers and are diligostats, and therefore the reactions must involve either three inversions, or two retentions and one inversion. The three-reaction cycles of Chart VIII that are trilogostatic involve three chiomers, and therefore the reactions must either all proceed with retention, or with one retention and two inversions.

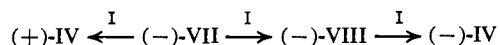
Chart IX provides a different example from sulfur

Chart IX<sup>a</sup>



<sup>a</sup> Tol = *p*-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>; Ts = *p*-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>; Men = menthyl.

chemistry.<sup>23</sup> The sequence

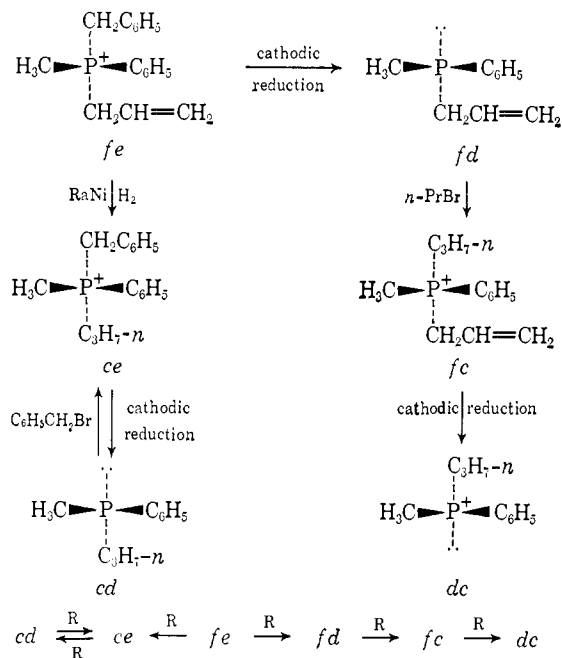


is a three-reaction, trilogostatic, antipodal cycle and contains no LM. The presence of the asymmetric centers in the menthyl group of VII in no way affects the applications of the principles developed above.

(23) A. Nudelman, R. E. Booms, and D. J. Cram, unpublished results; A. Nudelman and D. J. Cram, *J. Amer. Chem. Soc.*, **90**, 3869 (1968).

Of the variety of stereochemical reaction cycles centered around tetrahedral phosphorus, we have selected a diligostatic example.<sup>24</sup> The five reactions of the cycle (Chart X) all go with retention, and the

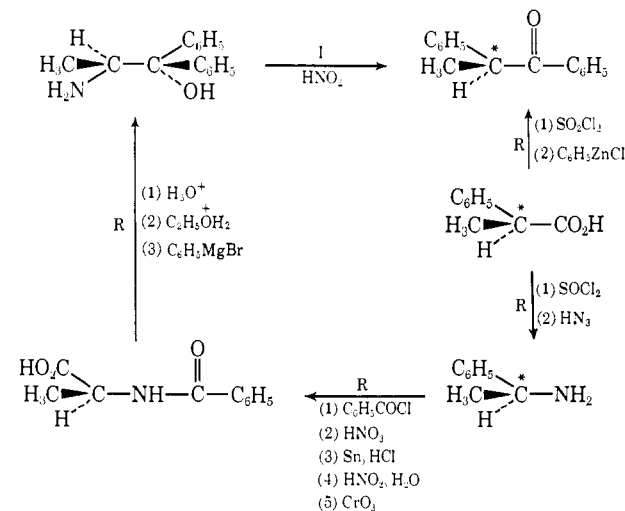
Chart X



cycle is antipodal and contains an LM. The last feature follows from the ligand metathesis intrinsic to the overall process, but which can be abbreviated by the sequence,  $cd \rightarrow fd \rightarrow fc \rightarrow dc$ . An essentially identical cycle also exists that involves a series of organoarsenic compounds.<sup>25</sup>

We could find no example of a stereochemical reaction cycle involving chiral silicon that is other than trilogostatic, although diligostats could undoubtedly be designed. Some of the principles outlined here that

Chart XI



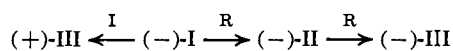
(24) L. Horner, H. Fuchs, H. Winkler, and A. Rapp, *Tetrahedron Lett.*, 965 (1963). See also K. E. DeBruin and K. Mislow [*J. Amer. Chem. Soc.*, **91**, 7393 (1969)] for a good example of a four-reaction, podal, diligostatic stereochemical cycle that contains one R, three I's, and one LM. The authors refer to the symmetry properties of their cycle as "something of a stereochemical curiosity."

(25) L. Horner and H. Fuchs, *Tetrahedron Lett.*, 1573 (1963).



apply to triglostats have been used with great success in silicon chemistry.<sup>7</sup>

Chart I outlines the most quoted example of the Walden inversion cycle



This three-reaction stereochemical cycle is antipodal and triglostatic. A different type of cycle that involves carbon was closed by Bernstein and Whitmore<sup>26</sup> and is illustrated in Chart XI. The cycle is large and

(26) H. I. Bernstein and F. C. Whitmore, *J. Amer. Chem. Soc.*, **61**, 1324 (1939).

is composed of many elegant interconversions such as a semipinacolic deamination<sup>27</sup> and conversion of a phenyl ring to a carboxyl group.<sup>28</sup> This multireaction cycle is podal and diligostatic and contains one I and one LM. Although the deaminative rearrangement is a simultaneous double ligand substitution,<sup>16</sup> the character of the cycle is not affected. The sequence of retention reactions effects a ligand metathesis which may be counted as an additional inversion and results in a podal cycle.

(27) A. McKenzie, R. Roger, and G. O. Wills, *J. Chem. Soc.*, 779 (1926).

(28) W. Leithe, *Ber.*, **64**, 2827 (1931).

## Intrinsic and Torsional Diastereomers. The Optical Purity of (+)-(*S*)-Deoxyephedrine<sup>1</sup>

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Contribution from the Department of Chemistry, Clemson University, Clemson, South Carolina 29631. Received January 6, 1970

**Abstract:** The optical purity of (+)-(*S*)-deoxyephedrine (**1**) has been determined by an nmr method. A combination of intrinsic and torsional diastereomerism, which precludes a reliable determination of the enantiomeric homogeneity of **1** at room temperature, leads to deceptively complex nmr spectra of the *O*-methylmandelamide of **1**. At sufficiently elevated temperatures only intrinsic diastereomerism is observed and the optical purity of **1** can be determined.

Both intrinsic<sup>2</sup> and torsional<sup>3</sup> diastereomerism<sup>4</sup> of amides have been reported; the nuclear magnetic resonance (nmr) consequences of both types of isomerism have been discussed.<sup>2,3</sup> In the determination of the optical purity of (+)-(*S*)-deoxyephedrine (**1**) by an nmr technique<sup>2</sup> both types of isomerism are encountered simultaneously, leading to deceptively complex nmr spectra at room temperature.

Thus, reaction of optically pure (*vide infra*) **1** with optically pure (*S*)-*O*-methylmandelyl chloride (**2**) afforded *N*-methyl-*N*-((*S*)-1-phenyl-2-propyl)-(*S*)-*O*-methylmandelamide (**3**), which exhibited the nmr spectrum depicted in Figure 1. Similarly, reaction of excess optically pure **1** with racemic **2** afforded an equimolar mixture of **3** and its intrinsic diastereomer **4**. The nmr spectrum of this mixture and an expanded scale spectrum of the *C*-methyl ( $\text{HCCH}_3$ ) signals of both samples are depicted in Figures 2 and 3, respectively.

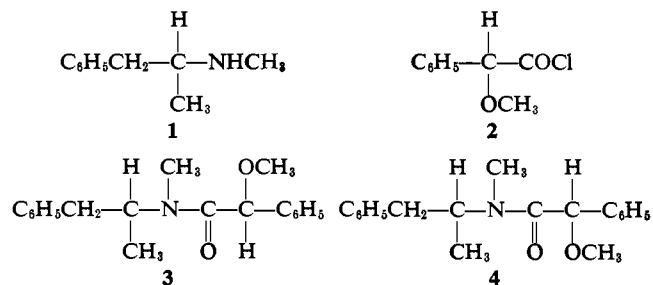
(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) (a) M. Raban and K. Mislow, *Top. Stereochem.*, **2**, 199 (1967); (b) J. Jacobus, M. Raban, and K. Mislow, *J. Org. Chem.*, **33**, 1142 (1968); (c) J. Jacobus and M. Raban, *J. Chem. Educ.*, **46**, 351 (1969).

(3) (a) J. A. Pople, W. J. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 366 ff; (b) Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban, *J. Amer. Chem. Soc.*, **89**, 4910 (1967), and references cited therein.

(4) The extension of the term "diastereomer" to include all stereoisomers which are not enantiomers has been advocated by Mislow.<sup>5</sup>

(5) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, N. Y., 1966, p 50 ff.



### Discussion

In general, the determination of the optical purity of a compound **A** by the nmr technique<sup>2</sup> requires that it be converted to a mixture of diastereomers (**AB/AB**) with a second chiral substance (**B/B**). The nmr spectrum of the resultant mixture of diastereomers generally exhibits "resonance doubling" since the corresponding groups in the compounds in the mixture are diastereotopic by external comparison and, consequently, are anisochronous in the nmr spectrum.<sup>6</sup> If a pure enantiomer **A** is allowed to react with a second optically pure substance **B**, only a single diastereomer (**AB**) is produced and the absence of resonance doubling is indicative of the enantiomeric homogeneity of both **A** and **B**.<sup>7</sup> This technique has recently been discussed<sup>2</sup> and has received wide application.<sup>2,8</sup>

(6) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1966).

(7) This statement is correct if and only if resonance doubling has been demonstrated for an optically impure sample of either **A** or **B**.