

Review

Isolation of rotational isomers and developments derived therefrom

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Abstract: Isolation of rotational isomer models of ethane-type molecules is described. We could experimentally prove that, if rotational isomers whose molecular shape was chiral, the molecule could be optically active, even though it did not carry an asymmetric carbon atom. As an extension, other types of stereochemically fundamental and optically active molecules were isolated and their absolute stereochemistry was determined. One example is the model of *meso*-tartaric acid, for which optical inactivity had been attributed to internal compensation but is now explained as follows. On dissolution of *meso*-tartaric acid in a solvent, the molecule gives two kinds of conformers, one of which is a C_i molecule and the other is a C_1 molecule. Although the latter is intrinsically optically active, the optical activity is cancelled by its enantiomer. The theory of internal compensation is recommended to be abandoned. As an extension to another area, some reactions of conformers are also discussed.

Keywords: stable rotational isomers, stable conformers, chiral conformers, absolute conformation, internal compensation

Introduction

Isolation of rotational isomers, rotamers, conformational isomers, or conformers, at room temperature had been a challenging problem. Though many chemists challenged the problem, it remained unsolved for a long time. The existence of barriers to rotation in ethane was discovered in 1936^{1),2)} and that of rotational isomers became evident in substituted ethanes in 1930–40s.³⁾ We launched a project of isolating stable rotational isomers at room temperature in late 1950s. The objective of the project was two folds. The first was to isolate optically active rotational isomers of model compounds of simple molecules, examining whether chiral conformer could really be optically active, and the second was to prove that the theory of internal compensation, which was developed 130 years ago by Landolt,⁴⁾ was incorrect by isolating optically active rotational isomers of *meso*-tartaric

acid itself or its model compound. However, at the time, when we launched the project, our knowledge about the conditions of isolating rotational isomers such as 1,2-dichloroethane or its model compound was scant. This article is an account of the series of works which have revealed that the models of the simple molecules can indeed be optically active and conformational isomers of a model compound of *meso*-tartaric acid were optically active, thus rejecting the internal compensation theory. In the following discussion, we use *R,S*-tartaric acid and *R*,R**-tartaric acid instead of *meso*-tartaric acid and optically active tartaric acid, respectively, for brevity and clarity. The specification of stereochemistry is that proposed by Cahn, Ingold, and Prelog in 1956,⁵⁾ and its usage is now recommended by IUPAC.⁶⁾

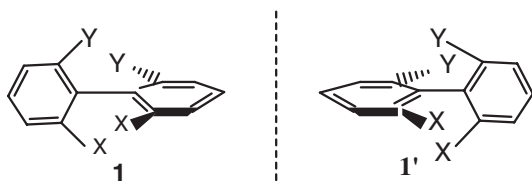
Isolation of rotational isomers

While the barrier to rotation in ethane was said to be ca. 3 kcal/mol (1 kcal = 4.184 J)⁷⁾ and the barrier to rotation required for isolation of rotational isomers, seemed to be much higher than 3 kcal/mol, the way of raising the barrier had been a big question. Only series of compounds, which were known to be separable into rotational isomers, was biphenyl derivatives (**1**).⁸⁾ Compounds **1** and **1'** are mirror

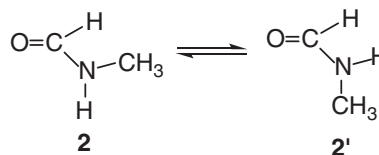
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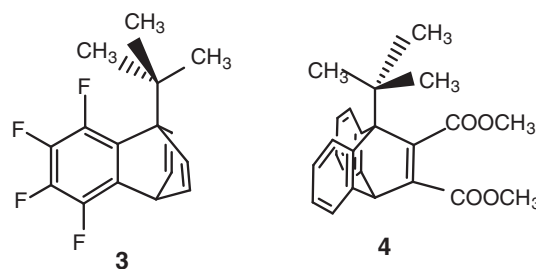
Scheme 1. Optically active biphenyls.

Scheme 2. Rotational isomers of *N*-methylformamide.

images but are not superimposable: They are optical isomers, if isolated.

The results led to a conclusion that the separation of rotational isomers became easier when X and Y were large substituents, and thus it was widely believed that, the bulkier were the substituents X and Y, the easier was the separation of rotational isomers in the case of biphenyls. We followed the general belief at the outset but soon experienced that the bulky substituents did not necessarily raise the barrier to internal rotation in the case of aliphatic compounds. The dynamic NMR technique, the study of the line shapes of NMR spectra at various temperatures, was introduced to organic chemistry in late 1950s.⁹⁾ The new technique provided us useful information for understanding necessary conditions for isolation of rotational isomers: It provided information about not only the estimate that the minimum barrier to rotation should be ca. 23.5 kcal/mol,^{10,11)} for isolating the rotational isomers at room temperature, but also factors which could enhance the barrier as well as those which could reduce the barrier. In these studies, *N*-methylformamide (**2**) was found to show that the barrier to rotation for the process **2'**→**2**, was 20.6 kcal/mol¹²⁾ which was close to the minimum requirement of 23.5 kcal/mol for isolation of the rotational isomers at room temperature. As the consequence, rotational isomers of several amides, including *N*-benzyl-*N*-methylformamide,¹³⁾ were obtained as stable entities at ambient or a little lower than ambient temperature.¹³⁾

In 1967, Brewer, Heaney, and Marples published a brief report that they were able to add tetrafluorobenzene to *tert*-butylbenzene.¹⁴⁾ The *tert*-butyl protons of the adduct (**3**) showed that their line-shapes of ¹H NMR spectra were temperature dependent. We calculated the barrier to rotation of the *tert*-butyl group by using the coalescence method. The barrier was ca. 20 kcal/mol. Though this barrier height was not high enough for isolation of rotational isomers, we thought that, by modifying the bridges which connected the position 1 of *tert*-butylbenzene

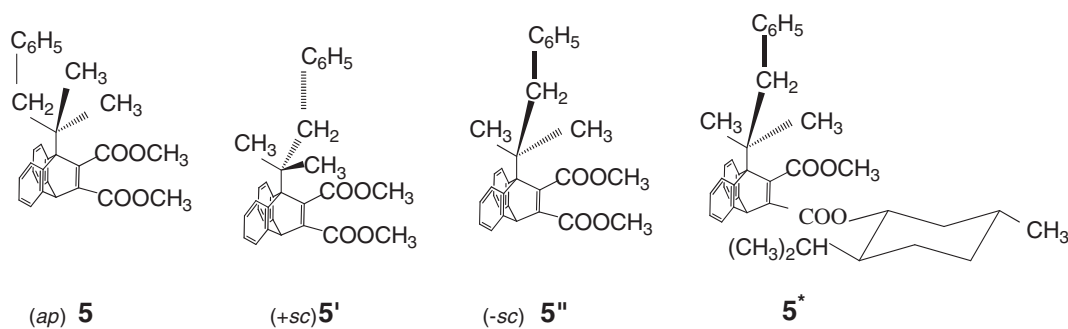


Scheme 3. Compounds which showed hopeful rotational barriers.

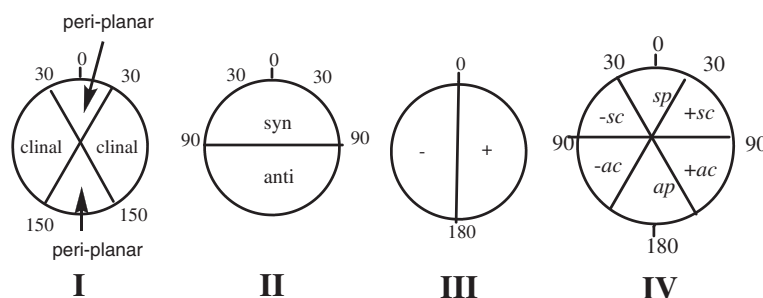
with the position 4 of the same ring, we might be able to raise the barrier to rotation. Thus we prepared compound **4** by treating 9-*tert*-butylanthracene with dimethyl acetylenedicarboxylate.¹⁵⁾ The ¹H NMR spectrum of the product showed two signals with a 1:2 intensity ratio for the methyl protons of the *tert*-butyl group. The split methyl signals survived even at 132 °C. Calculation of the barrier to rotation in this compound showed that it was higher than 25 kcal/mol.

In order to make the presence of rotational isomers possible, it is necessary to mark one of the methyl groups in the *tert*-butyl. We introduced a phenyl group to one of the methyls of the *tert*-butyl group in **4**. Thus compound **5** was prepared by addition of dimethyl acetylenedicarboxylate to 9-[(1,1-dimethyl-2-phenyl)ethyl]-anthracene.¹⁶⁾

In principle, three rotational isomers (**5**, **5'**, and **5''**) of **5**, an *ap*-isomer **5**, a +*sc*-isomer **5'**, and a -*sc*-isomer **5''** are possible. The specification of conformations employed here is that proposed by Klyne and Prelog¹⁷⁾ and its usage is now recommended by IUPAC.⁶⁾ Indeed, chromatographic treatment of the reaction product afforded two fractions. One fraction in chromatography showed a ¹H NMR spectrum in which two methyl groups as well as the benzylic methylene protons in the 9-substituent were equivalent and the other showed the methyl groups as well as the benzylic methylene protons in the 9-substituent were nonequivalent. The features of the ¹H NMR spectrum of the first-mentioned eluent were consistent with structure **5** because it possesses a plane



Scheme 4. First example of which rotational isomers were separately isolated.



Scheme 5. Division of circles for the Klyne-Prelog convention.

of symmetry (the plane of the paper) and with that the isomer is a C_s symmetry molecule. Whereas the spectral features of the second-mentioned fraction were consistent with structures **5'** and **5''**, these being enantiomers with each other, and being expected that these were optically active isomers. The mixture of **5'** and **5''** was hydrolyzed with a potassium hydroxide solution and the resulted carboxylic acid was converted to its *l*-menthyl ester. Upon treatment of the product with petroleum ether, one isomer crystallized¹⁸⁾ which was submitted to X-ray crystallographic analysis.¹⁹⁾ The compound was found to contain the *l*-menthyl group in the less hindered site and, because the stereochemistry of the *l*-menthyl group was known, it was possible to know the sense of the C—C bond rotation which connected the 9-substituent with the 9,10-dihydro-9,10-ethenoanthracene skeleton: It was the rotation about the bond in question anticlockwise, as will be described

later in this account. The *l*-menthyl group was removed by hydrolysis and the produced carboxylic acid was converted to the corresponding methyl ester. The methyl ester thus obtained, using *l*-menthol, must have the structure (*-sc*)-**5''**. The original mixture of **5'** and **5''** was treated similarly, this time with the use of *d*-menthol.¹⁹⁾ The product was confirmed to be related to (*+sc*)-**5'**, after hydrolysis followed by methylation. The sequence of treatments of the product established that the structure of the compound here was undoubtedly (*+sc*)-**5'**. Now it is possible to measure specific rotations of **5'** and **5''**. Thus it became possible to correlate the sense of rotation about the pivot bond, that connects the 9-substituent with the 9,10-dihydro-9,10-ethenoanthracene skeleton, with the specific rotation.*,¹⁹⁾

It will be worthwhile to mention briefly here about the Klyne-Prelog convention for specification of conformation for the readers who are not familiar with this convention. According to the Klyne-Prelog convention, the conformation is specified as a function of dihedral angles. The two planes in question are selected from those involving fiducial groups, the first plane being defined by the bond connecting the fiducial group to the main axis of rotation and the rotational axis, and the second being defined by

* A referee argued that the specific rotation must be indicated that the measurement was made at the sodium D lines. We agree that it is true, strictly speaking. However, it is a normal practice that we use sodium D lines for optical rotation of the plane of polarized light of sodium D lines for measurement of optical rotation of organic compounds. Therefore, we wish to use specific rotation, as it means specific rotation of the plane of polarized light of sodium D lines for brevity and for avoiding redundancy except for one case in "summary".

the bond which connects the other fiducial group to the rotational axis and the rotational axis itself. The first plane is usually assumed to be a reference plane. That is, it is assumed to be at angle 0° . The second plane can be shown in **I** in Scheme 5, by a line which originates at the center of the circle and reaches the circle line, of which relative angle from the reference is determined by the dihedral angle made by the second plane. For the sake of specification, the area of various rotational angles which are meaningful on the stand point of stereochemistry, is classified as are shown in Scheme 5. The numerals around the circles in **I** and **II** are to show angles, which are made by the two planes. The areas of peri-planar and clinal regions are selected as in **I**. The whole area is divided into two, one being on the same side of the reference fiducial group and being called syn, whereas the other part being called anti as in **II**. The right half of the circle is the plus area, because in this convention clockwise rotation is taken as plus and anticlockwise rotation minus. Combining these symbols, we obtain dihedral angle regions, syn-periplanar, anti-periplanar, syn-clinal and anti-clinal. To make the symbols short, acronyms are used and shown by italicized lower case characters (**IV**). Normally, the internally rotational isomers exist as $+sc$ or $-sc$ forms, because in such conformations, molecules are thought stable due to least repulsive interactions. Though theoretically, it is possible that a conformer is stable in $\pm ac$ conformations, we have not encountered this type of conformation throughout our works. The reasons for this are not clear yet.

It may be summarized that, in the Klyne–Prelog convention, the conformation of a conformer is designated by the rotational angle (in degrees), which is needed for the reference plane becomes eclipsing another plane, which involves the bond, that connects another fiducial group to the rotational axis.

Absolute conformation

We are now able to mention that this conformer is dextrorotatory and this conformer is levorotatory. Today a term, absolute configuration, is widely used, because the traditional assignment of stereochemistry of dextrorotatory tartaric acid was shown to be correct, by Bijvoet and collaborators in 1951.²⁰⁾ When the true configuration of an asymmetric center is known, we call the configuration as absolute configuration.

Our results connect the sense of rotation of the plane of polarized light and the sense of rotation about the axis bond. We have proposed that, if an

isolated conformer and any of the optical properties are directly connected with the well defined conformer, the conformation of the conformer be called absolute conformation.²¹⁾ Clearly, if two conformers are in the relation of a body and its mirror image but the two forms are not superimposable, the molecules must be optically active, even in the absence of an asymmetric carbon atom.

For specification of absolute conformation, we recommend the way proposed by Klyne and Prelog¹⁷⁾ and was later recommended by IUPAC,⁶⁾ be used. If the sense of rotation of the pivot bond is clockwise, it is plus rotation and specified by *P*. For example, if the fiducial groups in **5'**, the benzyl group and the etheno bridge which carries two methoxycarbonyl groups have become eclipsed when clockwise (plus) rotation has taken place about the bond, which connects the 9-substituent with the skeleton of 9,10-dihydro-9,10-ethenoanthracene, then the absolute conformation of **5'** is specified by *Psc* and shown as such. If it is anticlockwise (minus) rotation, the anticlockwise rotation is specified by *M*. Thus *M* or *Msc* is used for specification, as *Msc-5'*. Specific rotations of *Msc-5''* and *Psc-5'* forms are -30.4 and $+30.5$, respectively. If one wishes to show sense of specific rotation, it is possible to do so, by adding (+) or (−) sign after *Msc* or *Psc*, as *Psc-(+)-5'* or *Msc-(−)-5''*.

In Scheme 6, is shown an ORTEP diagram of the *l*-menthyl ester **5*** which carries methoxycarbonyl and *l*-menthoxy carbonyl groups. The ORTEP diagram clearly shows that the benzylic carbon, C₁₆, in 9-[(1,1-dimethyl-2-phenyl)ethyl]-11-methoxycarbonyl-12-*l*-menthoxy carbonyl-9,10-dihydroanthracene, is up above the paper plane, and for eclipsing the plane which involves the C₁₁ and C₁₂, and carry the two ester groups, ester groups, anticlockwise rotation of the benzylic fiducial group is necessary. Here the *l*-menthyl group acts as an internal reference of stereochemistry, and the ORTEP diagram should be drawn in the way in which the stereochemistry of the *l*-menthyl group is in conformity with the known absolute configurations of the *l*-menthyl group. The results compel us to conclude that the sense of rotation of the pivot bond is anticlockwise and the absolute conformation of **5*** is *Msc*.

Other systems which afford stable conformers

After the isolation of stable conformers of 9-*tert*-alkyl-9,10-dihydro-9,10-ethenoanthracene skeleton (**5**), we immediately began to use the 9-*tert*-alkyl-

tritycene skeleton for construction of stable conformers, because the basic structures of the triptycenes (**6**) and **5** were alike. The basic skeleton **6** afforded other stable conformers, which provided us useful information on stable rotational isomers.²²⁾

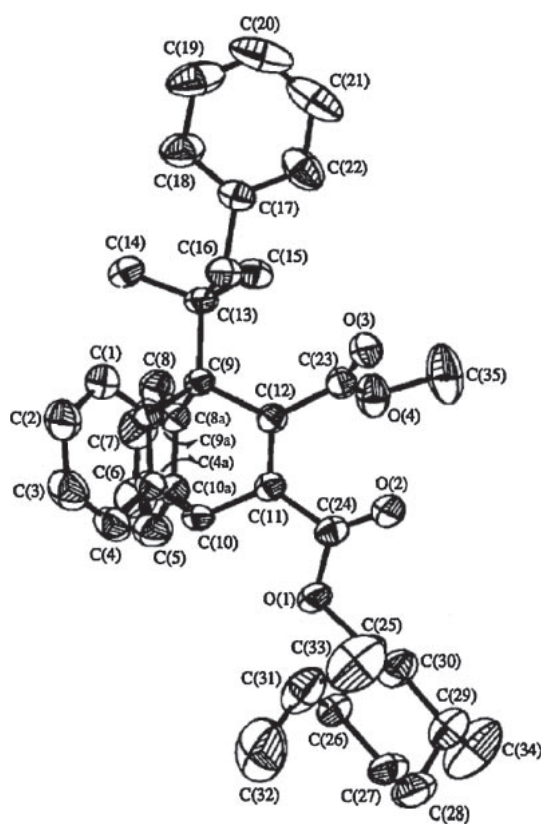
One of the important lessons we learned from triptycenes **6** was that by increasing the bulkiness of the substituent W, we observed the decrease in barrier to rotation in compound **6**, contrary to the hope that the manipulation would increase barrier height. The molecules are congested and the energy of the original state was fairly high. Thus, if we

introduce a bulky substituent, because of the increase in repulsive interactions between the substituent W and the other parts of the molecule, it tends to lower the activation energy for the reaction to form other rotational isomers.²²⁾ Other examples of this sort are also known.²³⁾

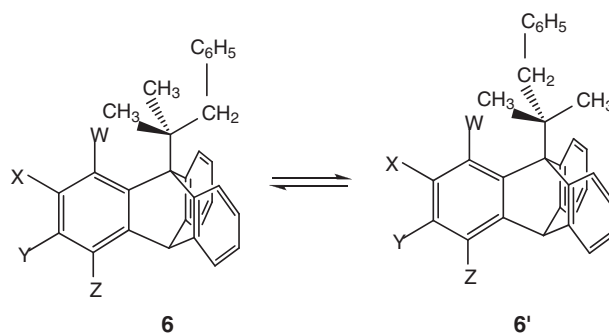
On the other hand, the barrier to rotation in purely aliphatic compounds had become known as the results of development in dynamic NMR spectroscopy: When one connects two modified *tert*-butyl groups at each central carbon atom, the rotational barrier was ca. 10 kcal/mol except special cases.²⁴⁾ Therefore, we decided to abandon the trials of isolating rotational isomers of purely aliphatic compounds.

As a result, we inclined to the use of skeletons like bis[9,10-dihydro-9,10-ethenoanthracenyl], a dimer (**7**) of the lower half of compounds **4** or **5** or bitriptycyl **8** (only one conformer is shown for brevity).

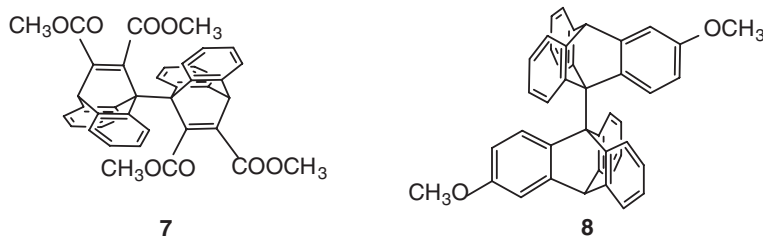
It was just this timing when Schwartz *et al.* published a paper, reporting that they succeeded in isolation of optically active and inactive bitriptycyls (**9**), when the bitriptycyl system carried a methoxycarbonyl group in one of the three benzeno bridges in each triptycyl group. The barrier to rotation was reported to be higher than 55 kcal/mol.²⁵⁾ The very



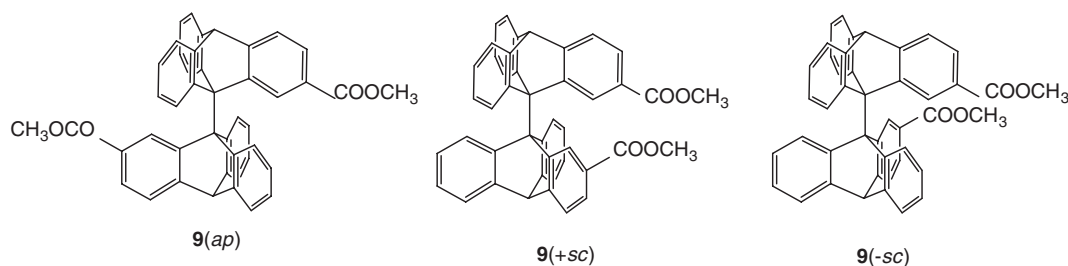
Scheme 6. ORTEP diagram of **5***.



Scheme 7. Isolated rotational isomers of triptycene derivatives.



Scheme 8. Possible skeletons which were expected to provide stable rotational isomers.

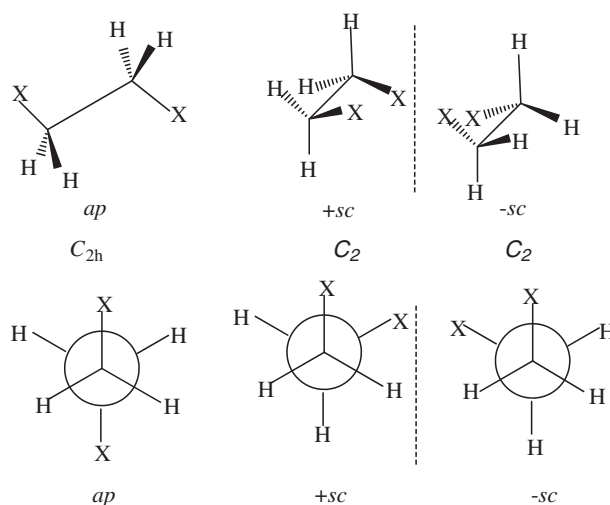
Scheme 9. Bitriptycyls of which rotational isomers were separated by Schwartz *et al.*²⁵⁾

high barrier to rotation in the bitriptycyls was understood by considering the energy of the original state and that of the transition state for the internal rotation. In the original state, the tips of the benzeno bridges in the top triptycyl group are comfortably accommodated in the notches made by the benzeno bridges of the bottom triptycene. And in the transition state for rotation, the tips of the benzeno bridges must pass over the benzeno bridges of the other triptycyl group. Probably, some deformation of the benzeno bridges will be required. This requirement demands also much energy, thus making the free energy for rotation very high.

We thought that the bitriptycyl system, which showed a high barrier to rotation, was an excellent model of ethane derivatives. The reasons for using the bitriptycyls as models of ethane derivatives are at least two folds. Firstly, their constitutions are made basically by connecting two triptycyl groups with a single bond, which is the basic structure of ethane derivatives. Secondly, each triptycyl group carries three benzeno bridges, enabling us to distinguish one benzeno bridge from other benzeno bridges by introducing a substituent to the benzeno bridge. Above all, the triptycyl group can make each benzeno group different from others by introducing appropriate substituent(s) to the benzeno bridge(s). The last feature of the triptycyl group means that each triptycyl group can carry three different substituents, making bitriptycyls excellent models of tartaric acid.

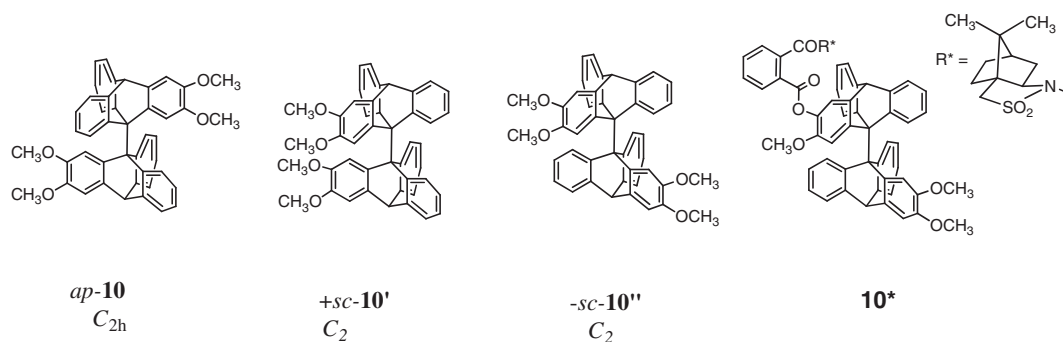
The simplest organic compound which can give rotational isomers by internal rotation is butane or 1,2-dichloroethane. The extended form or the *ap*-form is a molecule of C_{2h} symmetry. Its internal rotation about the C_2 – C_3 axis can form *-sc* or *+sc* isomers, which are expected to be optical isomers. The three dimensional perspective structures and Newman projections of all the possible conformers of the compounds are shown in Scheme 10.

While the C_{2h} form will be optically inactive because of the presence of the plane of symmetry in

Scheme 10. Stereostructures of C_{2h} molecules, butane ($X = CH_3$) and 1,2-dichloroethane ($X = Cl$), and their rotamers in perspectives and in Newman projections.

this molecule, the rotational isomers of the C_{2h} form are C_2 molecules and, as are seen in Scheme 10, one C_2 form and the other C_2 form are in the relation of a real body and its mirror image and are not superimposable. These must be optically active, when isolated.

The model compounds of the rotational isomers of butane or 1,2-dichloroethane can be constructed by considering the following points. In these compounds, one carbon atom carries a unique substituent and two identical substituents, and another carbon atom does the same set of substituents with the aforementioned carbon atom, these two carbon atoms forming the skeleton of the compounds: That is, four identical substituents exist, being divided equally to two carbon atoms, which form the basic skeleton. Considering the requisites of the model formation of butane, we had become aware that compounds **9** which were prepared and separated into each rotational isomer, by Schwartz



Scheme 11. Three rotational isomers of **10**, optically inactive and active, and a compound **10*** used for determination of absolute conformation by Toyota *et al.*²⁶⁾

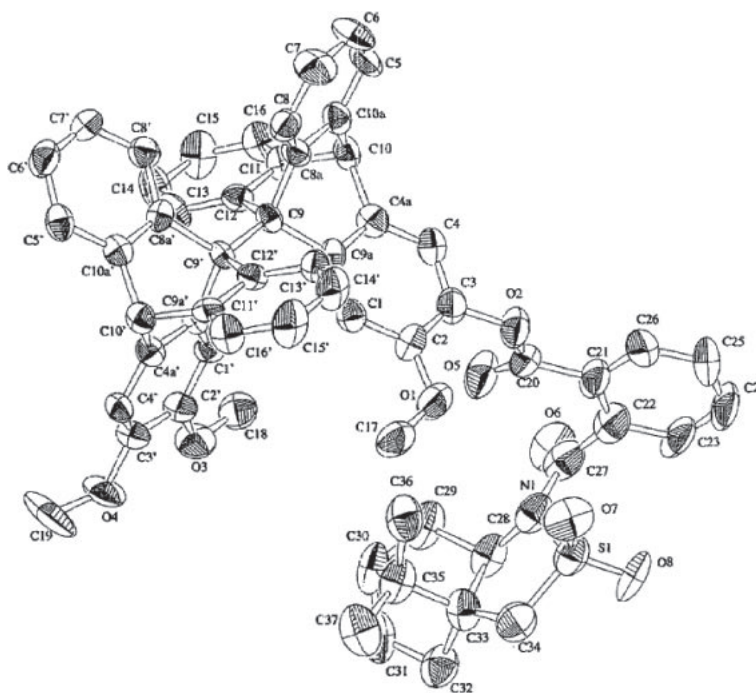
and collaborators,²⁵⁾ fall exactly into this category. However, because these authors were interested only in separation of optically active rotational isomers, and the barrier to rotation, they ignored the significance of isolating conformers of the fundamental compound. We thus decided to prepare the same type of compounds and to point out the significance of isolating rotational isomers of this type of compounds by using other set of substituents. The compounds were **10**.²⁶⁾ Here, the four identical ligands which are connected to two carbon atoms, two each to a carbon atom, are modeled by unsubstituted benzeno bridges because of the convenience of synthesis. We added 4,5-dimethoxybenzoyne to 9,9'-bianthryl to prepare the model compounds. Identification of the fractions of normal chromatography was easily made by considering the symmetry of the molecules, because the C_{2h} form should possess 4 equivalent unsubstituted benzeno bridges, whereas in the chiral forms, two unsubstituted benzeno bridges in one triptycyl group should be nonequivalent. Thus, if we examine ^{13}C NMR, the C_{2h} form should exhibit 12 aromatic C signals, whereas the C_2 forms should show 18 aromatic C signals. In practice, one fraction showed 12 aromatic C signals and another fraction 17 aromatic C signals. The latter fraction was separated by chromatography, using a chiral stationary phase to obtain optically active enantiomers of **10**.²⁶⁾

The absolute conformations of the enantiomers were determined in the following way. One of the four methoxy groups in the racemic (\pm)-**10** was demethylated by using ethanethiolate and the resulted monophenol was converted to *o*-(camphorsultamylcarbonyl)benzoate, the resulted ester was separated, and the better crystallized isomer was submitted

to X-ray structure analysis, which revealed the compound in question was the $-sc$ form. The *o*-(camphorsultamylcarbonyl)benzoyl group was removed by hydrolysis and the resulted phenol was transformed to **10**, and the specific rotation of the $-sc$ -form was confirmed to be -7.6 . The absolute conformation is now known. The $-sc$ form is *Msc*-(-)-**10**,²⁶⁾ the specific rotation of *Psc*-(+)-**10** being $+7.8$.

The results of X-ray crystallography for determination of absolute conformation of **10*** is shown as an ORTEP diagram in Scheme 12. The ORTEP diagram is complicated, because many carbon atoms are involved in construction of this molecule. A brief explanation of the feature of this diagram would help one understand the structure of this compound. The camphorsultam group is shown at the bottom of the diagram. Note that the gem-dimethyl groups are up above the average plane of the camphor moiety to make the stereochemistry of camphorsultam group in conformity with the known stereochemistry. Here, the camphorsultamyl group serves as an internal reference of stereochemistry. We discuss first the stereochemistry of a benzeno group in the left-side triptycene, of which carbon atoms are numbered with a prime, because the conformation of this compound is easily understood by using this benzeno group as the reference plane. The plane in question is a benzeno ring which carries two methoxy groups and is composed of C_1' through C_4' with C_{4a}' and C_{9a}' . Let us call this benzeno group as benzeno ring 1.

The nitrogen atom of the camphorsultamyl group is connected to a benzene ring by a carbonyl, to the ortho of which there is an ester moiety, which connects the benzene ring to a benzeno group, which

Scheme 12. ORTEP diagram of **10***.

is a part of another triptycyl group. The second plane which involves another fiducial group is the benzeno ring, which is composed of C₁ through C₄ with C_{4a} and C_{9a}. This benzeno ring also carries a methoxy group which is attached to C₂. Let us call this benzeno ring as benzeno ring 2. Benzeno rings 1 and 2 are fiducial groups and we may take the benzeno ring 1 as a reference plane. Clearly, for eclipsing the benzeno ring 2, the reference plane, benzeno ring 1, must rotate anticlockwise. This confirms that the conformation of **10*** is *Msc*. Compound **10** which was derived from **10*** had *Msc* conformation.

Models of tartaric acids

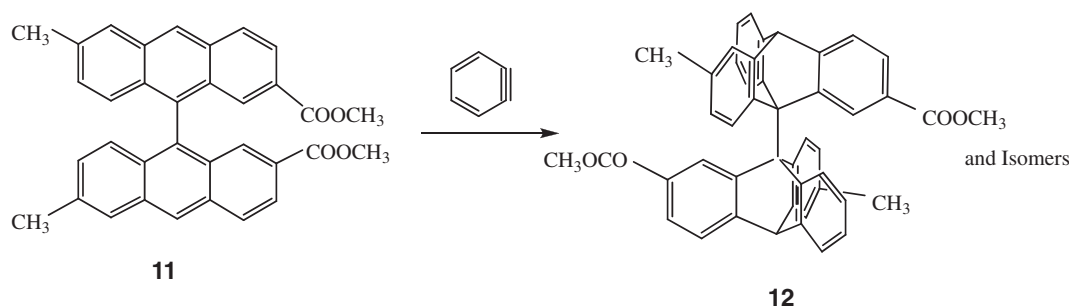
Let us discuss how we construct models of tartaric acid, both *R,S*- and *R*,R**-stereoisomers, using the bitriptycyl skeleton. The structural features of tartaric acid, when they are viewed as ethane derivatives, are that the three substituents are attached to one carbon, none of which is identical with any of the remaining two, while the same set of the three substituents which are attached to one carbon atom are attached to another carbon atom. Therefore, a bitriptycyl derivative, that is composed of a triptycyl group which carries three different benzeno bridges and another triptycyl group which carries the same set of three substituents can be a

valid model of tartaric acid. As already discussed, a triptycyl group can carry three different substituents on three benzeno bridges. We have selected a bitriptycyl **12**, which is composed of the following triptycyls. In one of the triptycyl groups, a benzeno bridge carries a methoxycarbonyl group, another benzeno bridge does a methyl group, and the last benzeno bridge is unsubstituted. In Scheme 13, the method of synthesis of compound **12** is shown, being the Diels–Alder addition of benzyne to a substituted 9,9'-bianthryl **11**.²⁷⁾

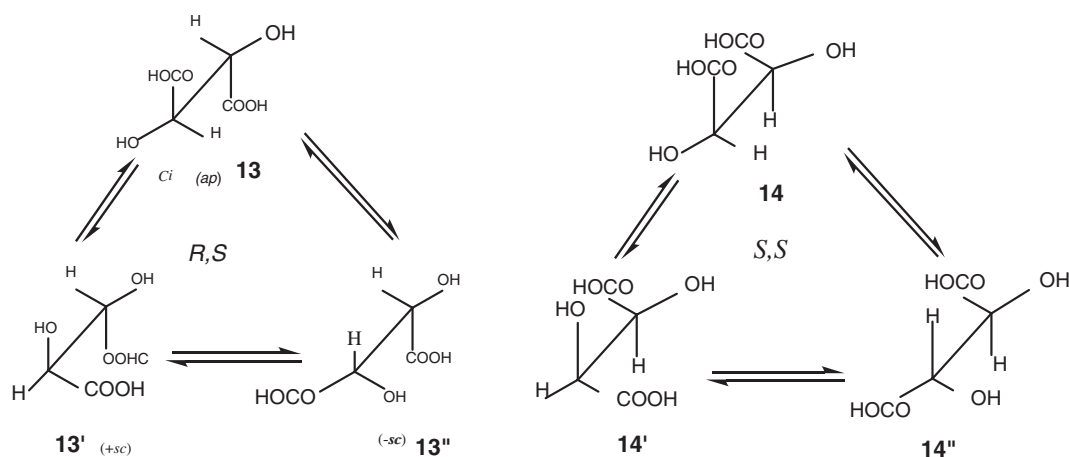
The explanation of optical inactivity of *R,S*-tartaric acid by “internal compensation” by Landolt, seems to be his intuition, because he did not mention on any of the reasons for internal compensation in his book.⁴⁾

In 1930s, the existence of rotational isomers in ethane-type molecules became evident.^{1)–3)} At least two chemists pointed out that the Landolt’s internal compensation theory was in error.^{28),29)} To prove or disprove these proposals, it is necessary to consider the models for optically inactive *R,S*- and optically active *R*,R**-tartaric acids.

The rotational circuits of conformational isomers of tartaric acids are shown in Scheme 14. On the left, are models of the conformers of *R,S*-tartaric acid, and, on the right, are conformers of *S,S*-tartaric acid,



Scheme 13. Synthesis of the model compound of tartaric acid.

Scheme 14. Rotational circuits of *R,S*- and *R*,R**-tartaric acids.

which represent *R*,R**-tartaric acid. Among conformers of *R,S*-tartaric acid, the most important conformer is **13**, which is a C_i molecule, possessing a center of symmetry.

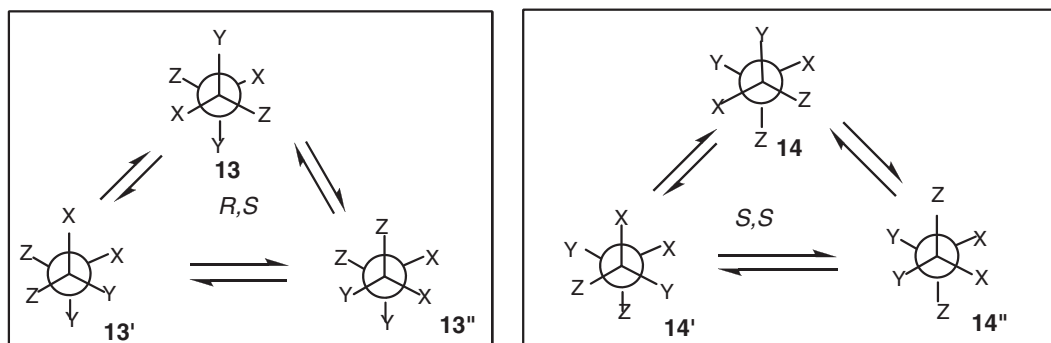
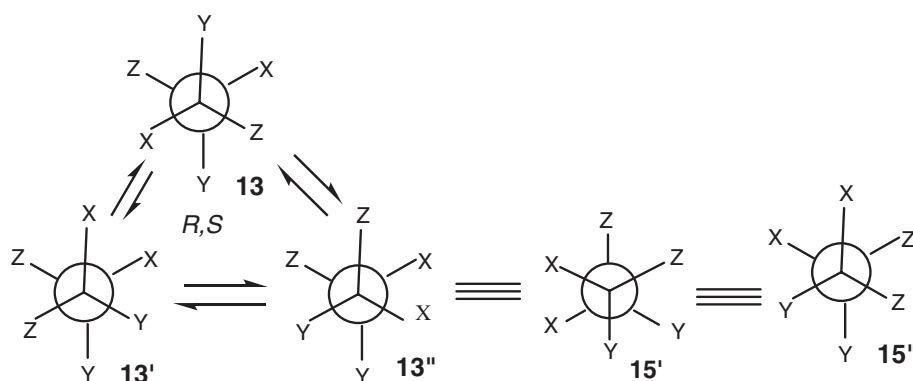
The method of synthesis shown in Scheme 13 inevitably affords not only the models of *R,S*-tartaric acid but also those of *R,R*- or *S,S*-tartaric acid. It is necessary to count the number of isomers that we should obtain by the synthesis, because it shows the number of isomers which we must separate. These conformers will be obtained as independent compounds, because internal rotation is blocked.

For consideration of molecular symmetry, Scheme 14 is a little too complicated. Simplified Newman projections would help one understand symmetry of the molecules. Thus perspective structures in Scheme 14 are transformed to Newman projections in Schemes 15 and 16, in which the substituents are all simplified to single characters. The conformers shown in Scheme 14, will be simplified to those which are shown in Scheme 15, where substituent OH is replaced by X, substituent

COOH is shown by Y and substituent H by Z. By clockwise internal rotation of the front carbon atom in **13** by 120° about the central C–C bond with the configurations of both carbon atoms intact, one gets conformer **13''**. Similarly, one can anticlockwise rotate the front carbon atom in **13** by 120° , while the rear carbon atom is fixed. Then one gets **13'**.

Conformers **13'** and **13''** are C_1 molecules and must be optically active. If they are independent molecules, their enantiomers will be formed in the same amounts to form racemic mixtures, which will form fractions in chromatography. Though the similar clockwise and anticlockwise rotations of the rear carbon by 120° with fixing the front carbon intact are possible, one realizes that such manipulation produces **13'** and **13''**, respectively. No new structure appears.

This kind of internal rotation can also be considered for *S,S*-tartaric acid **14**. By the similar anticlockwise rotation of the front carbon atom in **14** by 120° , one gets **14''**. The similar clockwise rotation

Scheme 15. Simplified rotational circuits of R,S - and R^*,R^* -tartaric acids.Scheme 16. Newman projections for correlation of $13'$ with $13''$.

of the front carbon atom by 120° affords $14'$. By rotation of the front carbon in 14 by 240° clockwise or anticlockwise, one gets $14''$ or $14'$. No other conformer appears. This means that consideration of 3 racemic mixtures for the R^*,R^* -tartaric acid models suffices.

For consideration of the stereochemical relationship of conformers $13'$ and $13''$, these conformers are reproduced in Scheme 16, where simplified Newman projections are used.

If one views conformer $13''$ from the rear, one gets conformer $15'$. If one further rotates the whole body of $15'$ by 60° clockwise, about the C—C axis, one realizes that the figure thus obtained, $15''$, is a mirror image of $13'$, but $13'$ and $15''$ are not superimposable to each other. Thus these are enantiomers. Now it can be concluded that there will be two fractions, 13 and a racemic mixture ($13'$ and $13''$), to be separated, for models of R,S -tartaric acid. If we add fractions expected for R^*,R^* -tartaric acid, the total fractions to be separated are five. Actually, we obtained four fractions in chromatography out of possible five.³⁰⁾

When one examines the environments of substituents in 13 and $13'$ or $15'$, one notices that, although in 13 , all the substituents are located in the same environment, the environments of the same substituents are different in $13'$ or $15'$. That is, in 13 , X is always flanked by Y and Z, Y is always flanked by X and Z, and Z is always flanked by X and Y, whereas, in $13'$ or $15'$, there is an X which is flanked by X and Z, but another X is flanked by X and Y. There is possibility that these substituents show NMR signals at different chemical shifts. The conclusion of the discussion on the model compounds of R,S -tartaric acid up to this point is that there will be two fractions which can be separated by chromatography and one of the two could show NMR spectra which exhibit signals at identical chemical shifts and another which possibly exhibits signals at slightly different chemical shifts for the same substituent.

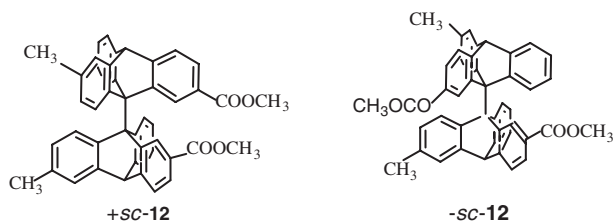
We also notice that, in R^*,R^* -tartaric acid models, all the substituents are in the same environment. Examination of the environments of the substituents in R^*,R^* -tartaric acid models reveals that the environment of every substituent, X, Y,

and Z in *S,S*-tartaric acid models in Scheme 15 is equivalent. The conformer **13'** is unique in a sense that it might show two lines in NMR spectra for the same substituent.²⁷⁾

One more problem remains unsolved. That is, there is no clue for distinguishing **13** from optically active *R*,R**-tartaric acid models, as far as the NMR spectra concern. In these two models all the substituents are expected to show a single line in NMR spectra. We decided to use an empirical rule in chromatography which states that the least polar substance is eluted first. Undoubtedly, compound **13** is the least polar molecule, because it is a *C_i* molecule. Though we tried to resolve the first fraction of chromatography by using various chiral stationary phases, all trials to resolve this compound into optical isomers by chromatography ended in failure. We finally submitted this material to X-ray crystallography, which showed that indeed this compound was the *C_i* molecule **13**.²⁷⁾

Fortunately, the second fraction afforded good crystals for X-ray crystallography which showed that the compound in question was one of the *R*,R**-tartaric acids, the specific stereochemistry, being a *Psc*-(*S,S*), and *Msc*-(*R,R*)-tartaric acid model.

Fraction 3 in chromatography showed two signals in ¹H NMR spectrum for methyls, though the spacing was very small: 2.25(s) and 2.26(s) for the aromatic methyls and 3.50(s) and 3.51(s) for the ester methyls. In addition, ¹³C NMR spectrum indicated that the aromatic rings in these compounds were nonequivalent, showing 33 aromatic C lines, whereas the theoretical number of aromatic C signals is 36 for **13'** and **13''**.²⁷⁾ Then the fraction, which was concluded to be a racemic mixture, was submitted to chromatography on a chiral stationary phase and two chiral forms, *+sc*-**12** and *-sc*-**12** were separated, specific rotations being +31 and -31.³⁰⁾ We thus found that the *C_i* molecule **13** is an optically inactive compound and **13'** and **13''** are optically active compounds which formed a racemic mixture.



Scheme 17. Optically active models of *R,S*-tartaric acid conformers.

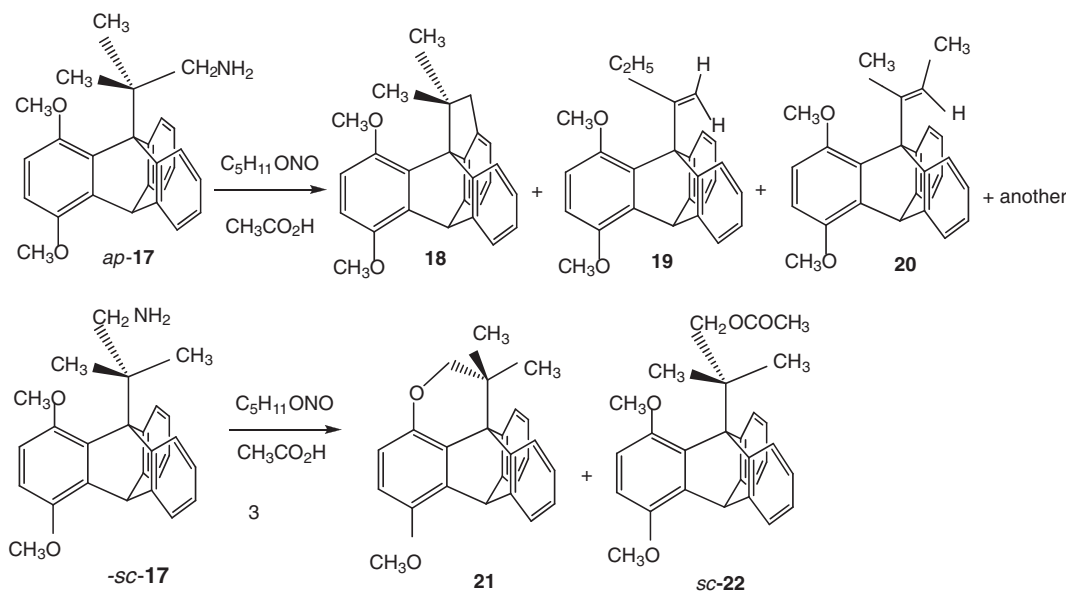
For determination of absolute conformation, the paucity of the samples prevented us from chemical derivation of these isomers to a compound which contained an organic group of known absolute stereochemistry. Thus we used the method of calculation for determination of absolute conformations.

While the data presented above may be taken as sufficient to claim that these are enantiomers, we further confirmed that these isomers were enantiomers with each other by comparing the CD spectra, which gave better chance for calculations than specific rotation. For the (–)-isomer, a medium trough (220 nm), a strong peak (231 nm), a small peak (264 nm), and a medium trough (275 nm) were found. These CD features were satisfactorily reproduced by the TDDFT calculation for the *-sc*-isomer. Now the absolute conformation of *-sc*-**12** is *Msc*-(–)-**12**.³⁰⁾ The specific rotations are -31 and +31 for *Msc*-**12** and *Psc*-**12**, respectively.

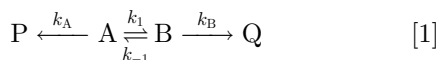
By obtaining optically active conformers of the *R,S*-tartaric acid models, we believe that the internal compensation theory is rejected by experiment, because, if internal compensation theory were correct, a molecule must be optically inactive, in whatsoever conformation it might exist. We recommend the theory of internal compensation be abandoned. The internal compensation was the concept in the days, when chemists had not known the existence of rotational isomers. Though we miss a fraction in chromatography, we believe that the missing fraction in chromatography must be one of the *R*,R**-tartaric acid models, because all the necessary fractions of *R,S*-tartaric acid models were separated and identified. Thus the missing of a fraction in chromatography does not jeopardize our conclusion.

Reactions of rotational isomers

While reactions of organic compounds are very often carried out in solutions, we must recognize that conformers will appear in solution. If the conformers are enantiomers, they behave the same under achiral conditions, but, if they are diastereomers, the reactivities are different under achiral conditions. It will be very complicated to treat these mixtures uniformly. Curtin has discussed stereochemical control of organic reactions and has mentioned that the conformation of the original state is rather unimportant in product control and important is the transition state energy of producing the products in the reaction which is also affected by the steric effects.³¹⁾ This theory is now called the Curtin–Hammett principle,³²⁾ and is often cited when one

Scheme 18. Diazotization of primary amine **17** conformers.

discusses the products from a mixture of species which are in equilibrium. The principle can be shown by Eqs. [1] and [2]. The simplest case is that there are two species A and B, which exhibit different reaction rates to give products P and Q, respectively. Then the ratio of the products $[P]/[Q]$ is given by Eq. [2]. Today it is often possible to estimate populations of conformers by the NMR technique and, if the rates of reactions of each equilibrating system are known, it will be possible to predict the product ratio fairly accurately. Unfortunately, at the time when Curtin discussed the theory, the model compounds were limited, thus forcing him to utilize the reactions, which proceeded with well-known mechanisms for compounds of known stereochemistry. Now that we are able to isolate rotational isomers in varieties, we should be able to provide better examples of rotational isomers for prediction of the product ratios in a given reaction. We began to see reactivities of conformers to contribute to this end.



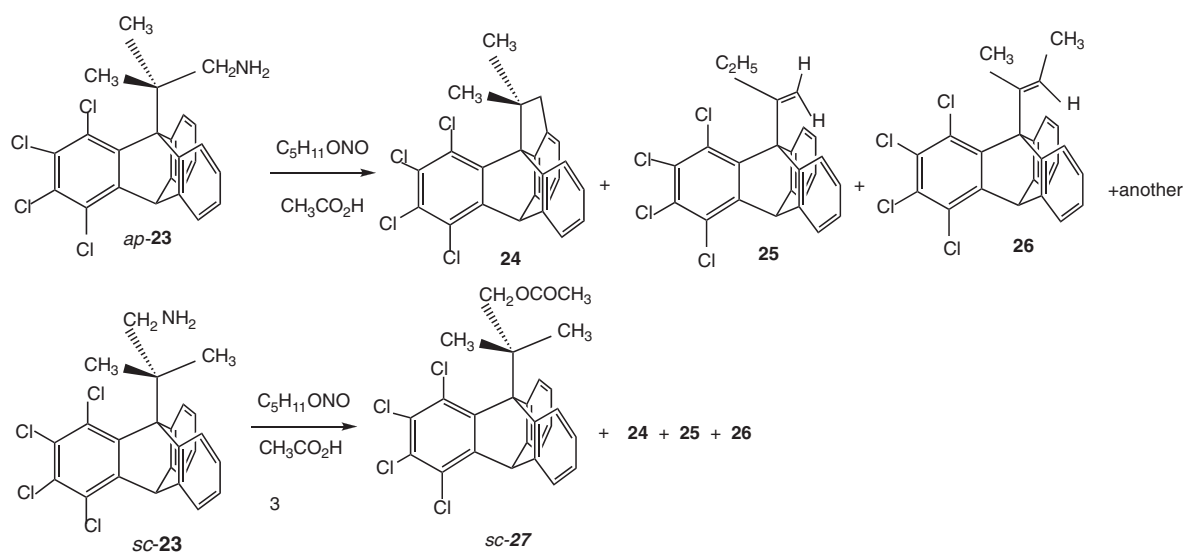
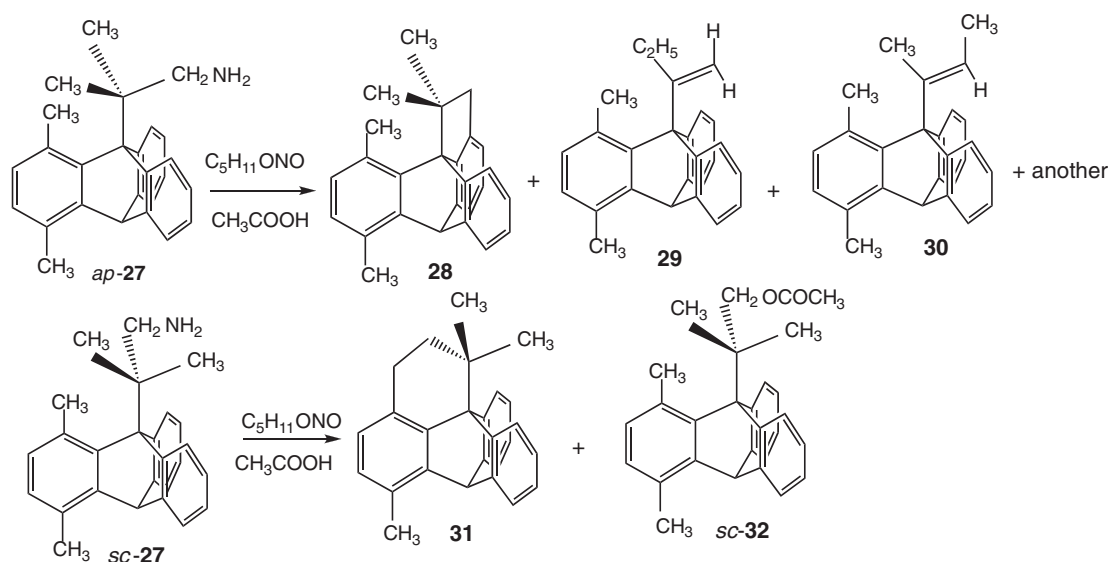
$$[P]/[Q] = k_A[A]/k_B[B] = K^{-1} \cdot k_A/k_B \quad [2]$$

Cation-forming reactions. Cation-forming and radical-forming reactions of conformers have mainly been investigated. An example of cation-forming reactions is shown in Scheme 18, where the cation was produced by diazotization of the corresponding primary amine **17**.³³⁾ The main products

from *ap*-**17** were a cyclized compound **18**, and olefins **18**, **19**, **20**, and another. When the intermediate cation reacts with the near-by benzeno bridge, it produces the cyclized compound **18**. The intermediate cation could perform Wagner–Meerwein rearrangement. When the reactions are followed by the loss of a proton, olefins, **18**, **19**, and another are formed. However, in the *sc*-isomer *sc*-**17**, a methoxy-oxygen exists in proximity of the cation and the oxygen will react to form an oxonium ion, which loses the methyl group by the action of an anion in the system to give a cyclic ether **21**. If the intervening cation reacts, before rearrangement, with the acetate anion in the system, the product is *sc*-**22**.

Therefore, detection of *sc*-**22** is evidence for that the intermediate cation was stabilized and had prolonged life-time, which led to formation of *sc*-**22**. The cyclic ether **21** and the acetate *sc*-**22** were obtained in 95:5 ratio.³⁴⁾ Other products such as **18**, **19**, and **20**, which were obtained from the same reaction of *ap*-**17**, were not detected from *sc*-**17**.³⁴⁾ The absence of olefins **19**, **20**, and another in the reaction products of *sc*-**17** can be interpreted that the participation of the oxygen atom in the 1-substituent was so strong that it prevented the Wagner–Meerwein rearrangement of the intermediate.

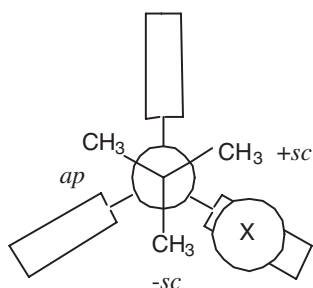
While diazotization of *ap*-**23** afforded the similar results with *ap*-**17**, producing minor products **24–26** in ca. 10% or less yields, *sc*-**23** gave an acetate *sc*-**27** in 18% yield and minor products in yields of 10% or

Scheme 19. Diazotization of rotamers of tetrachloro compounds **23**.Scheme 20. Expected and unexpected products from diazotization of rotameric primary amines **27** with 1,4-dimethyl substituents.

less. Even though the yield of the acetate was not remarkably high, its formation in 18% yield was evidence for the participation of the chloro group, by which elongation of the life-time of the intervening cation resulted (Scheme 19).³⁴⁾

Our surprise was that even a hydrocarbon moiety acted as a base, *sc*-**27** allowing the insertion of the formed cation to the methyl group to produce **31** and affording the corresponding acetate *sc*-**32**, while *ap*-**27** yielded normal minor products, formation of which was expected from the amines with other substituents.³⁵⁾ If the conformation of **27** is *ap*, the site of

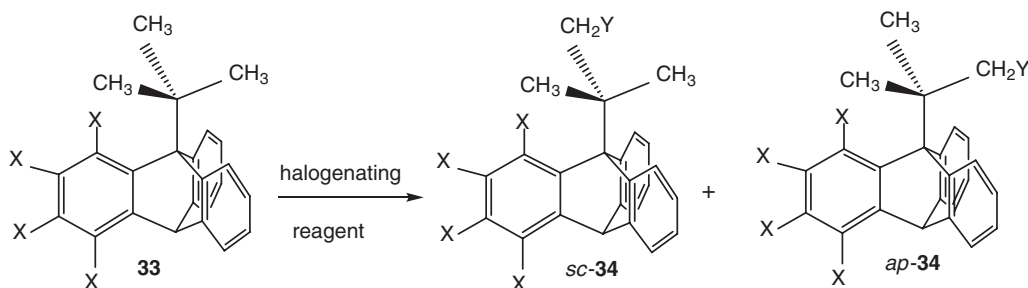
cation formation is remote from the methyl group, whereas in the *sc* conformation, the cation forming site is close to the methyl C–H group. We believe that a kind of interaction between the carbocation and the methyl C–H group must take place to cause formation of **31** and *sc*-**32**. The results shown in Scheme 20 indicate very clearly the outcome of the interaction between a carbocation and the methyl C–H, because the formation of the cyclic hydrocarbon **31** is reasonably explained by formation of a coordination compound of the C–H group to the carbocation, which then isomerizes to a C–C bond coordinatin to a



Scheme 21. A Newman-type projection of 1-*tert*-butyl-1-halo-triptycene.

Table 1. Relative rates of halogenations of 9-*tert*-butyl-1,2,3,4-tetrahalotriptycene³⁹⁾

33	Reagent	Relative reactivities	
		$\pm sc$	<i>ap</i>
X			
Cl	SO ₂ Cl ₂	0.95 \pm 0.05	0.60 \pm 0.03
Cl	Cl ₂	0.84 \pm 0.02	0.83 \pm 0.05
Cl	Br ₂	2.78 \pm 0.3	0.89 \pm 0.04
Cl	Br ₂ -NBS	1.16 \pm 0.08	0.82 \pm 0.04
Br	Br ₂ -NBS	4.1 \pm 0.8	0.8 \pm 0.2



Scheme 22. Halogenation of 9-*tert*-butyl-1,2,3,4-tetrahalotriptycene.

proton, then deprotonation from the C–C–H⁺ complex gives **31**. *sc*-**32** can be formed by the attack of the acetate anion on the carbocation intermediate which is stabilized by coordination of the C–H group.³⁵⁾ Thus formation of the acetate *sc*-**32** is evidence for stabilization of the intervening carbocation. In contrast, the *ap*-isomer *ap*-**27** gives products **28**–**30** after extensive Wagner–Meerwein rearrangements of the carbocation, yields being ca. 10% or less for each product. The yield of *sc*-**32** was 10%, being significantly higher than those of the minor products.

Radical-forming reactions. We describe here radical halogenations of a *tert*-butyl group, which should show different reactivities of methyl groups in a *tert*-butyl, because this reaction gave the most interesting results among radical reactions examined. As often cited in this article, in the triptycene system, when a *tert*-butyl group is bonded to the 9-position of triptycene and the triptycene moiety carries a substituent at the 1-position, then the rotation of the *tert*-butyl group is practically blocked. The methyl groups in the *tert*-butyl are divided into two groups, enantiotopic and diastereotopic pairs (Scheme 21). The $\pm sc$ methyls and *ap*-methyl are diastereotopic, whereas $+sc$ and $-sc$ methyls are enantiotopic.

Under achiral conditions, the enantiotopic methyls should show the same reactivity, whereas the diastereotopic methyls should behave differently.

Substituted 9-*tert*-butyltriptycene was treated under radical reaction conditions: When a mixture of **33** (X = Cl) and sulfuryl chloride in chlorobenzene was heated in the presence of dibenzoyl peroxide,³⁶⁾ the reaction afforded a 3.2:1 mixture of *sc*-**34** (X = Y = Cl) and *ap*-**34** (X = Y = Cl).

Because there are two *sc*-methyls, whereas the *ap*-methyl is only one, we divide the formation ratio of *sc*-**34** by two. Thus the $\pm sc$ -methyl was more reactive than the *ap*-methyl by a factor of 1.6. In contrast, when an elementary halogen, chlorine, was dissolved with 9-*tert*-butyl-1,2,3,4-tetrachloro-triptycene **33** (X = Cl) in carbon tetrachloride and the solution was shined for 10–15 min. The products, *ap*-**34** (X = Y = Cl) and *sc*-**34** (X = Y = Cl) were formed in 1:2 ratio, meaning that the *ap* and *sc*-methyls showed the same reactivity. This is reasonable because chlorine atom produced from elementary chlorine is very reactive and nonselective.^{37),38)} In contrast, chlorination with sulfuryl chloride had been known more selective than elementary chlorine.^{37),38)} Incidentally, the rate-determining step of halogenation is the abstraction of a hydrogen atom from a methyl group.³⁸⁾

We then turned our attention to a question: Could we halogenate more selectively the *sc*-methyl of the *tert*-butyl group? We studied this problem by changing the halogenating reagents as well as

the substituent. The results of this endeavor³⁹⁾ are summarized in Table 1. Bromine atom produced from bromine molecule is known to be less reactive than chlorine but gives better selectivity than chlorine.⁴⁰⁾ We notice that chlorination with elementary chlorine was scarcely selective, whereas bromination gives much better selectivity, as are shown in Table 1 (compare entries 2 and 3). It may be interpreted that the bromine atom produced by photolysis of bromine molecule must be in relatively low energy state and the amount of energy required to attain the transition state is relatively much with respect to the chlorine case to make the bromination more selective than the chlorination. For the entries 4 and 5 in Table 1, we used *N*-bromosuccinimide-bromine mixture. In the bromination of a hydrocarbon, hydrogen bromide is formed and the role of *N*-bromosuccinimide had been thought to be scavenging the hydrogen bromide.³⁷⁾ However, our results clearly show that the *sc/ap* value for the 4th entry in Table 1 is 1.5 ± 0.1 , which is a decrease from 3.1 ± 0.06 of the bromination with bromine alone.

Our results are not consistent with the idea that *N*-bromosuccinimide works just as a scavenger of hydrogen bromide but suggest that it might play as well other roles, because, if it simply acted as a scavenger of hydrogen bromide, the formation ratio *sc-34* ($X = Cl, Y = Br$)/*ap-34* ($X = Cl, Y = Br$) would not have been affected by the presence of *N*-bromosuccinimide. Skell and Day discussed on the stand point that succinimidyl radicals were participating in hydrogen-abstraction from an alkyl group.⁴¹⁾

The reasons for changing the substituent in entry 5, were that we found a paper which reported that the radicals were more easily formed in vicinity of a heavy atom.⁴²⁾ It was also known that the bromo group accelerates formation of radicals in vicinity with respect to the chloro group.⁴⁰⁾ We thought that it might be possible to raise the reactivity of a methyl group which was close to the substituent. In order to facilitate hydrogen abstraction from the *sc*-methyls, we used 1,2,3,4-tetrabromo-9-*tert*-butyltritycene **33** ($X = Br$). As expected, the change in the substrate raised the *sc/ap* ratio to 5 and the product was almost pure *sc*-bromomethyl compound, *sc-34* ($X = Y = Br$), being ca. 5.³⁹⁾

Incidentally, the results presented here are the first examples which showed that the methyls in a *tert*-butyl group could behave differently on the laboratory bench, though hydrogens in a methyl group had been known to behave differently in biological systems.⁴³⁾

At any rate, because the relative reactivity ratio *sc/ap* of ca. 5 means that we actually get products in 10:1 ratio, this type of bromination of **33** ($X = Br$) may be useful as a synthetic method of this type of compounds.

For those who are interested in some other examples of reactions of rotamers, we refer them to published review articles.^{44)–46)}

Summary

We were able to isolate stable conformers at room temperature, using the basic skeleton of 9-*tert*-alkyl-9,10-dihydro-9,10-ethenoanthracene, 9-*tert*-alkyltritycene, or substituted bitriptycyl. Of compounds which were composed of these skeletons, one conformer was found to be optically inactive because of the symmetry of the molecule. The structures of the optically inactive conformers were of C_s , C_{2h} , or C_i symmetry. However, these molecules can become chiral by internal rotation. These chiral conformers were separated by chromatography with a chiral stationary phase or by other means. A term of "absolute conformation" was proposed to distinguish a conformer of which at least one of its chiroptical properties is connected with the conformation. We also have noticed that all the *Msc*-conformers of compounds discussed in this account exhibited the levorotatory property of the plane of the polarized light of sodium D lines. Is it inherent or fortuitous? This problem was not solved until today, but is left for future research.

Acknowledgement

Because this project had continued over 40 years, there were numerous collaborators, all of whose names are impossible to list in this account. We instead wish to mention names of people who were influential and played major roles in developing this work. The late Professor Yoshiyuki Urusibara with The University of Tokyo, inspired the present author to this stimulating project. Professor Hiizu Iwamura with The University of Tokyo helped us understand physics and mathematics which were necessary for understanding and discussing the results of physical measurements. Dr. Minoru Suda and Professor Gaku Yamamoto, with Kitasato University, developed the new systems, which were suitable for conformer isolation. Professor Shinji Toyota with Okayama University of Science collaborated in synthesizing and determining absolute conformations of the aforementioned fundamental types of organic compounds. He also helped us

complete the manuscript of this account. Professor Yuji Ohashi with Tokyo Institute of Technology collaborated with us in determining structure of an important compound by X-ray crystallography. Professor Kan Wakamatsu with Okayama University of Science collaborated with us in determining absolute conformation of optically active models of *R,S*-tartaric acid through calculation. Without collaboration with these people, it would not have been possible to develop the work to the present stage. It was our pleasure to collaborate with these competent and enthusiastic chemists.

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Profile

Michinori Ōki was born in 1928 in Hyogo and was graduated from The University of Tokyo in 1950, when he obtained a position at Tokyo Metropolitan University as an assistant. He spent two years with Nelson J. Leonard at University of Illinois, when he published several papers on the transannular interactions between an amino-nitrogen and a carbonyl group. He was promoted to an associate professor at Tokyo Metropolitan University in 1956 and moved to The University of Tokyo as an associate professor in 1956. He began studies on the interactions between the hydroxyl group and π -electron systems, which developed to finding of the existence of rotational isomers about the C–O bond of aliphatic alcohols. He began to apply NMR spectroscopy to the studies of molecular interactions and applied the new technique to studies on the dynamics in molecules. The study of molecular dynamics by the NMR spectroscopy helped him greatly in the field of studies on rotational isomers. While he and his group succeeded in isolation of stable rotamers of an ethane derivative at room temperature in 1972, they were able to separate a diastereomeric rotamer pair of another series of compounds, 9-arylfluorenes, in 1974. They studied differences in reactivities of these rotamers extensively. An interesting phenomenon which concerned with the dynamic NMR spectroscopy was found at about the same time with the isolation of the rotamers by a student in his research group. The finding was that the methylene protons in 2-chloro-1,3-dithiane were nonequivalent in nonpolar solvents at low temperatures, whereas they became equivalent at elevated temperatures or in polar solvents. This finding was interpreted that ionic dissociation took place in polar solvents or at elevated temperatures and was developed to a general method of determining the rates of ionic dissociation by NMR. He became interested in molecular structures in detail and tried to use X-ray crystallography, when necessary for discussion of the molecular structure in crystals. These works had been continued toward the end of his career in The University of Tokyo and, on movement to Okayama University of Science in 1988, he began to petition to the University to install an X-ray diffractometer and was able to install one in 1991, when he began to determine the absolute conformations of optically active rotational isomers. The work developed to the successful determination of absolute conformations of fundamental compounds or their model compounds in organic stereochemistry.

