

# Learning Organic Chemistry Through Natural Products

## 2. Determination of Absolute Stereochemistry

*N R Krishnaswamy*

**N R Krishnaswamy** was initiated into the world of natural products by T R Seshadri at University of Delhi and has carried on the glorious traditions of his mentor. He has taught at Bangalore University, Calicut University and Sri Sathya Sai Institute of Higher Learning. Generations of students would vouch for the fact that he has the uncanny ability to present the chemistry of natural products logically and with feeling.

**Chemical methods to determine the conformations and absolute configurations of menthol, a cyclohexane derivative with 3 chiral centres, are described.**

Structures of organic compounds are usually determined using data generated by chemical and instrumental methods. A chemist then invariably attempts to confirm the proposed structure by synthesis. The above approach was described in the previous part of this series, using geraniol as an illustrative example. This molecule had sufficient complexity to highlight the steps of the deductive process. However, geraniol lacks an important feature present in many organic compounds, in general, and in natural products, in particular. The molecular structure of geraniol is superimposable on its mirror image and hence it is achiral. The problem of structure determination has an added dimension in molecules which are chiral.

Though the ultimate method of determining the absolute stereo-chemistry of a compound is X-ray diffraction analysis, an organic chemist gets more satisfaction from a chemical approach which also generates new chemistry.

Chirality or “handedness” of organic molecules usually arises due to the tetrahedral geometry of tetra-coordinate carbon. If the four substituents on a carbon atom in a molecule are different, a chiral centre is present. In such molecules, there are two ways of arranging the substituents leading to non-superimposable structures. These are called enantiomorphs. In such chiral molecules, it is not enough to identify the bond connectivities of all the atoms. We also need to find out the precise stereo-chemical relationship involving the substituents (or equivalently, the absolute configuration at the chiral centre).

The problem becomes more complex if more chiral centres are present in the same molecule. For a molecule with  $n$  asymmetric

*Address for correspondence*

N R Krishnaswamy,  
Visiting Professor,  
NMKRV College for Women  
with PG Centre,  
Jayanagar III Block,  
Bangalore 560011, India.

centres, there are theoretically  $2^n$  possible stereo-isomers. In this part of the series, we will discuss how the absolute stereochemistry of a compound can be delineated using chemical methods, with the help of an example containing multiple chiral centres.

The example we have chosen addresses another interesting structural problem. Molecules do not necessarily have rigid geometries. They can adopt many flexible 'conformations'. In ring systems, some conformations are especially preferred. The molecule we have chosen illustrates concepts associated with ring conformations as well as absolute configurations at chiral centres.

### Menthol - a Chiral Cyclohexane Derivative

As our illustrative example we have chosen Menthol which is a monocyclic monoterpene alcohol. It is 2-isopropyl-5-methylcyclohexanol and has three chiral centres as shown in *Scheme 1*. Therefore,  $2^3$  or eight optically active stereoisomers of this structure are possible and are known. These are (+) and (-) menthol, (+) and (-) neomenthol, (+) and (-) isomenthol, and (+) and (-) isoneomenthol. Further, being cyclohexane derivatives, menthol and its stereoisomers also exhibit conformational isomerism. Thus, this example can illustrate the principles involved in conformational analysis as well as configurational assignments.

The problem is to assign the correct stereostructure to each of the eight isomers mentioned above. The first step would be to find out the relative configurations of the three asymmetric centres in each enantiomeric pair of the four diastereoisomers. Determination of the absolute configuration would then lead to a unique stereostructure for each and every optical isomer. *Scheme 1* shows all the possible structures.

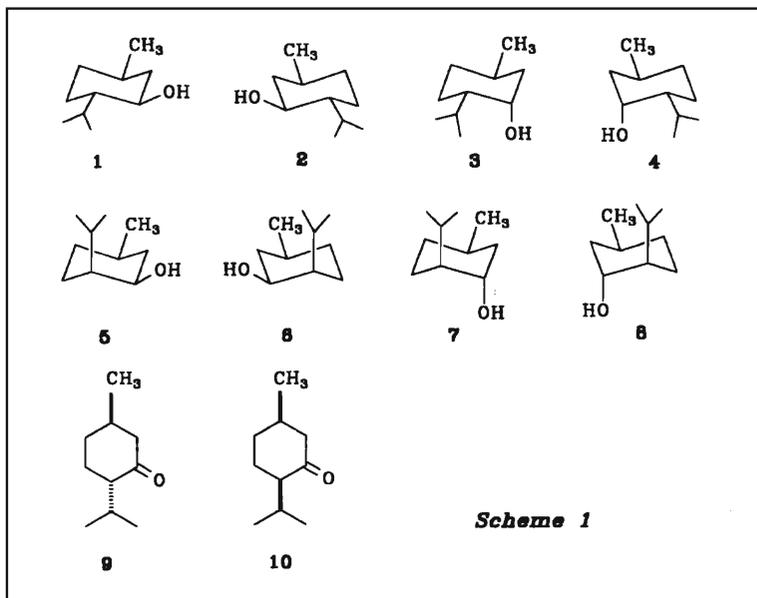
Examination of the structures shows that compounds 1 and 2 which form a pair of enantiomorphs, are degenerate (that is they have the same energy) and should represent the thermodynamically

Molecules do not necessarily have rigid geometries. They can adopt many flexible 'conformations'.

(-) Menthol is a constituent of the peppermint oil which is the essential oil of *Mentha piperita*.

Enantiomorphs do not differ in physical or chemical properties except in the sign of optical rotation, whereas diastereoisomers differ in physical and chemical properties.





Cyclohexane prefers the chair conformation and bulky substituents opt for the equatorial position.

An axial substituent may encounter severe 1,3-diaxial steric and/or repulsive polar interactions thus causing a strain in the system.

cally most stable enantiomeric pair among the four pairs of diastereoisomers. Incidentally, it should be noted that enantiomorphs do not differ in energy content whereas diastereoisomers do. Compounds 1 and 2 are thermodynamically the most stable because all the three substituents attached to the cyclohexane framework are equatorially oriented. Therefore, the strain due to steric interactions between them, if any, will be at a minimum. On the other hand, each axial substituent introduces a finite amount of steric strain thus increasing the energy of the system. In structures 7 and 8, two of the substituents, namely the hydroxyl and the isopropyl groups are axially oriented and these should possess greater energy than 1 and 2.

An idea of the free energy contents and therefore, relative thermodynamic stabilities is given by the differences in boiling points, densities and refractive indices of the different stereo-isomers. As the energy content decreases, that is as the stability increases, the boiling point, density and refractive index decrease. An empirical relationship correlating thermodynamic stability with these physical properties is known as the *von Auwers-Skita rule*. A comparison of the physical properties of the four pairs of diastereoisomers

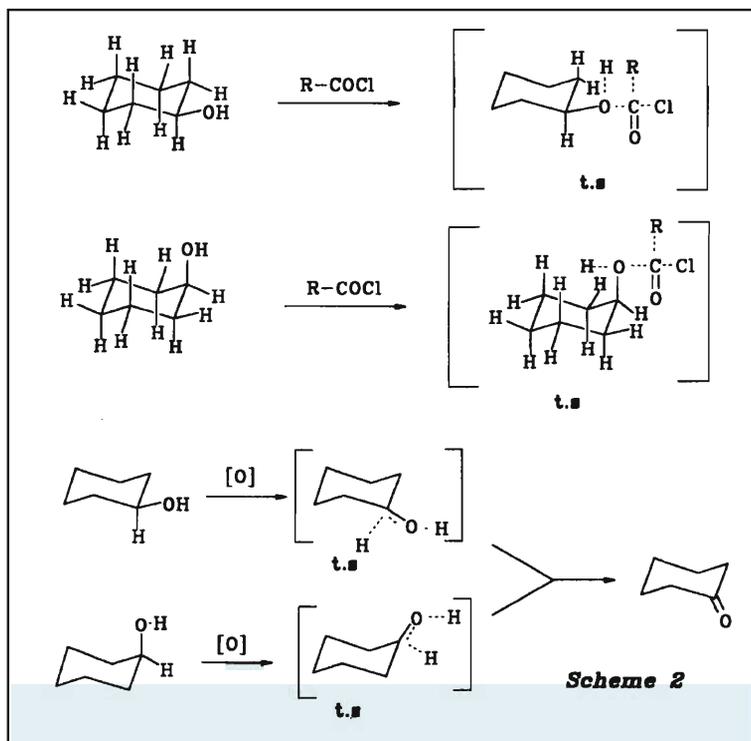
shows that the two enantiomorphous forms of menthol are the most stable and, therefore, these can be assigned the structures 1 and 2.

Menthol and neomenthol both yield, on oxidation, the same ketone, menthone (9). Similarly, isomenthol and neoisomenthol give isomenthone (10). Hence, menthol and neomenthol are epimers differing in configuration only at carbon-1. Since we have already assigned structures 1 and 2 to the two enantiomorphous forms of menthol on the basis of von Auwers-Skita rules, neomenthol can be given structures 3 and 4. In these structures the hydroxyl group takes an axial orientation. By using conformational methods of analysis, Eliel was able to confirm these structural assignments as explained below.

Equatorial cyclohexanols undergo acylation more readily than the corresponding axial isomers. In contrast, the axial isomers can be oxidised at a faster rate than their equatorial isomers, both yielding the same ketone. These observations can be explained on the basis of relative differences in the energies of the transition states. In the acylation reaction, the transition state for the axial alcohol experiences an increase in steric strain due to an increase in the size of the axial substituent. In the transition state of the equatorial isomer, on the other hand, the increase in the size of the substituent does not cause any appreciable increase in steric strain as the group is oriented away from the ring. The situation is just the reverse in the oxidation reaction wherein a  $sp^3$  carbon gets converted into a  $sp^2$  carbon. This leads to a flattening of that part of the ring system and with that any axial-axial repulsion disappears. Thus, in the case of the axial alcohol, there is a decrease in steric strain in the transition state as the oxygen atom of the hydroxyl group leans away from its original vertical position to finally fall into the plane of the ring in the product ketone. In the equatorial isomer, a corresponding decrease in energy is not seen as the hydroxyl group is already, more or less, in the plane of the ring. These changes are pictorially shown in *Scheme 2*.

Every reaction has to go through a transition state (t.s.) and the height of the energy barrier separating the reactant and the t.s. controls the rate of the reaction.

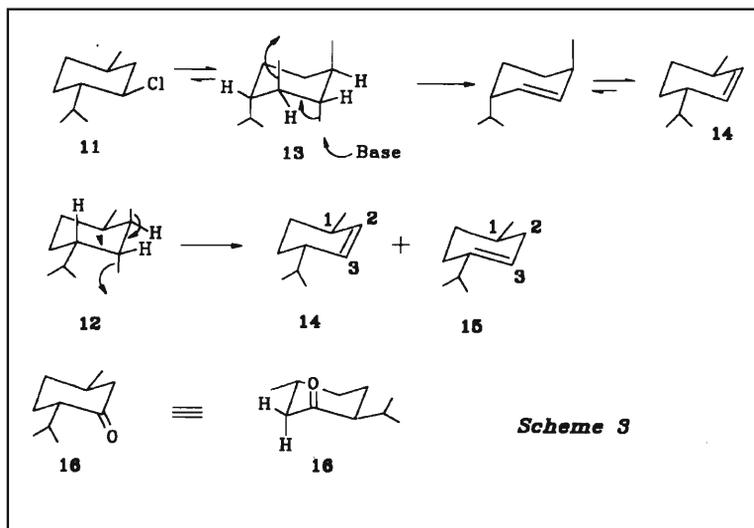




Now, it is known that the rates of acylation of the isomeric menthols follow the order: menthol > isomenthol > neoisomenthol > neomenthol. Therefore, in menthol and isomenthol, the hydroxyl group should be equatorially oriented whereas in neomenthol and neoisomenthol it takes an axial position. This is supported by the observation that neomenthol and neoisomenthol undergo oxidation at faster rates than menthol and isomenthol respectively.

*Scheme 3* depicts another approach to the same problem. This is based on differences in the rates of base-catalysed E2 elimination of HCl from menthyl chloride 11 and neomenthyl chloride 12. In this reaction, neomenthyl chloride reacts 200 times faster than menthyl chloride. The E2 reaction is a concerted reaction unlike the E1. The two leaving groups, hydrogen as proton and chlorine as chloride ion, should be *anti*- to each other for simultaneous expulsion so that the reaction path follows a straight line as shown in the Scheme. This can be compared to shooting an arrow

The E2 reaction is a one-step concerted process; no reactive intermediates are involved.



through a tree forming a straight hole in the trunk of the tree. An *anti*- arrangement of the hydrogen and chlorine is seen only in 12. On the other hand, 11 must first undergo a conformational change into the energetically less favourable conformer 13 where the chlorine is now axially oriented before it can undergo the E2 reaction. That is why 12 reacts several times faster than 11. Another consequence of the stereochemical differences between 12 and 13 is that in 13 only one *anti*-elimination is possible resulting in the exclusive formation of menth-2-ene (14) whereas two possibilities exist in 12 which gives a mixture of 14 and the isomeric menth-3-ene (15); the latter is the major product as it is thermodynamically more stable than 14. The formation of 15 as the major product can be predicted on the basis of the Saytzeff rule.

The final problem is the determination of the absolute stereochemistry of (-) menthol. As mentioned earlier, this compound can have either structure 1 or 2. The configurations in 1, according to the sequence rule, are 1R, 2S and 3S. Isomer 2, accordingly, has the 1S, 2R, 3R configuration. On oxidation, (-) menthol yields (-) menthone whose absolute stereochemistry can be determined using the octant rule. This semi-empirical rule is based on the relationship between the sign of the Cotton effect in the optical rotatory dispersion spectrum and absolute configuration

The change of 11 into 13 involves ring flipping where one chair form gets converted into an alternative chair. This is a conformational change with the configurations remaining unaffected.

The sequence rule formulated by Cahn, Ingold and Prelog is a method of designation of configurations which is not linked to an arbitrary reference compound like the earlier D,L nomenclature.

The ORD phenomenon is the increase in optical rotation with decrease in wavelength of the incident light. If the optically active compound has a chromophore like the carbonyl group near one or more asymmetric centres its ORD spectrum will show the Cotton effect.

of a chiral cyclohexanone. Since (-) menthone shows a (+) Cotton effect, it should have the absolute stereochemistry as in 16. Therefore, (-) menthol should have the structure 1 and (+) menthol the structure 2. (+) Neomenthol can be assigned structure 3 as (-) menthol and (+) neomenthol both yield the same ketone, (-) menthone, on oxidation. Therefore, (-) neomenthol is 4.

A similar approach can be used to elucidate the absolute stereochemistry of the remaining isomers 5-8.

### Suggested Reading

D Nasipuri. *Stereochemistry of Organic Compounds - Principles and Applications (Second Edition)*. Wiley-Eastern. 1994.



**Lesson from a mining accident ...** At the beginning of the 18th century mining accidents due to broken elevator chains became more frequent. Many scholars including the famous Gottfried Wilhelm Leibniz, tried to improve the iron chains, but without success. Finally a senior mining adviser, W Albert (who was a lawyer by training), came up with the idea of replacing the chains with wire ropes or cables. This made it possible to exploit one of the most important properties of iron — its high tensile strength. (from *Quantum*, September-October 1995)



**A tragic mix-up ...** John Tyndall, a famous British physicist of the 19th century, could have been among the first to understand the perils of the greenhouse effect. But, alas, that was not to be. One wintry morning in 1893 his young wife Louise gave him a giant dose of chloral instead of the normal big dose of magnesia for his indigestion. Tyndall swallowed the dose and remarked that it tasted sweet. "John, I gave you chloral!", Louise told him. "Yes, my poor darling", Tyndall told her, "you have killed your John". He was dead before sundown. (from *Next Hundred Years* by J Weiner).

