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On the Origin of the Optical Inactivity of *meso*-Tartaric Acid

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ABSTRACT

The structures of meso-tartaric acid and its optical inactivity have been re-examined. The experimental results strongly favour the staggered asymmetric (C_1) conformations of meso-tartaric acid in the solid state and in solution. The synthesis, isolation and optical resolution of the stereochemical analogues of the acid reaffirm the asymmetric structures of meso-tartaric acid. The optical inactivity of the acid is not because of its having a plane of symmetry (point group Cs) or centre of symmetry (point group Ci) but mainly because of the asymmetric gauche conformations P-sc and M-sc which constitute a racemic mixture.

Keywords: *meso*-Tartaric acid, stereochemical analogue, asymmetric, gauche, racemic mixture.

INTRODUCTION

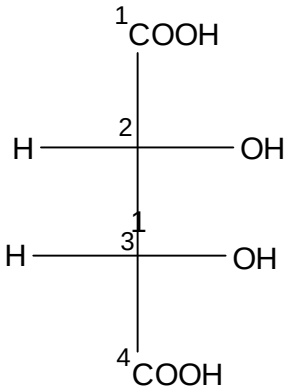
Tartaric acid occupies an important place in the early history[1-3] of organic stereochemistry. It has been discovered that the constitution of tartaric acid was settled about seven years before van't Hoff and Le Bel made their great discoveries and solved the problem of the origin of the stereoisomerism of tartaric acid [4]. It will be a matter of great interest to trace back the discovery of optical activity of tartaric acid and the epoch-making resolution of the enantiomers of tartaric acid by Louis Pasteur.

Optical activity and chirality: Historical perspective with respect to tartaric acid

Chemists recognised the tetrahedral configuration of tetracoordinated carbon almost one-half century before physical methods confirmed the idea with direct evidence. One consequence of the tetrahedral carbon is the ability of the tetracordinating centre to generate stereoisomers by exchange of a pair of ligands (exchanging positions) about the centre provided that the four ligands are different. Such property of the ligating centre is called **stereogenicity** and the ligating centre is termed a **stereocentre**. Such stereocentres are present in chiral molecules[5] (but not always) and are traditionally known as chiral centres. The useful terms **chiral** and **chirality** were coined by W.H Thompson(Lord Kelvin) in 1886 and are derived from **cheir**, the Greek word for a hand, indeed one of the most familiar chiral objects[6]. According to Vladimir Prelog[6] "An object is chiral if it cannot be brought into congruence with its mirrior image by translation and rotation, such objects are devoid of symmetry elements which include reflection, mirror planes, inversion centres or improper rotation axes". Several new terms related to chirality like homochiral, heterochiral etc. have also been introduced[7,8]. The phenomena of **optical activity** and **chirality** played important key roles in the development of organic stereochemistry. Since chirality is a term used to describe a condition in which an object and its mirror image are not superimposable, it is capable of being described without recourse to any measurable physical or chemical properties. The relationship between **chirality** and **optical activity** is historically such a close one, however, that chemists are prone to use the descriptions optically active and chirality interchangeably. Optical activity refers to one property of chiral molecules, namely the ability to rotate the plane of polarised light. Measurements of the optical activity have proven to be highly useful, especially in the study of reaction mechanisms, where the stereochemical relationship between the starting material and product, as indicated by the sign and magnitude of optical rotation, provides valuable information about the topology of the transition states and intermediates involved.

The first chemical substance in which optical activity was observed happened to be quartz. It was discovered that when quartz crystal is cut in a certain way and exposed to polarised light along a particular axis, the plane of polarised light is rotated. Abbe Rene Just Hauy (1743 - 1822), a French crystallographer, had shown that there are two kinds of quartz crystals, which are related as object and its non-congruent mirror image. In 1815, the French chemist Jean-Baptist Biot (1774 - 1862) observed that quartz exists as both levorotatory and dextrorotatory crystals. Sir John F.W. Herschel (1792 - 1871), a British astronomer found a correlation between these crystal forms and their optical activities; one of these forms of crystal is dextrorotatory and the other levorotatory. These were the seminal discoveries that clearly associated the chirality of a substance with the phenomenon of optical activity.

However, the earliest example of an organic compound that can exhibit optical activity and enatiomerism and hence, the existence of enantiomeric forms is tartaric acid **1**.



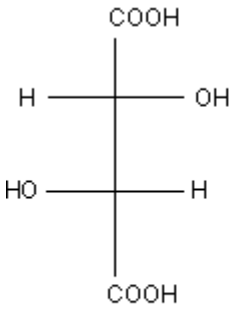
The acid had been known by the ancient Romans as its monopotassium salt ‘tartar’ which deposits from fermenting grape juice. Tartaric acid derived from ‘tartar’ was one of the compounds examined by Biot for optical activity; he found that it has a positive rotation. An isomer of tartaric acid discovered in crude tartar called racemic acid (racemus, Latin, a ‘bunch of grapes’) was also studied by Biot and found to be optically inactive. The exact structural relationship of (+)-tartaric acid and its isomer racemic acid remained obscure then.

One day in 1848 Louis Pasteur (1822 - 1895), the French chemist and Biologist was examining the crystals of sodium ammonium double salts of (+)-tartaric acid and racemic acid under a microscope. He found that the crystals of the salt of (+)-tartaric acid were hemihedral (chiral) and the racemic acid salt was a mixture of hemihedral crystals. Some crystals of the racemic acid were “right handed” like those in the corresponding salt of (+)-tartaric acid and some were “left handed”. He could meticulously separate the two types of crystals with a pair of tweezers and found that the right handed crystals were identical in every respect to the crystals of the salt of (+)-tartaric acid. When equally concentrated solution of the two types of crystals were prepared, the optical rotation of the left and right-handed crystals were equal in magnitude, but opposite in sign. Pasteur had thus performed the first enantiomeric resolution by human hands. Racemic acid, then was the first organic compound shown to exist as enantiomers[9], object and non-congruent mirror image.

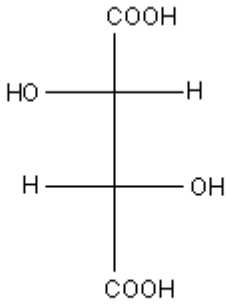
Stereoisomerism of tartaric acid

Stereoisomerism of tartaric acid is one of the most thoroughly exploited examples in teaching stereochemistry to the undergraduate students. The usual lesson a student learns from a standard text book is that tartaric acid has two chiral centres C(2) and C(3) which are in fact, stereocentres and since the groups attached to C(2) and C(3) are similar only three stereoisomers are possible. They are (R,R) **2a** and (S,S)**2b** or d(+)- and l(-)-tartaric acids and the third one is an optically inactive form known as *meso* (R,S) - tartaric acid **2c**.

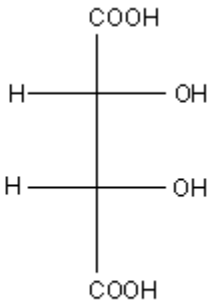
The *d*-tartaric acid (also dubbed “natural tartaric acid”) and *l*-tartaric acid (“unnatural tartaric acid”) are enantiomers and hence are identical in achiral environments. On the other hand *meso*-tartaric acid (“unresolvable tartaric acid”) since it is a diastereomer of both of these, will have properties different from those of the other two forms. The physical properties of the different forms of tartaric acid are given in table1 [10].



2a



2b



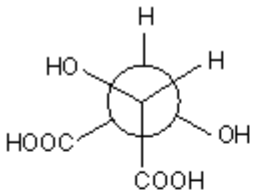
2c

Table 1: Comparison of tartaric acids

Form	$[\alpha]_D^{20}H_2O$		mp(^{0}C)
d	+11.98		168-170
l	-11.98		168-170
meso	0.00		140
dl	0.00		206

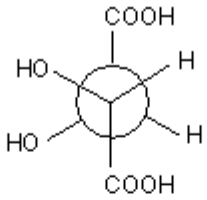
An interesting feature is the appearance of a fourth entry, the so-called "*dl*-tartaric acid" ("resolvable tartaric acid"). The '*dl*' is the designation of the racemic modification suggesting that it is somehow different from what we might have expected from a mixture of enantiomers. The sharp melting point and other data indicate that "dl-tartaric acid" is a distinct substance in the solid state. Such a compound is called a racemate. It is impossible to predict whether a given racemic modification will form a racemate in the solid state.

The optical activity of (+) and (-) tartaric acids has been attributed to the chirality of the molecule. The optically active tartaric acid (for instance the (+)-isomer **2a**) has three different staggered conformations **3a, 3b** and **3c** which are interconvertible by rotation about the C(2) - C(3) single bond. Each of the three staggered conformations has C_2 symmetry and is chiral and each can exist as a pair of non-superimposable (resolvable) mirror images. There is no possibility of racemization during the rotation about the C(2) - C(3) bond as the molecule will not pass through any achiral structure during rotation.



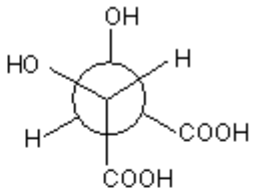
ap

3a



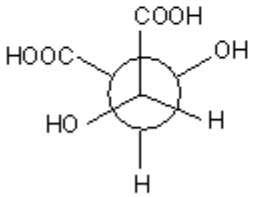
M-sc

3b

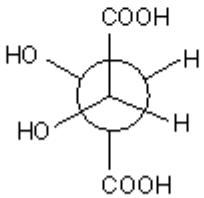


P-sc

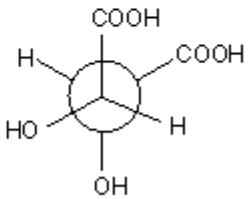
3c



3á



3b́



3ć

In fact, the corresponding staggered conformations **3′a, 3′b, 3′c** of the (-)-isomer **2b** are the mirror images (enantiomers) of **3a**, **3b** and **3c**. In other words, rotation about the single bond (conformational interconversions) will not render the molecule optically inactive; i.e. the molecule will remain chiral in any of the conformations. Hence, the optical activity of (+) or (-)-tartaric acid is quite obvious. However, it is not so clear, regarding the optical inactivity of *meso*-tartaric acid.

Optical inactivity of *meso*-tartaric acid

We usually come across in many standard text books of organic chemistry that *meso*-tartaric acid is optically inactive simply because it has a plane of symmetry [11-13] (point group Cs) and an imaginary mirror plane is drawn across the molecule in a Fischer projection as shown in Fig. 1.

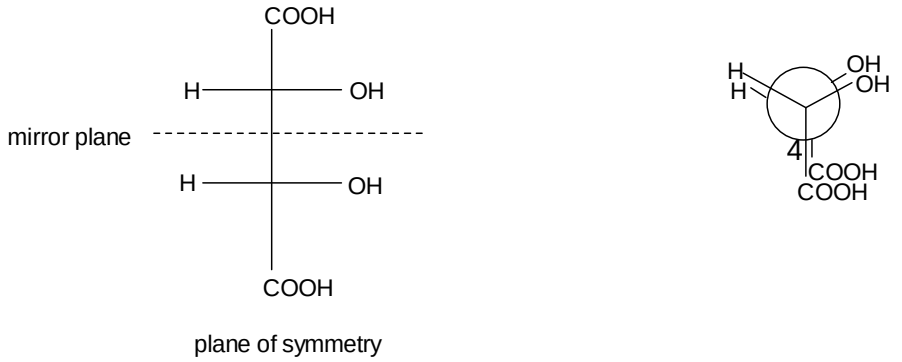


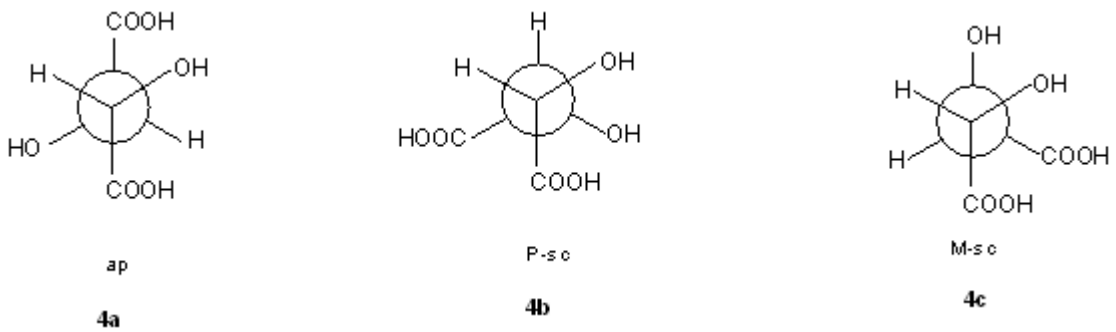
Fig.1 *meso*-tartaric acid having a plane of symmetry

When we convert the structure in the Fischer projection into Newman projection, it is found that it represents an eclipsed conformation **4** which is one of the most unstable conformations. The question arises then why *meso*-tartaric acid and for that matter any molecule should exist in the high energy eclipsed conformation while other more stable conformations are possible. It is highly unlikely that *meso*-tartaric acid may exist in a structure having a plane of symmetry. One may ask then what causes *meso*-tartaric acid optically inactive.

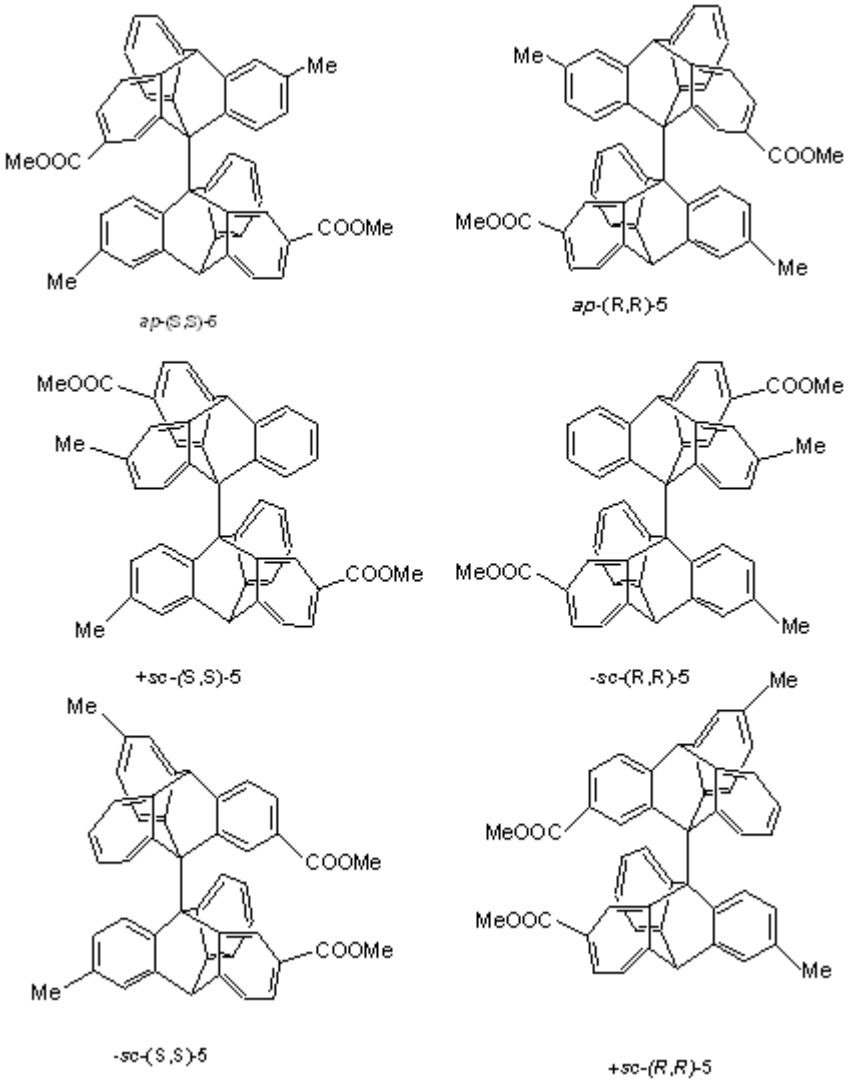
The lack of optical activity of *meso*-tartaric acid was usually ascribed to intramolecular compensation. The two halves of the molecule were supposed to be mutually related either by a mirror plane or by a centre of symmetry, the second possibility being accepted as the more probable one on account of the steric interactions. Some authors go to the extent of stating that the optical inactivity of the meso-tartaric acid is because of the cancellation[14] of the rotation due to (R)-stereocentre by that caused by the (S) stereocentre. Whereas the presence of the plane of symmetry would justify the optical inactivity (achiral structure) of a molecule, the question arises whether the molecule would exist in such structures at all on energy considerations. The presence of centre of symmetry in a molecule would also render the molecule optically inactive, but one has to examine whether it is the preferred structure. It therefore calls for the need to have a relook at the structures of *meso*-tartaric acid and explore the concrete reasons for its optical inactivity.

The best explanation for the optical inactivity of *meso*-tartaric acid is that the compound exists in solution (in staggered conformations) as a mixture of an achiral *ap*-(antiperiplanar)-conformation **4a** (Ci symmetry) and two asymmetric conformations P-*sc* (plus synclinal) **4b** and M-*sc*(Minus synclinal) **4c** with P(Plus) and M(Minus) helicity. Nevertheless, the bulk properties of the *meso*-acid are achiral, because the chiral conformers **4b** and **4c** are enantiomeric and hence of equal energy and concentration, i.e. they constitute a racemic mixture.

Some leading authors subscribe to this explanation[15-17]. According to Mislow[17], the *meso*-tartaric acid is a mixture of one symmetric (point group S_2 or Ci) antiparallel and two interconvertible enantiomeric gauche (or syn-skew) conformers; as a result, the *meso*-isomer is optically inactive. The question of internal compensation (if there is any) for *meso* compounds in general for optical inactivity appears to be intermolecular[18] rather than intramolecular. In other words, *meso*-tartaric acid exists in most cases, as a pair of enantiomers (constituting a racemic mixture) and hence optically inactive.



Kroon et al[19] have studied the crystal structure of potassium *m*-tartrate as well as those of several forms of the free acid. That found for the anion is dissymetric (chiral); potassium *m*-tartrate is, in fact, a racemate containing *d*- and *l*-anions in equal proportions. It is stated that the free acid adopts a similar conformation in several different crystalline forms of the compound, which is apparently favourable by considerable steric factors and they suggest that it may exist in solution also. If this is so, then separation of *m*-tartaric acid into *d*- and *l*- forms is at least theoretically possible. Almost certainly this should be feasible by crystallization with an active base[20]. The existence of *meso*-tartaric acid in staggered asymmetric conformations in the solid state and not in the generally assumed centrosymmetric conformation had also been illustrated by crystallographic studies. The crystals have been found to be racemates, their lack of optical activity being caused by intermolecular compensation of the conformational antipodes[21]. Such asymmetric (C_1 symmetry) conformation of *meso*-tartaric acid and preference of the P-*sc* and M-*sc* isomers to the *ap*-isomer were also supported by the crystal and molecular structure of the dimethyl ester of *meso*-tartaric acid[22]. ^{1}H and ^{13}C NMR studies[23] also reveal that meso-tartaric acid preferably exists in the chiral conformaitons rather than the *ap*-conformation in solutions. The vicinal ^{1}H-^{1}H ($^{3}J_{HH}$)spin coupling constants determined for various pH values (ranging from 1.40 to 12.60) were within the range [$^{3}J_{HH} \approx$ 2.60 to 3.10(Hz)] which are compatible with the gauche conformations (± *sc*) of *meso*-tartaric acid (dihedral angle ~ 60^0) and not with the *ap*-conformation (dihedral angle ~ 180^0)for which the $^{3}J_{HH}$ values must be larger (~ 7.00Hz). Recently, on the basis of X-ray and NMR investigations[24], it has been reported that in the esters and amides of chiral tartaric acid, the four atom carbon chain is overwhemingly *trans*, whereas, it is gauche(*sc*) in chiral tartarodinitriles. Conversely, in *meso*-tartaric acid, its esters and amides display a tendency for the gauche (*sc*) conformation, but *meso*-tartarodinitrites usually have the *trans* conformations.



From the discussion so far, it is undoubtedly clear that *meso*-tartaric acid does not exist in the eclipsed conformation (having a plane of symmetry), but rather exists as an equilibrium mixture of three staggered conformations **4a**(*ap*), **4b**(+*sc*) and **4c**(-*sc*); the **4b** and **4c** being the major contributors to the equilibrium mixture. The conformational

isomers **4a**, **4b**, **4c** are interconvertible by rotation about the C(2) and C(3) bond and hence are not resolvable. If the rotation about the C(2) and C(3) bond is frozen, it should be possible to isolate three stereoisomers of *meso*-tartaric acid.

As a consequence of concerted efforts to design the synthesis of sterically hindered stereochemical analog of *meso*-tartaric acid, Toyota et al[25] reported the successful preparation and separation of all possible rotamers of the stereochemical analogue of *meso*-tartaric acid, optically inactive and optically active isomers of (R,S)-2,2′-bis (methoxycarbonyl)-6,6′-dimethyl-9,9′-bitriptycyl **5**(Fig. 2). They have also reported[26] the synthesis, enantiomeric resolution and absolute stereochemistry of the stable rotamers which are the stereochemical analogues of *dl*-Tartaric acid. Recently we have reported[27] another scheme for the synthesis of the frozen stereochemical analogue of *meso*-tartaric acid. These successful syntheses reaffirm the existence of *meso*-tartaric acid in staggered conformations.

We would like to end this essay on *meso*- tartaric acid with the following quotation: "The real trouble with this world of ours is not that it is an unreasonable world, nor even that it is a reasonable one. The commonest kind of trouble is that it is nearly reasonable but not quite.... It looks just a little more mathematical and regular than it is; its exactitude is obvious but its inexactitude is hidden; its wildness lies in wait" [28]

CONCLUSION

The optical inactivity of *meso*-tartaric acid is not because of its having a plane of symmetry nor the generally assumed centre of symmetry. The best explanation for its optical inactivity is that it exists in solution as a mixture of various sets of enantiomers. Each set is equally populated by *d* and *l* forms which are mirror image conformations and illustrate the phenomenon of conformational enantiomerism.

Acknowledgement
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