Absolute Conformation Revisited: Experimental Approach

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We propose that the term "absolute conformation" be used when one of the chiroptical properties is correlated with one of a pair of enantiomeric conformations. We present examples of compounds for which absolute conformations are known, as well as their syntheses, enantiomer resolution, and determination of absolute conformations, and discuss specifications of those conformations. The examples were selected from molecules for which one conformation is optically inactive but, by internal rotation about a $C(sp^3)$–$C(sp^3)$ bond, optically active conformers are produced. There are some problems, which we discuss as Future Problems, that arise when conformations are taken into account, even though the classical treatment of stereochemistry is well established in such areas.

Introduction

Bijvoet and collaborators demonstrated in 1951 that the spatial arrangement of atoms and groups in tartaric acid can be correlated with its chiroptical property.[1] This stereochemistry is now called the absolute configuration and is well accepted. If we can make a similar correlation between the spatial arrangement of atoms and/or groups of a pair of enantiomeric conformations of a molecule and one of the chiroptical properties of the molecule, we may call the spatial arrangement of those groups and atoms in the conformation in question its "absolute conformation". It has been difficult, however, to isolate conformational isomers at ambient temperature and the chiroptical properties of a conformation have been believed to be impossible to measure, because even if we could isolate an optically active conformational isomer it would rapidly interchange to its enantiomer and, thus, racemization would take place in most cases at room temperature.

Thus, in contrast to absolute configurations, little is known about absolute conformations. The objectives of this

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Professor Michinori Ōki was born in 1928 and graduated from The University of Tokyo in 1950. He commenced his career as a chemist by studying the conformation of diethylstilbesterol. Since then he has been interested in molecular interactions. He studied OH···π interactions, electron-donor−carbonyl interactions, and others that affect the stability of conformations of molecules. These interests led him to apply dynamic NMR spectroscopy not only to molecular dynamics (kinetics of internal rotation and/or inversion), but also to the kinetics of dissociation of various covalent bonds. This experience led him to the discovery of a series of compounds that exist as stable rotamers at room temperature and to the development of a new field of chemistry, namely the chemistry of rotational isomers, in which he has examined reactions, including isomerization, of conformational isomers and their chiroptical properties.

Professor Shinji Toyota, who was born in 1964 in Kagawa Prefecture, Japan, studied chemistry at The University of Tokyo. He received his Masters degree there in 1988 under the supervision of Prof. Michinori Ōki, and then became a research assistant at Okayama University of Science. After he received his Doctorate in 1992 from The University of Tokyo, with a thesis describing dynamic NMR spectroscopic studies of organoboron compounds, he was promoted to instructor (1993), associate professor (1998), and full professor (2002). He was a visiting researcher at the University of California, San Diego, in 1996−1997. He is interested in physical organic chemistry, supramolecular chemistry, and stereochemistry. Recently, he became engaged in research on the rotational isomerism of sterically hindered alkynes and the design of novel arene−alkyne oligomers.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

review are to define absolute conformation, to present some examples of absolute conformation, and to discuss the extension of this concept to various types of conformation.

The reasons for the ignorance in the chemical community toward absolute conformation seem to be twofold. First, as stated above, there have been no examples of it until recently. Secondly, it is a controversial topic. Although there have been scattered papers and even reviews[2,3] that discuss absolute conformation, one paper has been published in which the authors rejected the use of this term, saying that absolute configuration includes absolute conformation.[4] The authors of a book, which is considered widely to be one of the most authoritative books of stereochemistry today (which we refer to as "Eliel's book" hereafter),[5] avoided the use of this term because of this controversy.

We believe, however, if the use of the term "conformation" is banned, there will be many chemists who will feel inconvenienced verbally and in writing. Thus, we believe that the term "conformation" should be retained and usage of "absolute conformation" should be permitted, after having taken the historical controversy and new experimental results into account.

Because we have been able to isolate conformational isomers as stable entities at room temperature,[6] we believed that we could contribute to the problem of absolute conformation and launched a project to provide examples of optically active conformers of the ethane type. This review is a summary of these efforts. We propose to define absolute conformation in the following way. When a pair of enantiomeric conformers is available and the structure of one of them is correlated to its chiroptical properties, we say that the absolute conformation of the compound concerned is known. The use of the term absolute conformation should be avoided when the pair of enantiomers cannot be interchanged either experimentally or conceptually by internal rotation.

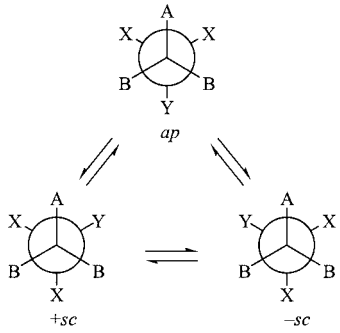
For discussion of the conformers, we exclusively use the system of naming conformations that was proposed by Klyne and Prelog[7] and is recommended by IUPAC.[8,9]

We propose usage of the descriptors *P* and *M* to define absolute conformations, which are examples of axial chirality, because the sense of helicity is best indicated by plus and minus in the C.I.P. rules. The addition of conformational descriptors will increase stereochemical information. Thus, we recommend the usage of *Psc* and *Msc* for $+sc$ and $-sc$[7] isomers when they are isolated and the relationship between their stereochemistry and a chiroptical property is known. We recommend also that the symbols $+sc$ and $-sc$ (in addition to $\pm sc$ for the racemic mixture) be retained when it is convenient to discuss the conformation but the absolute conformation is either unknown or unnecessary for the discussion. Here we emphasize that the plus and minus signs in $+sc$ and $-sc$ have no relation with the direction of rotation of the plane of polarized light, just as *R* and *S* do not mean dextrorotatory and levorotatory properties.

Readers will better understand the nomenclature of the conformations by looking at the following examples.

Example 1. Rotamers of C_s Molecules

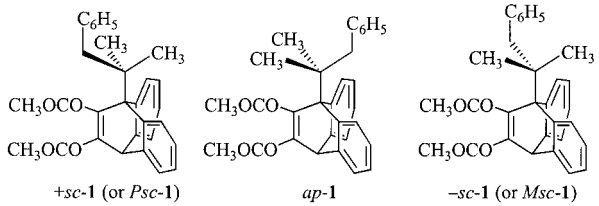
Consider a compound of the general formula AB_2C-CX_2Y. The *ap*[7] conformer of this compound is a C_s-symmetric molecule. Because there is a plane of symmetry in this molecule, it must be optically inactive. By internal rotation, however, this compound can adopt either $+sc$ or $-sc$ conformations (Scheme 1). In addition, the $-sc$ form is a mirror image of the $+sc$ form. These $+sc$ and $-sc$ isomers have C_1 symmetry and should be optically active, when isolated.



Scheme 1. Rotational circuit of AB_2C-CX_2Y

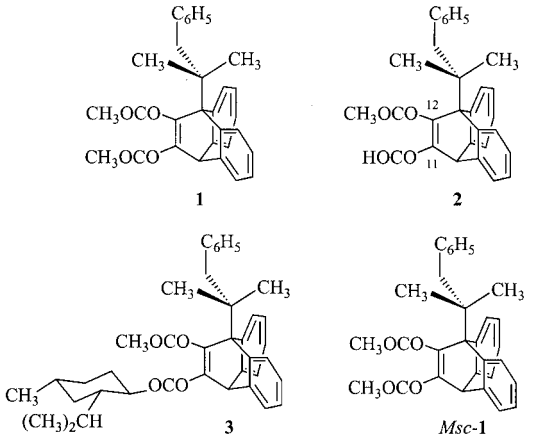
This type of compound is the most extensively studied and includes the first isolated optically active compound for which absolute conformations are known.

Compound **1**, 9-(1,1-dimethyl-2-phenylethyl)-11,12-bis(methoxycarbonyl)DEA (DEA: 9,10-dihydro-9,10-ethenoanthracene), is the first compound for which rotational isomers were successfully isolated at room temperature (Scheme 2).[11] The rotamers can be identified by taking advantage of the molecular symmetry. Because the *ap* form has a plane of symmetry, the methyl groups and the methylene protons are enantiotopic and they each present a singlet in the ^{1}H NMR spectra; the *sc* compound, however, possesses diastereotopic methyl units and diastereotopic methylene protons and, thus, presents two singlets for the methyl units and an AB quadruplet signal for the benzylic methylene protons in the ^{1}H NMR spectrum (Scheme 2). Compound **1** was prepared by Diels–Alder reaction of dimethyl acetylenedicarboxylate with 9-(1,1-dimethyl-2-phenylethyl)-anthracene. The conformational isomers were isolated by chromatography and identified by their characteristic ^{1}H NMR spectra; the barrier to rotation was found to be 33 kcal/mol.



Scheme 2. Three rotamers of compound **1**

The *sc* compound was resolved by treating it in the following way (Scheme 3).[11] Alkaline hydrolysis of the ester groups in **1** took place only at the 11-position because of steric effects: the formation of a tetrahedral carbon atom was too slow to make the hydrolysis of the ester group at the 12-position occur. The monocarboxylic acid **2** that formed was converted into its *l*-menthyl ester **3** via its acid chloride. One of the diastereoisomers thus formed crystallized preferentially. One of these crystals was submitted to X-ray crystallography and its structure was solved by taking advantage of the known stereochemistry of *l*-menthol.[12] This diastereoisomer happened to be the *l*-menthyl ester **3** of −*sc*-**1** (Scheme 3). The *l*-menthyl ester was hydrolyzed again and methylated to give optically active −*sc*-**1** ($[\alpha]_D^{23} = -30.4$). Thus, the conformation of **1** and its chiroptical property were related.[13] The CD spectrum of +*sc*-**1** ($[\alpha]_D^{23} = +30.5$) is presented in Figure 1.



Scheme 3. Compounds related to the resolution and determination of absolute conformation of compound **1**

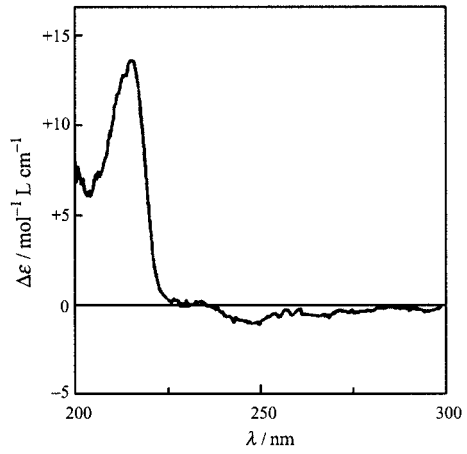
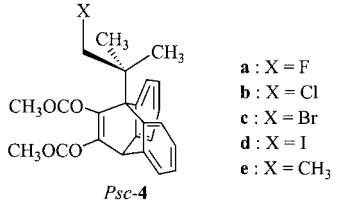


Figure 1. CD spectrum of *Psc*-**1**

As proposed in the Introduction, we call the −*sc*-**1** form *Msc*-**1** and its enantiomer *Psc*-**1** because the sense of helicity in the former is minus and that in the latter is plus. In the future, conformational isomers about other single bonds may also be separated. In those cases, we propose to specify the bond about which internal rotation is frozen. Thus *Msc*-**1** may be formally written as *Msc*-9(1′)-**1**. This nomenclature is an analogy of the specification of the location of a double bond in alkenes.

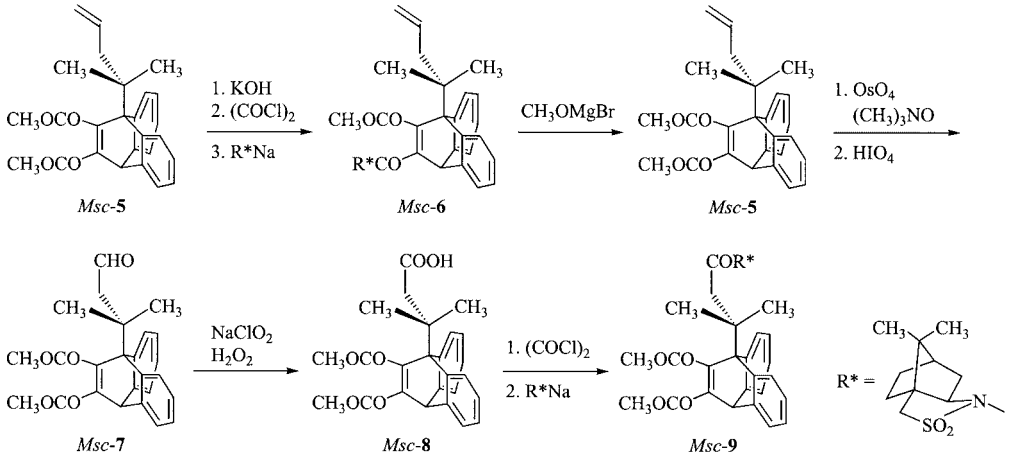
We should like to make a comment at this point on the definition of conformation presented in Eliel's book, which says that conformation is changed by (rapid) rotation about a single bond. This description provides some ambiguity, however, because the rates of internal rotation are affected by temperature. We must mention the temperature at which the conformational change is rapid or slow. Although the rates of internal rotation in compound **1** are too small to allow isomerization to be observed at room temperature, the isomerization becomes visible above 100 °C and takes place with measurable rates at 150 °C. Because the isomers of **1** are interchanged by rotation, we believe that they should be called rotational isomers and, hence, conformers. We know from experience, that it is possible to isolate a rotational isomer when its half-life exceeds 1 h. This isolation becomes possible if the barrier to rotation exceeds 25 kcal/mol at 25 °C. The rotational barrier in butane, from the +*sc* isomer to the −*sc*, is calculated to be 2.7 kcal/mol.[14] Theoretically, from the results of calculations, it should be possible to isolate the rotamers of butane if the temperature is below −230 °C. Today, it is possible to work at −30 °C and in the future it may become possible to work at temperatures as low as −100 °C. Then it will become possible to isolate isomers, in which internal rotation takes place with a barrier to rotation higher than 10 kcal/mol. Indeed, the equatorial form of chlorocyclohexane was isolated in a pure form at −150 °C.[15]

The work on compound **1** was extended to similar compounds, namely 9-(2-substituted 1,1-dimethylethyl)-11,12-bis(methoxycarbonyl)DEA (**4**) (Scheme 4), to see the effects of substituents on the CD spectra.[16]



Scheme 4. 9-(2-Substituted 1,1-dimethylethyl)-11,12-bis(methoxycarbonyl)DEA (**4**)

Compound **5** was prepared by Diels−Alder reaction between 9-(1,1-dimethyl-3-butenyl)anthracene and dimethyl acetylenedicarboxylate, and its rotational isomers, *ap* and *sc*, were separated by chromatography. The racemic mixture of ±*sc*-**5** was treated as shown in Scheme 5 to give racemic carboxylic acid ±*sc*-**8**, which was then converted into cam-



Scheme 5. Compounds related to the synthesis of *Msc*-**9** and the determination of the absolute conformations of the intermediates

phorsultamamide **9**, the diastereoisomers of which were separated by chromatography.

One diastereoisomer of **9**, which eluted faster than the other, gave good crystals that we analyzed by X-ray crystallography. Again, the structure was solved so that it gave the correct stereochemistry of camphorsultam.[17] This camphorsultamamide happened to be the *Msc* form with respect to the conformation of the skeleton (Scheme 5).

Because it was difficult to remove the camphorsultam moiety in *Msc*-**9** without affecting the other functional groups, we decided to take another route to determine the absolute conformations of the intermediates **5**, **7**, and **8**.[16] The ester group at position 11 of compound ±*sc*-**5** was hydrolyzed as described above and converted into the camphorsultam amide **6**. The diastereoisomers of **6**, which we prepared from racemic **5** via the corresponding 11-acid, were separated by chromatography. The more slowly eluting isomer was submitted (Scheme 5) to a reaction with methoxymagnesium bromide to obtain **5**, which was oxidized to produce the aldehyde **7**. This aldehyde was oxidized to the carboxylic acid **8** and then converted into the camphorsultamamide, which was identical to compound *Msc*-**9** for which we had determined the structure by X-ray crystallography. Thus, it became clear that the series of compounds **5**, **7**, and **8**, which all derived from the more slowly eluting camphrosultamamide **6**, belong to the *Msc* series. Similarly, the *Psc* series of the dimethyl esters, **5**, **7**, and **8** were prepared; the values of the specific rotation of these compounds are compiled in Table 1.

Table 1. Specific rotations $[\alpha]_D$ of intermediates in the synthesis of compound **9**

Compound	*Psc* form	*Msc* form
5	+4.4	−5.0
7	−29	+27
8	+1.1	−1.3

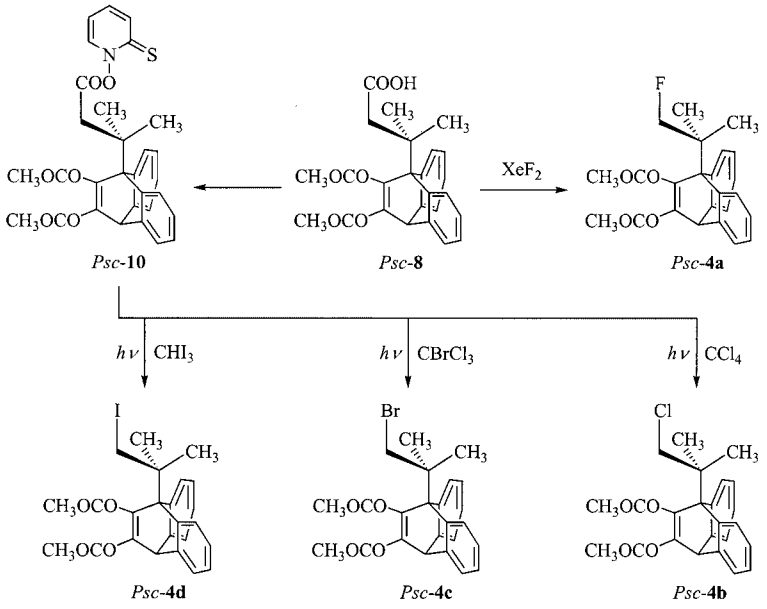
Optically active **4a**−**d** (Scheme 4) were prepared by photolyzing the corresponding Burton's ester **10** of the carboxylic acid **8** in the presence of appropriate halogen sources[16] or treating the same carboxylic acid with xenon difluoride (Scheme 6).[18] Compound **4e** was prepared from the corresponding aldehyde **7** by reducing it to the primary alcohol, which was then converted into the iodide **11** and further reduced with Raney nickel (Scheme 7).[18]

The syntheses of compounds **4** would have been tedious because optically active **7** and **8** were obtained in minute amounts in the syntheses described in Scheme 5. Later, however, we found that it is possible to obtain optically active **7** on a preparative scale by resolving the racemic mixture ±*sc*-**7** by chiral chromatography using CHIRALPAK AD (Daicel) as a stationary phase. This procedure greatly facilitated the syntheses of compounds **4**. Compound *Psc*-**7** was converted into *Psc*-**8** by oxidation.

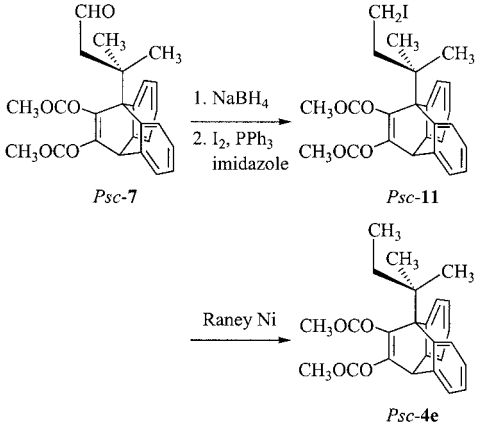
Because *Psc*-**7** became available in a quantity that sufficed for the preparation of **4**, it was used in the preparation of all compounds **4**; the CD spectra of compounds **4** are compiled in Figure 2. It immediately became clear that the spectra of all these compounds are very similar when X is a halogen atom. This observation is reasonable because absorption of light in the 250-nm region is attributed mainly to the skeleton of DEA, which is a common feature present in all these compounds.

One point may be argued here. The isomers of *Msc*-**4** that are formed by rotation about the $(CH_3)_2C(1')-CH_2X$ bond, where X is a halogen atom, are depicted in Scheme 8. If the halogen atom is a chlorine or larger atom, the rotational isomer will exist exclusively in the *ap* form, because the other isomers (+*sc* or −*sc* in Scheme 8), which carry the halogen atom inside the DEA skeleton, should be much more unstable than the halogen-outside isomer (*ap*). The ±*sc* forms may exist to some extent, however, when X is a fluorine atom because the fluorine atom is small.

As a result, it is not possible to postulate that we are handling compounds that can take only one conformation. Indeed, at low temperatures, such as −70 °C, another isomer of **4a** was observed by ^1H and ^{19}F NMR spectra. The equilibrium constants were obtained at various temperatures and the differences in enthalpy and entropy for the



Scheme 6. Synthetic route to **4a**−**d**



Scheme 7. Synthetic route to **4e**

process *ap* → ±*sc* were found to be 0.79 kcal/mol and 2.2 cal/(mol·K), respectively. If we extrapolate these values to 300 K, the free energy difference becomes only 0.13 kcal/mol. Clearly, the populations of *ap* (fluorine-outside) and *sc* (fluorine-inside) conformations are comparable. Yet the CD spectra are quite similar to those of the other halogen compounds. This feature again indicates that the CD spectra are mostly determined by the π system of the DEA moiety and the saturated part has nothing to do with the UV absorption. For a full understanding of the CD spectra, further knowledge of the roles and mechanisms of the factors that affect the CD spectra, is needed. The CD spectrum of compound **4e** (X = CH_3), however, is quite different from those of **4a**−**d** (X = halogen), even though the former displays almost the same UV absorption spectrum with those of the latter bearing halogen substituents. This observation indicates that the halogen atoms play some role in affecting the CD spectra. We must assume that the electric fields provided by the C−halogen bonds in these compounds have significant effects on the CD spectra.

In addition, the CD spectrum indicates that the optical activity of **4e** is very low (the absorption scale is expanded 10 times for the methyl compound in Figure 2 relative to those of the halogen compounds.). We believe this phenomenon results because the chirality is caused by only a slight difference between the methyl and ethyl groups. In classical studies, low optical activity has often been observed for compounds whose chirality is due to the difference in alkyl groups only.[19] In contrast, compound **1** displays a strong Cotton effect at the 215-nm region, which indicates that the phenyl group in the 9-substituent contributes strongly to the CD spectra.

Though the CD spectra are similar for **4a**−**d**, the specific rotations are different from one halogen compound to another, as Table 2 indicates. There is a trend in the values of these specific rotations: the fluoro compound gives the largest positive value for the *Msc* series, the specific rotation decreases as one descends in the periodic table; it is almost zero for the bromo compound and is negative for the iodo compound. Incidentally, the absolute conformation of compound **4c** was confirmed by the Bijvoet method.[16]

Triptycenes that carry a tertiary alkyl group at the 9-position are known to exhibit even higher barriers to rotation than do the DEA compounds discussed above. The barriers to rotation in triptycenes are somewhat dependent on the substituents, especially the one at the *peri* position, which is close to the 9-*tert*-alkyl substituent. The highest barrier to rotation is observed when a fluoro or a methoxy substituent is present at position 1 (ca. 43 kcal/mol). If a methyl group is present at position 1, the barrier to rotation is lowered to ca. 38 kcal/mol.

Absolute conformations of these compounds have also been studied.[20] The compounds related to the syntheses, together with the enantiomer resolution of these compounds, are summarized in Scheme 9.

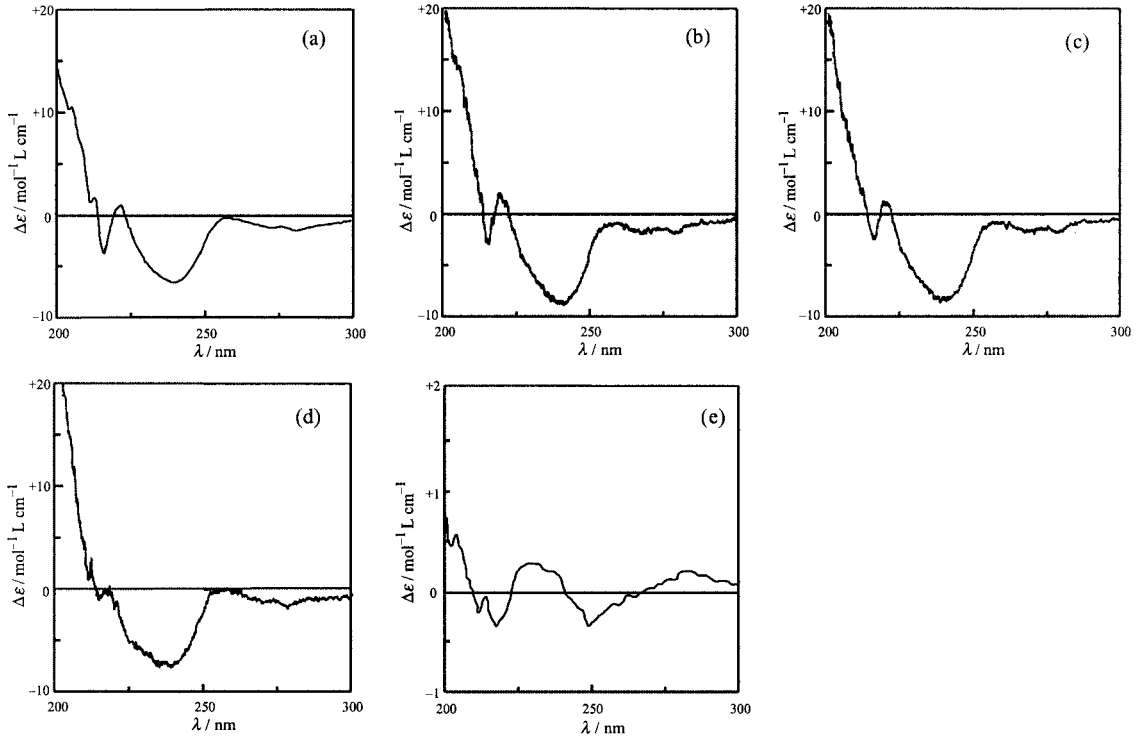
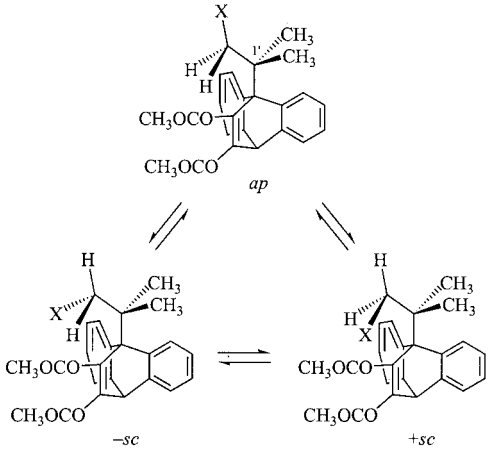


Figure 2. CD spectra of *Psc*-**4**: (a) **4a** (X = F), (b) **4b** (X = Cl), (c) **4c** (X = Br), (d) **4d** (X = I), (e) **4e** (X = CH_3)



Scheme 8. Possible rotamers of *Msc*-**4** about the C(1′)−CH_2X bond

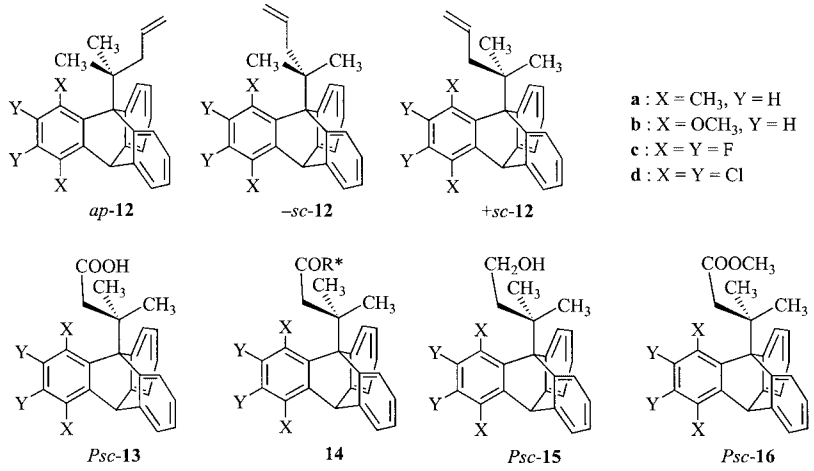
Table 2. Specific rotations $[\alpha]_D$ of compounds **4**

Compound	*Psc* form	*Msc* form
4a	−21.3	+22.2
4b	−9.7	+9.7
4c	+0.3	−0.3
4d	+13.2	−13.2
4e	+10.4	−10.5

The *ap* and *sc* forms of these triptycenes **12** are prepared conveniently if they carry two unsubstituted benzeno bridges in the triptycene units, because such compounds are prepared from 9-*tert*-alkylanthracenes. This feature makes these syntheses relatively easier than those for other complicated examples. 9-(1,1-Dimethyl-3-butenyl)triptycenes **12** that carry substituents in one of the benzeno bridges were prepared from the reaction of 9-(1,1-dimethyl-3-butenyl)-anthracene with a substituted benzyne. The *ap* and *sc* forms were separated by chromatography and were treated as follows. The method of conversion of **12** to the corresponding carboxylic acids **13** was the same as that described for compound **8** in Scheme 5.[20] The camphorsultamamide **14** was prepared as above. We found that **14** could be separated by either crystallization or by chromatography. Of the two diastereoisomers thus formed, the following fractions were found to afford crystals suitable for X-ray analysis: the faster eluting isomers of **14a** and **14d**, the isomer of **14c** that remained in solution after recrystallization, and the isomer of **14b** that first separated from solution during recrystallization. It so happens that the molecules that were submitted to X-ray crystallography all had *Psc* conformations.

Compound *Psc*-**14** was reduced with lithium aluminium hydride to obtain *Psc*-**15**. The alcohols **15** were oxidized to the corresponding carboxylic acids *Psc*-**13**. The CD spectra of the methyl esters *Psc*-**16** of these carboxylic acids are shown in Figure 3.

The CD spectra are seemingly different, but close examination indicates that they are similar. The positive Cotton effect at ca. 260 nm is present in all esters. In addition, the troughs and peaks at the shorter wavelengths occur at similar wavelengths. The different feature is the amplitude. In particular, the tetrachloro compound *Psc*-**16d** displays large Cotton effects. We may have to attribute these features of the tetrachloro compound to the quadrupole moment of



Scheme 9. Compounds related to the synthesis and resolution of compounds **16** (R*: see Scheme 5)

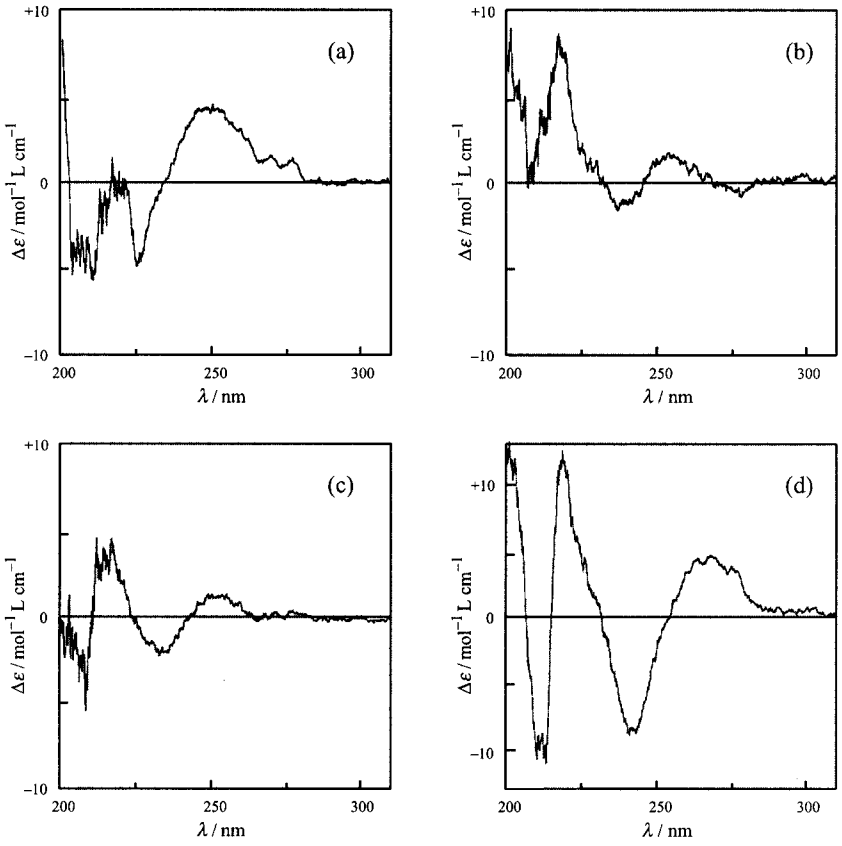


Figure 3. CD spectra of *Psc*-**16**: (a) **16a**, (b) **16b**, (c) **16c**, (d) **16d**

the chloro substituents. One might expect that because the direction of the electric transition as a whole in the tetrachloro and tetrafluoro compounds is opposite to that in the dimethyl- and dimethoxytriptycenes, their CD spectra should be different. We believe that the observed CD spectra are caused by the difference in the substitution patterns, because the halogen compounds carry halogen atoms at positions 1−4, whereas the others bear methyl or methoxyl groups at the 1- and 4-positions. These substitutions should affect the direction of the electric transition moments.

The specific rotations of compounds related to compounds **16** are listed in Table 3. The *Psc* forms seem to exhibit positive specific rotations in many cases.

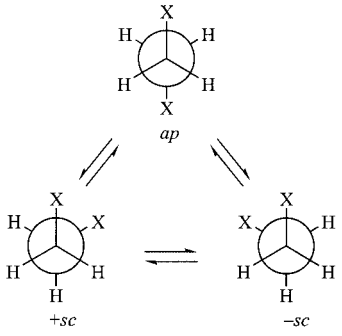
Example 2. Rotamers of a C_{2h} Molecule

Another group of compounds that are not chiral in the *ap* conformation but are chiral in *sc* conformations is that in which the *ap* conformation is a C_{2h}-symmetric molecule.

Table 3. Specific rotations $[\alpha]_D$ of triptycenes at 25 °C

Compound	*Psc* form	*Msc* form
13a	+27	−32
13b	+20	−21
13c	−0.7	+1.1
13d	+24	−26
15a	+17	−17
15b	+8.2	−8.8
15c	−6.2	+5.1
15d	+15	−16
16a	+32	−32
16b	+20	−20
16c	−2.2	+2.2
16d	+24	−23

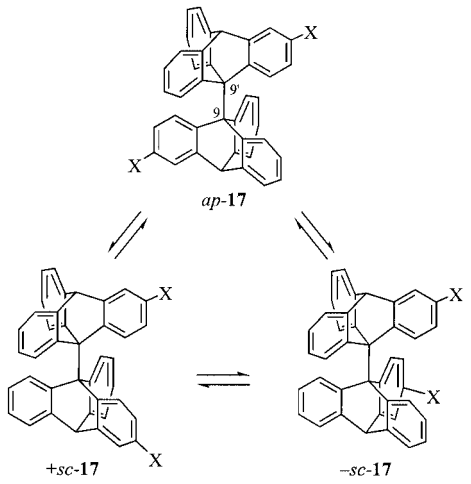
This group of compounds includes fundamental molecules such as butane and 1,2-dichloroethane. Let us consider a molecule XCH_2-CH_2X. Its rotational circuit is shown in Scheme 10.



Scheme 10. Rotational circuit of XH_2C-CH_2X

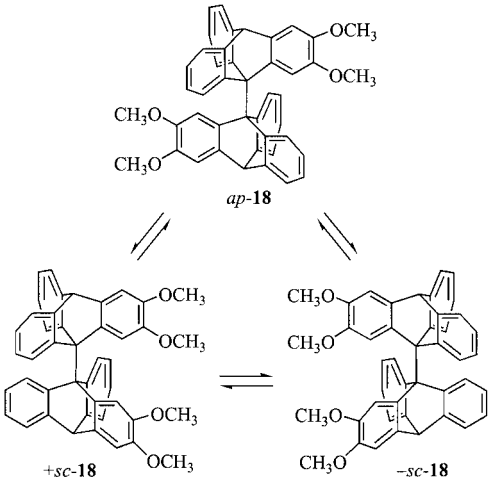
The *ap* conformation has a plane of symmetry in the molecule and should be optically inactive, but when it rotates to form the ±*sc* isomers, the latter are C_2 molecules and are chiral. The +*sc* form is a mirror image of −*sc* and, thus, these forms are enantiomers. It is not easy to block internal rotation in this type of compounds, if one sticks to purely aliphatic compounds, because to date the highest barrier known to rotation in purely aliphatic compounds is ca. 16 kcal/mol.[21] We may have to go down to −60 °C or lower to obtain rotamers of this kind as stable entities. In addition, the molecule must have the same substituents on the carbon atoms of both ends to have C_{2h} symmetry.

This problem can be solved by using triptycene systems. Through the work reported by Schwarz et al.,[22] it is known that the rotational barrier about the C9−C9′ bond in 9,9′-bitriptycyls is greater than 55 kcal/mol. Thus, the problem becomes one of having to introduce the same substituent(s) to the top half of bitriptycyls as those present in the bottom half of the same skeleton. A model compound **17** and its rotamers are depicted in Scheme 11.



Scheme 11. Rotational circuit of a 9,9′-bitriptycyl of which the *ap* form has C_{2h} symmetry

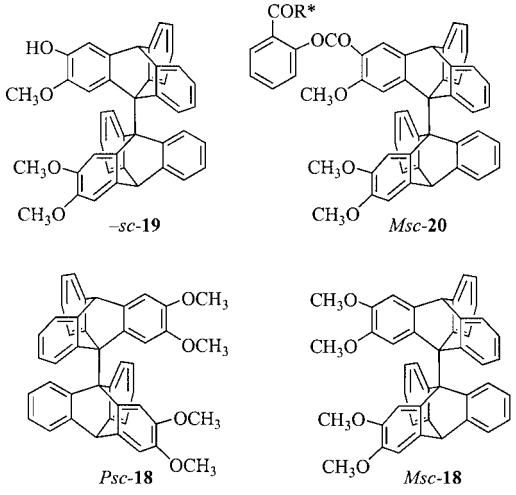
We selected 2,2′,3,3′-tetramethoxy-9,9′-bitriptycyl (**18**) as a target molecule.[23] It was prepared by Diels−Alder reaction of either 9,9′-bianthryl with 4,5-dimethoxybenzyne or unsubstituted benzyne with 2,2′,3,3′-tetramethoxy-9,9′-bianthryl. The identification of the *ap* and *sc* rotamers was carried out by taking advantage of the difference in their ^{13}C NMR spectra (Scheme 12). For the *ap* molecule, because of its symmetry, all the unsubstituted benzeno bridges should be equivalent, not only in the top half but also in the bottom half, while the dimethoxybenzeno bridges are equivalent. By contrast, the two unsubstituted benzeno bridges in the top half of the *sc* form are nonequivalent, as are the two benzeno bridges in the bottom half. While one of the unsubstituted benzeno bridges in the top half is equivalent to one of the two unsubstituted ones in the bottom half, the two dimethoxybenzeno bridges are equivalent: the number of signals expected for aromatic carbon atoms in the ^{13}C NMR spectrum of the *ap* form is, therefore, 12, whereas 18 signals are expected for the *sc* form. Actually,



Scheme 12. A 9,9′-bitriptycyl of which the *ap* form has C_{2h} symmetry

one of the isomers separated by chromatography displayed 17 signals for aromatic carbon atoms and the other presented 12. These results clearly show that the former is *sc*-**18** and the latter is *ap*-**18**.

Compound *sc*-**18** was treated with sodium ethanethiolate to demethylate the methoxy groups. This process resulted in the formation of compound *sc*-**19**, in which only one of the four methoxy groups was demethylated (Scheme 13). Compound *sc*-**19** was converted into *o*-(camphorsultamcarbonyl)benzoic acid ester *sc*-**20** and the diastereoisomers were separated by chromatography. The faster eluting fraction gave crystals suitable for X-ray crystallography, which revealed that the compound had the *Msc* conformation. The *Msc* form was hydrolyzed to remove the phthaloyl and camphorsultam groups. Compound *Msc*-**19** was methylated again to reproduce the tetramethoxy compound *Msc*-**18**, which has $[\alpha]_D^{25} = -7.6$ at 25 °C. Similarly, the *Psc* form of the ester *Psc*-**20** was separated by chromatography and has $[\alpha]_D^{25} = +7.8$. The CD spectrum of *Psc*-**18** is shown in Figure 4.



Scheme 13. A bitriptycyl of which the *ap* form has C_{2h} symmetry and those compounds related to its resolution (R*: see Scheme 5)

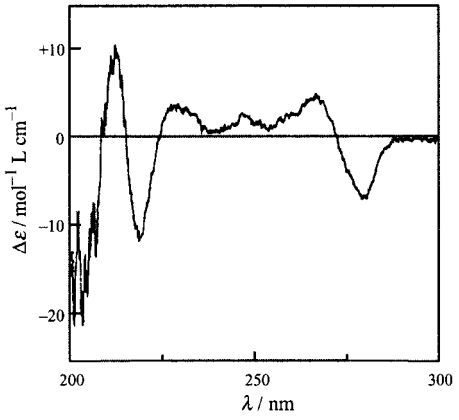
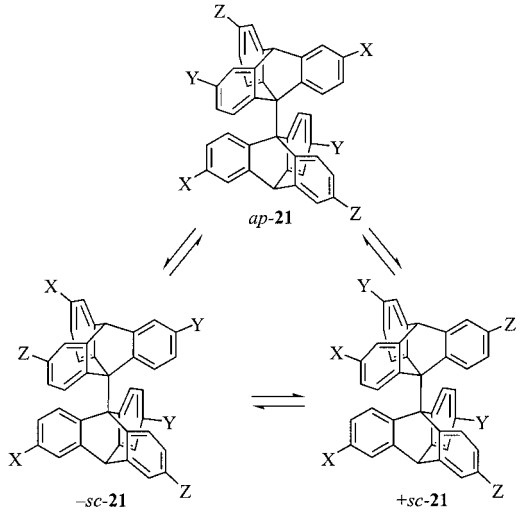


Figure 4. CD spectrum of *Psc*-**18**

Example 3. Rotamers of a C_i Molecule

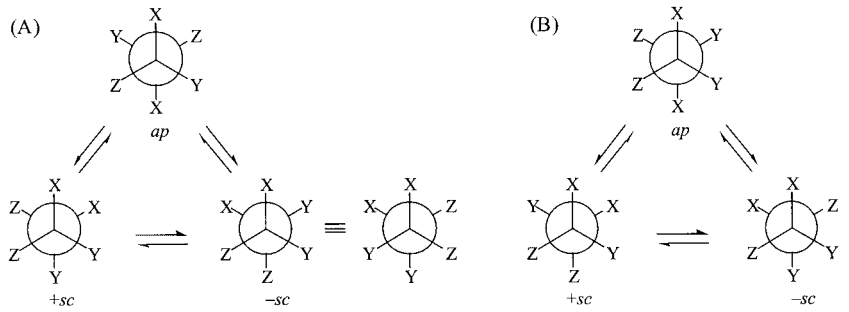
The final example of a compound in which the *ap* form is not optically active, because of its symmetry, is a C_i-symmetric molecule. The most well-known example of this class of compounds is *meso*-tartaric acid, which is an acid that has the structure (HOCO)H(HO)C−CH(OH)(COOH) with the two chiral centers having *R* and *S* configurations, respectively. For brevity and clarity, we choose to discuss this compound hereafter by naming it (*R*,*S*)-tartaric acid. Again, it is not possible at present to freeze the internal rotation of purely aliphatic compounds, but it is possible to do so if we use 9,9′-bitriptycyl units.

Let us consider a bitriptycyl whose benzeno bridges in the top half are different from each other while those in the bottom half have the same substituents that are present in the top half (Scheme 14). We can define the stereochemistry of this type of molecule as XYZC−CXYZ. The configuration of the carbon atoms in this molecule can be either *R* or *S*. If they are *R* and *S*, then the molecule is a stereochemical analog of (*R*,*S*)-tartaric acid. If both of the chiral centers are *R* or *S*, these molecules are analogs of optically active tartaric acid. Let us call this tartaric acid either (*R*,*R*)- or (*S*,*S*)-tartaric acid, which we can name, in general, as (*R**,*R**)-tartaric acid. The synthetic method described above is expected to produce all the stereoisomers of XYZC−CXYZ, not only the analogs of (*R*,*S*)-tartaric acid but also those of (*R**,*R**)-tartaric acid. If these isomers do not interchange because the barrier to rotation is very high, then the diastereoisomers shown in Scheme 15 are expected to exist. There are a total of five diastereoisomers that must be separated and identified.

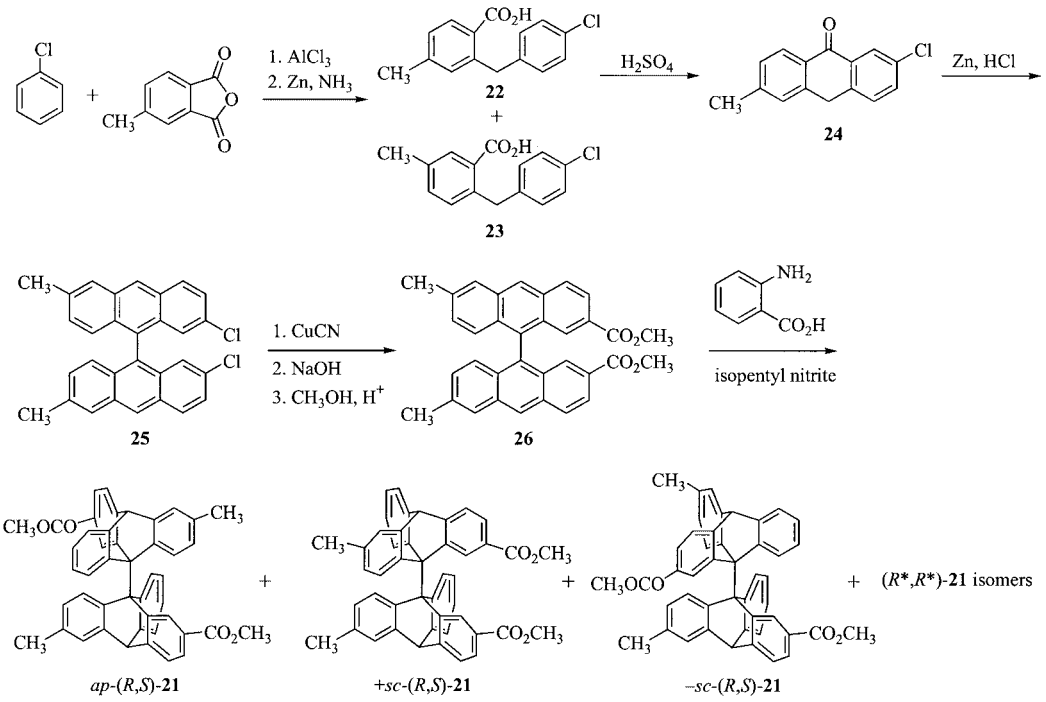


Scheme 14. Rotational circuit of an (*R*,*S*)-9,9′-bitriptycyl

The rotational circuits of XYZC−CXYZ are presented in Scheme 15. Conformers shown in Scheme 15 (A) correspond to the analogs of (*R*,*S*)-tartaric acid and those of (B) are analogs of (*R**,*R**)-tartaric acid. In Scheme 15 (A), a Newman projection — obtained by looking at the rear of the Newman projection of the −*sc* molecule and rotating it



Scheme 15. Rotational circuits of stereochemical analogs of tartaric acids: (A) models of (*R*,*S*)-tartaric acid and (B) those of (*R**,*R**)-tartaric acid (X: fiducial group)



Scheme 16. Synthetic route to compound **21**

by 60° anticlockwise — is shown in addition to the rotational circuit of (*R*,*S*)-XYZC−CXYZ, because the enantiomeric relationship between +*sc* and −*sc* conformers is not self-evident. The important point here is that, whereas the *ap* form has a center of symmetry in the molecule so that the pairs of X, Y, and Z units are all equivalent, the X unit that is attached to the front carbon atom in the *sc* form is not equivalent to the X unit attached to the rear carbon atom. This point is understood when one looks at the flanking substituents and examines the same substituent that is attached to the different carbon atoms. The +*sc* and −*sc* forms are C_1 molecules and, thus, they must be optically active and are enantiomers of one another. Scheme 15 (B) shows (*R*,*R*)-XYZC−CXYZ, which is an analog of (*R**,*R**)-tartaric acid. These molecules are all C_2-symmetric, including the *ap* form, and must be optically active when isolated. Note that the two X substituents are equivalent in all the rotamers of (*R*,*R*)-XYZC−CXYZ as well as in *ap*-(*R*,*S*)-**21**. Here we assume that the precedence in the C.I.P. rule is X > Y > Z > CXYZ.

We selected compound **21** as a target molecule.[24] This compound was selected because of the convenience of its synthesis, which is outlined in Scheme 16. Chlorobenzene was condensed with 4-methylphthalic anhydride, using aluminium chloride as the catalyst, to result in a mixture of isomers that was reduced with zinc and ammonia to produce a mixture of **22** and **23**. This mixture was cyclized upon treatment with concentrated sulfuric acid, affording a mixture of **24** and 2-chloro-7-methyl-9-anthrone, in which the former was the main component. After separation, **24** was reduced with zinc and hydrochloric acid to produce **25**, which was then converted into a dicyano compound upon treatment with copper(I) cyanide in *N*-methyl-2-pyrrolidone. The dinitrile was hydrolyzed and esterified to give **26**. Compound **26** was treated with benzyne generated in situ from anthranilic acid, and the products were separated cru-

dely by GPC. Further separation by HPLC afforded four fractions containing the desired compounds **21**. This result means that four diastereoisomers out of the possible five were obtained by this reaction sequence.

The *ap* form, *ap*-(*R*,*S*)-**21**, is expected to be eluted very quickly during chromatography because it is the least-polar compound and, indeed, there was a fraction that eluted early. This fraction crystallized and X-ray crystallography indicated that this compound was indeed *ap*-(*R*,*S*)-**21**. The discussion presented above indicates that if there is a compound that exhibits different NMR signals for a substituent, or if the aromatic carbon atoms provide 36 signals, then it must be either the +*sc* or −*sc* form of (*R*,*S*)-**21**. All other isomers of **21** should show 18 signals for the aromatic carbon atoms and identical signals due to the substituents. There was indeed a fraction that showed two peaks each for the aromatic methyl and the methoxycarbonyl methyl units. This compound displayed 33 signals for the aromatic carbon atoms out of a possible 36, whereas the other isomers all showed 18 signals in their ^{13}C NMR spectra. Next, we resolved ±*sc*-(*R*,*S*)-**21**, which was possible by carrying out chiral chromatography on a stationary phase of CHIRALCEL OD (Daicel). The faster eluting fraction has $[\alpha]_D^{22} = -56$ and the other has $[\alpha]_D^{22} = +54$. The CD spectra of the (+) and (−) isomers are shown in Figure 5. Thus, we obtained all the isomers of a stereochemical analog of (*R*,*S*)-tartaric acid. We were fortunate in that we were able to isolate all the diastereoisomers that are expected for (*R*,*S*)-**21**. All the data given above indicate that the optically active isomers of (*R*,*S*)-**21** are enantiomers of one another, although their absolute conformations have not yet been determined.

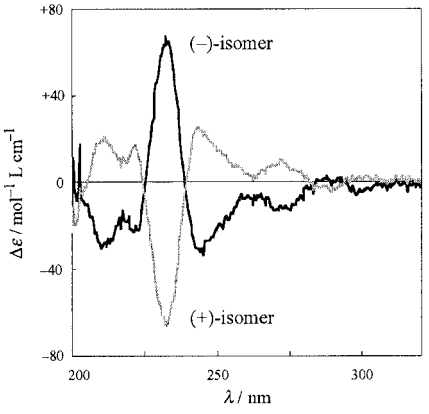


Figure 5. CD spectra of (+) and (−) isomers of ±*sc*-(*R*,*S*)-**21**

The remaining fraction must correspond to isomers of (*R**,*R**)-**21**, because all the possible isomers of (*R*,*S*)-**21** were isolated. Indeed, the two fractions obtained in addition to the (*R*,*S*)-**21** isomers could be resolved by chiral chromatography on CHIRALCEL OD. We cannot tell at the present time, however, which fractions corresponds to *ap*-, +*sc*-, and −*sc*-(*R**,*R**)-**21**. Assignments of absolute conformations to ±*sc*-(*R*,*S*)-**21**, as well as the search for the missing fifth fraction of (*R**,*R**)-**21**, are in progress.

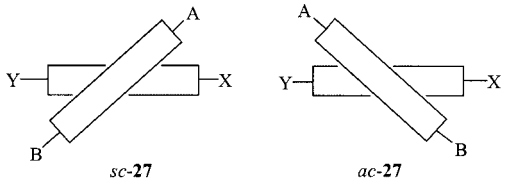
The results described above provide some insight into the optical inactivity of (*R*,*S*)-tartaric acid. "Internal compensation" was proposed more than a century ago.[23] Its incorrectness was pointed out by Noller,[24] but experimental verification of Noller's postulate has been lacking. Noller states that (*R*,*S*)-tartaric acid should be a mixture of a pair of C_1 forms and a C_i molecule in solution, as Scheme 15 indicates. The optically active isomer racemizes quickly at room temperature because its enantiomer is formed by internal rotation. Our compounds are those in which internal rotation is very slow. Even though the internal rotation is slow, cancellation of the optical activity of a compound occurs because the compound and its enantiomer exist in the same quantity because their free energies are the same. Our results described above comprise experimental proof of Noller's postulate.

Future Problems

So far we have discussed absolute conformations about a $C(sp^3)-C(sp^3)$ bond. In the rest of this review we wish to discuss conformations about a C−C bond having other hybridizations. We will confine ourselves to phenomena that have been neglected in classical works, but arise when conformations are considered, although the technique of freezing rotation is not yet known.

$C(sp^2)-C(sp^2)$ Bond

Typical examples of the chiral compounds about this type of bonds are biphenyls. The advances in this field of chemistry have been reviewed.[27] In the classical treatment, as well as in the C.I.P. rules,[10] the conformations of biaryls have been neglected. As shown in Scheme 17, however, it is clear that different conformations exist in a biphenyl compound with a given sense of helicity (*M* or *P*). We have pointed out this phenomenon on a few occasions.[6,13,28] Although this type of isomerism was discussed by Sato,[29] it has not attracted the interest of many chemists. To make the barrier to isomerization between *sc*-**27** and *ac*-**27** high, two techniques can be considered: one is to stabilize the original state and the other is to make the energy of the transition state for rotation high. If they are isolated, it should be possible to specify the stereochemistry by a combination of the torsion angle (*sc* or *ac*) and the sense of helicity (*M* or *P*).[30]



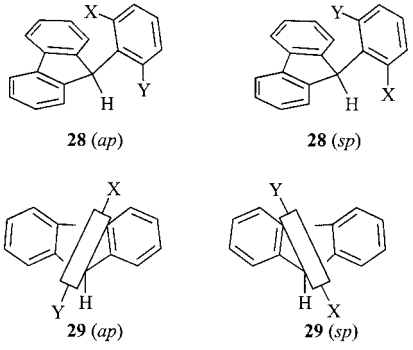
Scheme 17. Two conformations of a *P*-biphenyl (C.I.P. sequence A > B, X > Y)

There is another problem to be considered in this category. In the biaryl series, the conformation of the original state will be close to coplanarity, if there are no steric effects to hinder the coplanar structure. When the steric effect is severe, however, then the original state for internal rotation tends to take a structure in which the two aryl planes are orthogonal to one another. We have encountered such an example recently: the torsion angle in a 9,9′-bianthryl derivative is close to 90°.[31]

Because the Klyne−Prelog rule[7] was proposed for the convenience of naming the torsion angle of a C−C bond, one of whose carbon atoms is sp^3-hybridized, the Klyne−Prelog rule does not have a name for a torsion angle that is close to 90°. We should name the region when we want to discuss the torsion angles in biaryls.

C(sp^2)−C(sp^3) Bond

We have been able to isolate, in addition to the triptycene derivatives, rotational isomers of 9-arylfluorene compounds **28**.[6] Perspective views (**28**) and projections (**29**) along the C(aryl)−C(9 of fluorene) are given in Scheme 18. The barriers to rotation in these compounds are rather low, ca. 29 kcal/mol at the highest. The descriptors used in the scheme are consistent with the Klyne−Prelog rule, when X precedes Y in the C.I.P. sequence rule.[10] As we see in the projections **29**, the benzene ring plane of the aryl group is tilted from the bisecting plane of the fluorene ring; such tilting has been found by X-ray crystallography.[32,33] As a result, these molecules are chiral. They must be optically active when isolated, but a technique for freezing out the conformations has yet to be found. The naming of the absolute conformations will be possible by using the Klyne−Prelog rule for the conformation (*ap* or *sp*) and descriptors showing the sense of helicity (*M* or *P*).



Scheme 18. 9-Arylfluorenes and their projections (see text for descriptors)

Optically active paracyclophanes may be discussed here, because these compounds have conformers in which rotations about two bonds, which connect the *ansa* chain to the principal benzene ring, results in enantiomerization. Specification of the stereochemistry of paracyclophanes was defined by the original C.I.P. rule[10] and also in a revised form in a following paper.[34] In both of these documents, conformations about the bonds connecting the *ansa* chain and the main benzene ring have been ignored. One realizes, however, that one obtains various conformations by rotating about the bonds in question. The important conformations must be seen in ethylbenzene, which is a prototype of paracyclophane. Here, the torsion angle of ca. 90° is also important, because in ethylbenzene the conformation having a torsion angle is 90° the most stable one.[35]

Notes Added in Proof: The following two papers, which mention conformational problems relevant to those discussed in this review, have appeared after submission of the manuscript. G. Delogu, D. Fabbri, S. Menichetti, and C. Nativi, *Tetrahedron* **2003**, *59*, 2131−2136 reported that the reactivity of some biaryl derivatives is dependent on the torsion angles between the two phenyl rings in biaryls. G. Cinacchi and G. Prampolini, *J. Phys. Chem. A* **2003**, *107*, 5228−5232 discussed conformations of ethylbenzene. The results are in agreement with that in ref.[35] in that the most stable conformation is one in which the CH_2-CH_3 bond is perpendicular to the benzene plane.

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[30] If a biphenyl takes a conformation in which the two benzene rings are nearly coplanar, then one would be able to specify its absolute conformation with a combination of descriptors for the sense of chirality (*P* or *M*) and descriptors of torsion angles (*ap* or *sp*), or *Z* and *E*, which are recommended by IUPAC for specifying the stereochemistry of partial-double-bond-containing isomers of classical *s-cis* and *s-trans* conformations.[9] Because of steric effects, however, the torsion angles in biaryls that bear substituents in *ortho* positions tend to be between 70 and 90°.[29] Thus, we illustrate in Scheme 17 models that have torsion angles in the *sc* and *ac* regions.
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