Twenty five years before the tetrahedral structure for carbon was proposed in 1874 to explain the optical activity and other properties of organic compounds, Louis Pasteur discovered the existence of enantiomerism in tartaric acid. He separated the oppositely shaped crystals of tartaric acid by handpicking, found their optical rotation to be in opposite directions, and concluded that this optical property was attributable to the existence of two oppositely shaped tartaric acid molecules. Thus the new subject of stereochemistry was heralded.

Introduction

Ernest L Eliel, the author of the most popular and definitive textbook, *Stereochemistry of Carbon Compound*, dedicated its first edition published in 1962 to the memory of Louis Pasteur who discovered *levor*rotatory tartaric acid in 1848. This discovery was the “big-bang” of stereochemistry. Like the universe after the big-bang, stereochemistry has grown ever since and is still expanding fast. It encompasses many subjects of science that deal with the structure of molecules and their behaviour at all levels and under various circumstances. Though it is taught popularly as a course in chemistry, it is neither a hand-maid nor a branch of chemistry. In fact, it is an important aspect of study in not only all branches of chemistry, but also biology, medicine and many related fields. Its reach extends to physics and mathematics too in areas such as spectroscopy, crystallography, thermodynamics, quantum mechanics, symmetry and topology, that have contributed to its development and growth.

The germ of such a vast subject lies in a simple act of Pasteur’s viewing of a salt of racemic acid through a lens. Behind this act
lies the intuitive curiosity of a great mind to solve an enigmatic problem about tartaric acid. With the genius and sagacity of Pasteur it was not difficult to find the solution within a short span of time. The result is an example of the catchphrase he coined later, ‘chance favours only the prepared mind’.

Tartaric acid did not stop at being just the causative factor for the dawn of stereochemistry but it has also played an important role ever since in its development. In consideration of this fact, the present article focuses, albeit briefly, on the work of Pasteur on tartaric acid and its noteworthy part in the advancement of certain aspects of stereochemistry, particularly in the determination of the configuration of natural products such as carbohydrates and in designing enantioselective synthetic methodologies, for example, Sharpless epoxidation.

The Beginning: a Bunch of Grapes

In addition to being economically important industries, distilleries and breweries have been the hubs of considerable research activity, more so in the 19th century. Many seminal discoveries were made in chemistry and microbiology by studying fermentation processes, their underlying causes, the products and much else. Tartaric acid was one such product of winery, well known at the time of Pasteur. It was known to the famous Arab alchemist, Jabir ibn Hayyan, in the eighth century.

Tartaric acid is found in many plants such as grapes, tamarinds, pineapples, mulberries and so on. Wine lees (called mud in the US), the sediment collected during the fermentation of grapes, contains potassium bitartrate (potassium hydrogen tartrate) as its major component. The impure salt extracted from the sediments is called argol. The pure salt is obtained by boiling argol in water and cooling the clear solution. The pure salt is called cream of tartar. During storage, sometimes a second acid salt called paratartaric acid or racemic acid (from racemus, Latin for ‘bunch of grapes’) is deposited in casks. (A cask is made by joining staves – thin, slightly curved strips of wood or metal –
In 1769, Carl Wilhelm Scheele isolated the dibasic acid by boiling cream of tartar with dilute hydrochloric acid, followed by adding chalk, and treating the product with dilute sulphuric acid. The solution, on removal of calcium sulphate and concentration gave tartaric acid. This sequence, using present day formulae, is shown in Scheme 1.

Rotating Polarised Light

In 1809, Malus discovered plane-polarised light. Soon, Arago (1811) and Biot (1812) noted that the plane of such light is turned by quartz plates cut at right angles to its crystal axis, by an angle proportional to the thickness of the plate. Biot extended this study using other substances and in 1815 found that some organic substances (example: solutions of sucrose, camphor, tartaric acid, or liquids like turpentine) possessed the ability to rotate plane-polarised light, some to the right, and others to the left. He also noted that some of these substances exhibited this property in solid, liquid or gaseous states and in solution. This was not the case with quartz, which showed this property in solid state only and not in the molten condition.

Tartaric acid and racemic acid were considered to be one and the same substance.

Tartaric acid and racemic acid were considered to be one and the same substance as their elemental composition (C₄H₄O₆), and chemical behaviour were the same. Eilhard Mitscherlisch, an eminent contemporary crystallographer, had found that sodium ammonium salts of tartaric and racemic acids were isomorphous.
(isos = same, morph = shape), which also indicated that the two acids were identical. However, when Biot (1832) measured the optical rotation of these two acids, he found that tartaric acid turned the plane polarised light to the right, while racemic acid was inactive, i.e., it did not turn the plane of the polarised light. Biot and Mitschelisch were perhaps surprised by these results, but it seems that they did not bother to probe this anomaly further.

**The Prepared Mind Detects Enantiomeric Crystals**

Pasteur was trained as a crystallographer. His doctoral work under Antoine Balard was to grow crystals of chemical compounds and study their morphology. With his insightful understanding of the nature of crystals, Pasteur was puzzled about the difference in the optical behaviour of tartaric and racemic acids, although they were identical in other properties. His intense curiosity to find the reason for this discrepancy prompted him to examine the problem carefully. Following the work of Mitscherlisch, Pasteur prepared sodium ammonium racemate and crystallised it from an aqueous solution by the slow evaporation of water below 26 °C by just keeping the flask outside his laboratory.

Viewing the crystals under a microscope, Pasteur noticed that they were in two opposite forms (*Figure 1*). That is, they were related to each other in the manner of an object and its nonsuperimposable mirror-image, very much like our right and left hands, and were termed enantiomorphic (*enantios =

*Figure 1.*
opposite, morph = shape). He separated the two types of crystals patiently by hand using a pair of tweezers. To his astonishment and great delight, he found one of them to be identical to the earlier known tartaric acid salt that rotated plane polarised light to the right (dextro rotatory), while the other rotated the plane of polarised light to the left (levorotatory) to the same extent. He observed that their aqueous solutions also exhibited the dextro rotatory and levorotatory properties. However, when equal amounts of the two salts, or their aqueous solutions were mixed, the optical activity was lost. It was for the first time that levorotatory tartaric acid was obtained. It was also for the first time that an optically inactive mixture was resolved into its pure active components. Since the inactive mixture used was known as racemic acid, all such inactive mixtures of enantiomeric substances came to be known as racemic mixtures.

Quartz Gives Hands to Stereochemistry

It was clear from these experiments that enantiomorphism was not restricted to only solid state as in the case of quartz, but is present at the molecular level as well, i.e., molecules can exist in two opposite forms as an object and its nonsuperimposable mirror image. Thus was born the new science of stereochemistry, as a result of combining the principles of chemistry, crystallography and optics by the hard work and brilliance of Pasteur.

Until then, only quartz, in the solid state, was known to have the dextro rotatory and levorotatory properties that related to its opposite crystalline forms. Hauy had recognised in 1801 that quartz existed in two crystalline forms related to each other as an object and its nonsuperimposable mirror image. Based on the location of crystal faces, one form was identified as right-handed and the other as left-handed, i.e., they possessed handedness or chirality (chiros means hand in Greek). In 1812, Biot observed that the two types of crystals turn plane polarised light in opposite directions but they became inactive when melted. In 1822, Herschel could correlate the direction of rotation of plane polarised light with the shape of quartz crystals.
Pasteur had the vision to attribute the optical property of the two tartaric acids to the difference in their molecular structures as object and its nonsuperimposable mirror image. This was an extraordinary insight on his part at that point of time (1849), if we consider the fact that the principles of molecular structure were emerging just then through the efforts of Kekule (see, Resonance, May 2001), Couper, Butlerov, and others, and the idea of three dimensional structure for molecules came 25 years later in 1874 when van’t Hoff and LeBel independently proposed tetrahedral structure to carbon with its four substituents. The work of van’t Hoff was indeed the real take-off point for stereochemistry, which has been growing ever since.

Due to his contact with distillers and brewers, Pasteur was entrusted with the problems of fermentation in distilleries and breweries. As a result he turned his attention to yeasts and then to bacteria, and achieved great success in biology and medicine (See article by S Mahadevan in this issue.). Though Pasteur was a chemist, his only notable work in chemistry was on tartaric acid but it was enough to launch a whole new branch of science. Because tartaric acid was so important to the birth and growth of stereochemistry, a few of its uses in solving stereochemical problems are considered here.

**Tartaric Acid – the Adam of Stereoisomers**

The enantiomorphous crystals of (+)- and (–)-tartaric acid salts are given in *Figure 1*. Tartaric acid can be obtained in four forms, namely, (+)-tartaric acid, (–)-tartaric acid, racemic acid or (±)-tartaric acid and meso-tartaric acid. The first two acids are enantiomers, i.e., they are nonsuperimposable mirror images, are optically active and asymmetric. Racemic acid is a 1:1 mixture of the first two acids and is optically inactive. *Meso*-tartaric acid is a symmetric molecule, and is optically inactive. The configurational structures of the three acids are given in *Figure 2*.

These configurations were derived by correlating with the arbitrarily assigned configurations of (+)- and (–)-glyceraldehydes (*Figure 3*).
The Key to Absolute Configuration

The actual structure or absolute configuration of (+)-tartaric acid was determined in 1951 by Bijvoet using its sodium rubidium salt. It was a miraculous coincidence that it turned out to be identical to the previous arbitrarily assigned (R,R)-configuration. (It could well have been an (S,S)-configuration. Had it been so, imagine the consequence of changing all the configurational names of compounds given to them prior to 1951), (See Figure 2).

The absolute configuration of tartaric acid was the standard in determining the absolute configuration of many chiral molecules, such as sugars and other polyhydroxy compounds, which could be broken down to one or more of tartaric acid isomers. To illustrate this, the example of D-glucose is taken here.

(+)-Glucose has the elemental composition of \( C_6H_{12}O_6 \). It contains a camouflaged aldehyde (-CHO) group and five hydroxy (-OH) groups. With this information, and a few other inputs, one

![Figure 2.](image)

**Figure 2.**

![Figure 3.](image)

**Figure 3.**
can write the following simple structure for it (Figure 4).

The challenge was to establish the relative positions of the four substituents on each of the four chiral carbons 2-5.

In the degradative procedure the molecule was broken down, using a variety of reagents, to give smaller molecules, which included tartaric acid. Some of these reactions are summarised in Schemes 2 and 3.

Since the configuration of meso-tartaric acid was known, the configuration of the 4\textsuperscript{th} (C-4) and the 5\textsuperscript{th} (C-5) carbons was established.
The formation of dimethyl ether of (R,R)-tartaric acid settled the geometry of C-1 and C-2. The configuration of trimethoxyglutaric acid was also determined, among other reactions, by its degradation to (R,R)-tartaric acid. These results were vital inputs, along with other data, in assigning the configuration of (+)-glucose given in Figure 5.

**Directing the Delivery of Oxygen in Epoxidation – the Sharpless’ Way**

Epoxidation of prochiral olefins with peracids or hydroperoxides would yield racemic epoxides. Stereochemically pure epoxides are useful in the synthesis of drugs, natural products, biological molecules, etc. About 25 years ago, Sharpless et al achieved stereoselective epoxidation of allyl alcohols (olefins with –OH group on a carbon adjacent to the double bond) with t-butylhydroperoxide in the presence of titanium tetraisopropoxide and (+)- or (-)-tartaric acid diethyl ester (diethyl tartrate, DET, Scheme 4). The reaction is called Sharpless epoxidation.

If a given allyl alcohol, on Sharpless epoxidation, produces one enantiomeric epoxide of predictable configuration when (-)-DET is used, the use of (+)-DET will produce the epoxide of opposite configuration. This is illustrated with an exemplary reaction and its mechanism in Scheme 4.

Even these very few examples are enough to demonstrate the key role tartaric acid has played in starting and development of
stereochemistry. Because all this began with fermentation of grape juice, let us say cheers to grape juice and the product of its fermentation, which has been a source of pleasure for millions over the centuries.

Scheme 4.
Additional Notes

- Baking soda: NaHCO₃ mixed with tartaric acid.
- Rochelle salt: sodium potassium tartrate, a mild laxative.
- Cream of tartar: potassium bitartrate (potassium hydrogen tartrate), a by-product of wine-making.
- Tartar: A deposit (like tartar on teeth). In the present context, it is from fermentation of grapes. Hence, cream of tartar is an extract of tartar.
- Sodium ammonium tartrate was used by Pasteur as it forms more easily identifiable enantiomorphous prismatic crystals which could be separated by hand (using tweezers) under a microscope.
- Tartar emetic is antimony potassium tartrate. (An emetic causes vomiting).
- CuO can be removed from the blackened surfaces of copper or brass objects (vessels, decorative pieces, accessories, etc.) by rubbing with tartaric acid. Copper forms a water-soluble complex with tartaric acid and is washed off. Remember, tamarind fruits are used to shine household copper vessels.
- Tartaric acid is a muscle toxin; consuming large quantities is fatal. Yet, it is used in foods, beverages, and medicines within safe limits. (We consume tartaric acid through tamarind, pineapples, and grapes).
- Prochiral molecule/centre: If a substituent on an achiral centre is replaced by another or addition to an achiral face (e.g., a double bond) produces a chiral molecule.
- Absolute configuration: The true three dimensional dispositions of the atoms in a chiral molecule/centre.
- The configurations of chiral centres in a molecule are denoted by R-S notation following the Cahn-Ingold-Prelog (CIP) rules.

Suggested Reading


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