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Louis Pasteur's discovery of molecular chirality and spontaneous resolution in 1848, together with a complete review of his crystallographic and chemical work

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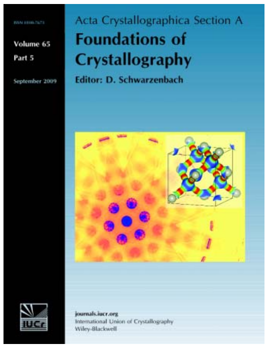

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Louis Pasteur's discovery of molecular chirality and spontaneous resolution in 1848, together with a complete review of his crystallographic and chemical work

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Pasteur's chemical and crystallographic work is described. The article commences with a brief overview of related science (chemical structure, crystallography, optical activity) before and after 1848, the year of the discovery of molecular chirality and spontaneous resolution. Concerning this discovery, three separate and varying reports are described. These are: (i) the publications in the scientific literature, (ii) the early (auto)biographies and (iii) Pasteur's handwritten laboratory notebooks. The three versions give differing views on the topic. Subsequently all of Pasteur's crystallographic and chemical work is passed in review, a topic very rarely broached. Pasteur's view in later life on this part of his work is examined. The article concludes with a discussion of the term dissymmetry used by Pasteur.

1. Introduction

Twenty-six years old and having recently obtained his PhD in chemistry and physics, in 1848 Louis Pasteur discovered spontaneous resolution in the crystallization of racemic sodium ammonium tartrate tetrahydrate from aqueous solution. This discovery was rapidly recognized as of the utmost importance to molecular chemistry. The present article places Pasteur's discovery in the context of then contemporary chemical, crystallographic and physical knowledge, known or unknown to Pasteur. Moreover, we present a review of all of Pasteur's further chemical and crystallographic work taking place over a period of some ten years. We shall also see how Pasteur viewed his own early work in the middle and near the end of his life. Fig. 1 shows a portrait of Pasteur in 1845 when he was a student at the Ecole Normale.

Pasteur rose to the status of a national hero during his lifetime. However, perhaps surprisingly, Geison (1995), a historian who has made a detailed study of Pasteur's life and work, is able to state: 'His contributions to basic science were extensive and very significant, but less revolutionary than his reputation suggests. Pasteur's most profound and most original contributions to science [*i.e.* these are the ones in the field of molecular chirality and crystallography] are also the least famous, and they came at the very outset of his career.' Bernal (1953), a crystallographer, concurs '. . . his first and in some ways his greatest scientific discovery'. It is our own intention to emphasize the real genius and inventiveness of Pasteur's work even if his interpretation of some results is in error due to a lack of suitable experimental and theoretical tools.

The present paper is written using modern chemical and crystallographic terminology and nomenclature. In his crystallographic work Pasteur made many observations of crystal morphology, *i.e.* the external shape of a crystal, which enabled him to determine whether this shape was chiral (*i.e.* the idealized macroscopic crystal was non-superposable on its mirror image) or achiral (*i.e.* the idealized macroscopic crystal was superposable on its mirror image). Crystal morphology is but one of many physical properties of a crystal and it is essential in this paper [as in previous ones, see Flack (2003)] to be clear which crystalline property is being described as chiral or achiral. Consequently we use expressions such as *crystal of chiral morphology*, *crystal of achiral morphology*, *chiral crystal structure* and *achiral crystal structure*. Of course, Pasteur had no direct way of observing molecular or crystal structure and had to proceed by deduction and supposition.

In his work Pasteur frequently used salts of the following carboxylic acids: tartaric, aspartic, malic, succinic and formic acids. Their chemical formulae are presented in Fig. 2. The stereochemical configuration of a carbon atom acting as a chiral centre (an asymmetric carbon atom in van't Hoff's nomenclature) is indicated using the Cahn–Ingold–Prelog (CIP) nomenclature (Cahn *et al.*, 1956, 1966*a*,*b*). The (2*R*) in (2*R*)-malic acid indicates both that carbon atom No. 2 of that molecule has the *R* configuration and that the bulk compound is enantiomerically pure. *rac*-Malic acid indicates that the bulk compound is a racemate composed of equimolecular proportions of (2*R*)-malic acid and (2*S*)-malic acid.

The first part of this article was written as the basis of a lecture given to the Société chimique de Genève by H. D.

Flack on his retirement. The date of the lecture corresponded closely with the 160th anniversary of the submission on 9 October 1848 of Pasteur's full paper on the discovery of spontaneous resolution. The topic seemed appropriate in view of Flack's interests in absolute-structure and absolute-configuration determination by X-ray crystallography. On researching the copious historical literature on Pasteur, it was apparent that no full account of Pasteur's chemical and crystallographic work was available. Moreover, the summary published accounts were generally written by historians using outdated terminology. Our detailed account of this part of Pasteur's work should thus serve for future generations as a source of well documented and critically analysed information.

2. Related science before and after 1848

An excellent review of this topic as related to Pasteur's work is to be found in Mauskopf's (1976) article on *Crystals and Compounds; Molecular structure and composition in Nineteenth-century French Science*. Another source is Kottler (1978). We only give a very bare outline in the following sections.

Figure 1
Portrait of Pasteur around 1845 as a student at the Ecole normale supérieure. Lead pencil drawing signed Charles Lebayle, courtesy of l'Institut Pasteur, Paris.

2.1. Chemical structure pre-1848

It is most important to bear in mind that at the time of Pasteur's discovery of spontaneous resolution it was generally accepted that compounds had a stoichiometric composition of chemical elements but next to nothing was known concerning valency, bonding, rigidity, connectivity and stereochemistry of molecules and solids. In particular, there was little notion of geometric or stereochemical shape of molecules; in effect molecules were virtually structureless. The atomic theory of matter was already in existence but in 1848 was not accepted by a vast majority of the chemical community. The prevalent ideas of the structure of molecules in crystals followed the school of Ampère (1814), who viewed molecules as classical convex regular polyhedra, thus allowing notions of composition and structure to be combined. Mauskopf (1976) states that at best this tradition of the Ampère school had been carried on by a small group of rather speculatively inclined scientists, none of whom positively influenced many of their contemporaries with their specific models and speculations. Although the existence of compounds of the same composition but with different chemical and physical properties was known (*i.e.* isomers), there was no theory available to explain their existence.

2.2. Crystallography pre-1848

The prime medium available for the description of the shape of chemical compounds came from the study of crystals based on Haüy's theory (Haüy, 1809). This states that external shape represents the internal shape of the repeating unit. Haüy developed his theory working from the idea that repeated cleaving of any crystal will lead to the basic nucleus or *molécule intégrante*. He developed such fundamental notions of crystallography as the unit cell, the periodic lattice and

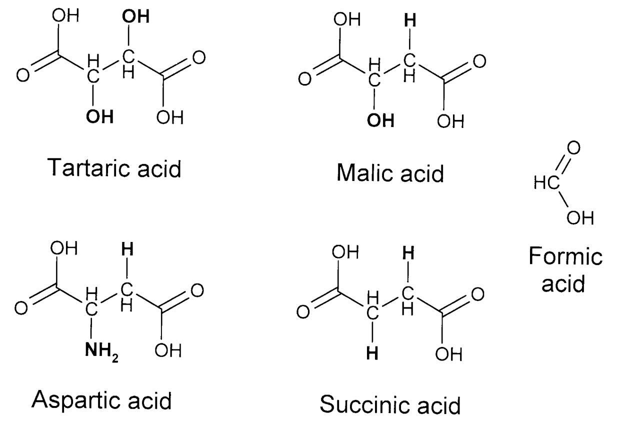


Figure 2
Chemical schema of tartaric, aspartic, malic, succinic and formic acids. Tartaric acid has two chiral centres; aspartic and malic acids each have one chiral centre; succinic and formic acids each have no chiral centres and consequently are achiral. In all cases the chiral centres are on C atoms.

symmetry. Haüy's notion of symmetry was rudimentary and limited the crystal morphology and crystal structure to one of seven crystal classes (systems) characteristic of the crystal lattice. In this way, all crystals (the morphology and the structure) should belong to one of these symmetries and be achiral. Delafosse (1843) in particular had worked on crystals which broke this rule by having minor crystal faces not repeated by Haüy's symmetry. The morphology of such a crystal could be either chiral or achiral. Many crystals of quartz (SiO_2) obey Haüy's symmetry rule, but Haüy himself had observed in 1815 that a few crystals possess small subsidiary faces showing the morphology and the structure of the crystal to be chiral. These faces can be seen in Prelog's (1976) photograph, reproduced in Fig. 3, of a pair of large left- and right-handed quartz crystals in which the minor faces are very prominent indeed.

The first link between chemical composition and crystal structure was due to Mitscherlich (1819) in his law of isomorphism. In essence Mitscherlich had observed that in series of salts (phosphates, arsenates and sulfates), compounds of similar composition have similar crystal morphology, cell dimensions and symmetry, and were also capable of forming mixed crystals (solid solutions). This forced the structureless view of the unit-cell contents of a crystal to be brought into question.

Miller's system of indexing crystal faces (Miller, 1839) was adopted and introduced into France by de Senarmont (Pasteur, 1857*c*). Pasteur (1853*a*) is the first publication in which he uses Miller indices.

2.3. Optical activity pre-1848

Arago (1811) observed colours in plane-polarized light transmitted through a quartz crystal and the following year Biot (1812–1814*a*,*b*) established that the effect was due to the rotation of the plane of polarized light. It is the optical rotation along the principal symmetry axis of quartz that can readily be measured and some quartz crystals turn the plane of polarized light to the right (dextrorotatory) and others to the left (laevorotatory), although the absolute values of the rotation normalized for the thickness of the specimen are the same. Later on Biot (1815) observed optical activity in certain natural organic compounds in solution or liquid. It was deduced that optical activity resided in individual molecules, even when randomly oriented, unlike quartz, where the optical activity is a property of the crystal structure and disappears in the melt or solution. A further major advance came from Fresnel's (1824) discovery of circularly polarized light, which explains the optical-rotation effect as being due to different refractive indices for the left- and right-polarized light. Fresnel (1824) went even further by postulating the nature of the difference between the left and right refractive indices as being due to structural effects. For example, he explicitly hypothesized an (enantiomerically pure) helicoidal arrangement of molecules in a medium and its different interaction with left- and right-circularly polarized light. He stated that the interaction of a right-handed helicoidal arrangement of molecules with right-circularly polarized light is both inverse to that of a left-handed helicoidal arrangement of molecules with left-circularly polarized light and different to that of a right-handed helicoidal arrangement of molecules with left-circularly polarized light. Fresnel had thus identified a structural basis for optical activity. Biot (1835) undertook optical-activity measurements on crystals of organic molecules (*i.e.* sucrose) but had failed to observe it because of the birefringence.

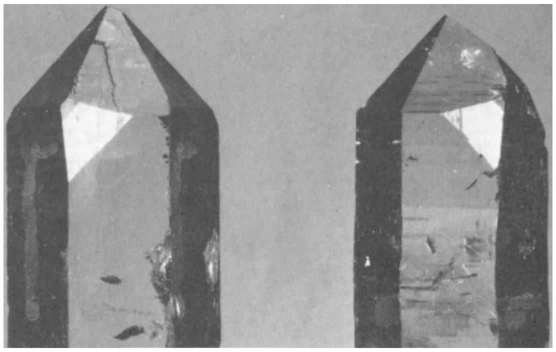


Figure 3
L- and D-Quartz crystals showing fully developed minor faces. Reproduced with permission from Prelog (1976). Copyright The Nobel Foundation.

So far we have described the effects of crystal morphology and optical rotation separately. The key link between the two was established by Herschel (1822) on studying quartz crystals. Herschel found that right-handed quartz crystals, as judged by their morphology, are dextrorotatory and left-handed quartz crystals are laevorotatory. A clear link between the chirality of the structure and the sense of optical rotation was thus established.

The results of a key experiment designed to demonstrate the intimate connection between electromagnetism and light was described by Faraday (1846). In this experiment Faraday observed optical activity in an otherwise inactive sample of lead borate glass subjected to a magnetic field parallel to the direction of propagation of the plane-polarized light. Faraday's experiment was a source of considerable confusion (not to Faraday, of course) by way of which the optical rotation due to the magnetic field was confused with that due to the chirality of the sample. In fact, a simple experiment demonstrates the difference between the two effects if one considers allowing the beam of light to traverse the sample twice, once in the forward direction and once in the reverse direction. For the chiral sample the resultant optical rotation is zero whereas for the Faraday rotation the optical rotation is doubled. In short, the physical nature and the symmetry properties of the chiral and the magnetic rotation are entirely different. Pasteur makes no reference to Faraday's publication in his scientific works.

2.4. Chemical structure and related work post-1848

In reading the current text it may be difficult for the reader to have a clear view of those facts and theories which were unknown at the time of the discoveries described. In an attempt to avoid such misunderstandings, we briefly mention relevant work which was unknown in 1848 and point out that, as discussed in §6, none of these advances was stimulated by Pasteur's discoveries of 1848.

There was considerable activity in the 1850s and 1860s by many chemists leading to the discovery of valence, in particular the tetravalence of carbon, to the two-dimensional topological schema of molecules still used today, and to the specification of atomic masses. A key discovery occurred with the publication of the Le Bel (1874) and van't Hoff (1874) concept of the asymmetrical tetrahedral carbon atom. The latter concept took a long time to be accepted by the chemical community. The ground-breaking work of Bravais (1849) on crystal classes and lattices is not cited in any of Pasteur's publications. The binary phase diagrams of enantiomeric mixtures were treated by Roozeboom (1899). The term *chirality* was coined by Lord Kelvin [see Mislow (1999) and Bentley (2009)]. Bragg (1913) published the first crystal-structure determination by X-ray diffraction.

3. The discovery of molecular chirality and spontaneous resolution in 1848

There are several sources of information concerning the discovery of molecular chirality and spontaneous resolution. Each serves a particular purpose and contains its own version of the events. The first report is contained in the published scientific papers (Pasteur, 1848*f*,*g*), whose conventional style of content is familiar to a scientist. Carefully selected experimental observations are arranged in an order to make the results clear, plausible and comprehensible. The second reports come from the (auto)biographies written during or shortly after Pasteur's lifetime. To a large extent these reports are designed to build or maintain a favourable public image of the man and his work, for the purposes of personal ambition, fund raising and prestige for the family, research, collaborators and the nation. The third and final reports are based on Pasteur's laboratory notes. They were studied to date by historians primarily in an effort to gain better insight into the process of scientific discovery.

We commence, however, with some scientific background specific to the discovery of spontaneous resolution. This was made using various salts of the tartrate anion and the free acid. Tartaric acid may be made from its most common salt, potassium hydrogen (2*R*,3*R*)-tartrate, called tartar, a compound naturally occurring in grapes and wine. A second form of tartaric acid (in fact it is now known to be *rac*-tartaric acid) was obtained from crude tartar around 1819 by P. Kestner, a French manufacturer from Thann, Alsace (Pasteur, 1853*b*). Gay-Lussac (1778–1850) coined the term racemic acid (*acide racémique*) from the Latin *racemus* for a bunch of grapes and demonstrated that it had the same chemical composition as (2*R*,3*R*)-tartaric acid. This was confirmed by Berzelius (1779–1848), who defined the two forms of tartaric acid as being isomers. In 1832 Biot found that (2*R*,3*R*)-tartaric acid in aqueous solution was optically active and in 1838 that *rac*-tartaric acid was inactive.

de la Provostaye (1841) had undertaken a very thorough study of the crystallography of the salts and acids of both the (2*R*,3*R*)- and *rac*-tartrates. In a short note to the *Académie des sciences* communicated by Biot (1844), Mitscherlich exposed the enigma of the topic, as follows in translation by the present author with added explanatory words in italics and parentheses: 'The double salt of sodium and ammonium paratartrate (*racemate*) and the tartrate (*enantiomerically pure*) have the same chemical composition, the same crystalline form with the same angles, the same density, the same double refraction and as a consequence the same angles between the optic axes. In aqueous solution, their indices of refraction are the same. But in aqueous solution, the tartrate (*enantiomerically pure*) turns the plane of polarized light whereas the paratartrate (*racemate*) is optically inactive, as Mr Biot found in a whole series of these two types of salt; but here the type and the number of the atoms, their arrangement and their distances are the same for the two bodies being compared.'

A major influence in Pasteur's early work was the now obscure French chemist Auguste Laurent (1807–1853) who worked at the Ecole Normale from late 1846 to April 1847. Laurent was interested in the crystallographic phenomena of isomorphism (different chemical compounds with similar crystal structures) and dimorphism (one chemical compound with two different crystal structures). Laurent's (and others') observations of dimorphism (and polymorphism) were in contradiction with Haüy's view of the *molécule integrante* of fixed shape in which the external shape of the crystal maps to the shape of the building unit. Dimorphism implies that the latter may have different shapes. Moreover, Laurent's notion of what constituted similarity of crystal structure in isomorphism was wider than that previously accepted. He allowed the isomorphic structures to belong to different crystal systems if the unit-cell dimensions were very similar. Furthermore, in Laurent's approach the chemical composition of isomorphic crystals was not necessarily identical. It allowed for the effect of molecules of solvent (water) and for the effects of protonation and deprotonation. In such an approach the building units were very similar but not identical. It is thus natural in this context that experimenters had to be very attentive to minor changes in crystal morphology. Owing to Laurent's influence, Pasteur's early (1846–1848) scientific work comprised synthetic inorganic chemistry (Pasteur, 1847*a*), studies of isomorphism and dimorphism in crystals of various compounds (Pasteur 1847*a*, 1848*a*,*b*,*c*,*d*,*e*), studies of optical rotation in liquids including various tartrates in solution (Pasteur, 1847*b*) and the interrelation of isomorphism and optical activity (Pasteur, 1847*b*).

3.1. Pasteur's published scientific report

The discovery was presented orally to the *Académie des sciences* on 22 May 1848 (Pasteur, 1848*f*). As was common at the time, the oral presentation allowed the orator freedom to express his views on the matter and contained little detailed information. Most fortunately for this discovery Pasteur prepared a full paper on his work which was received by the Academy on 9 October 1848 and published in *Annales de Chimie et de Physique* (Pasteur, 1848*g*).

Pasteur first described the study of the crystals of 13 compounds (salts and acid) of (2*R*,3*R*)-tartrates. In many cases (see §4.1 for exceptions) he observed minor faces that had been overlooked by de la Provostaye and Mitscherlich. These are just those faces that show that the morphology and structure of the crystals are chiral. Moreover, by arranging the crystals according to a common morphological criterion, the minor faces are all turned to the right. Pasteur deduced that the chirality of the molecules and their arrangement were all the same. So all of the crystals are right-handed and in aqueous solution they are all, with one exception, dextrorotatory. A clear connection between the enantiopurity of the *molécules integrantes*, as signalled by all the crystals being of the same chirality, and the constant sign of the optical rotation had been established. Pasteur then described the study of six compounds of *rac*-tartrate salts. It was reasonable to expect that the crystals would be achiral. For three racemates the crystals were so bad that he could not determine whether their morphologies were chiral or achiral. For just one racemate the morphology of the crystals was clearly achiral. However, for sodium ammonium and sodium potassium *rac*-tartrate the crystals showed minor faces clearly indicating that their morphology and structure were chiral. Pasteur's keen sense of observation and preparation made him carefully arrange the crystals to discover that one half of them were right-handed and the other half were left-handed. Taken into aqueous solution the right-handed crystals were dextrorotatory (exactly like the natural product from wine) and the left-handed crystals were laevorotatory, both with the same absolute value of the specific rotation.

Nowadays we say that sodium ammonium and sodium potassium *rac*-tartrates crystallize as *racemic conglomerates* (*i.e.* an equimolar mechanical mixture of crystals, each one of which contains only one of the two enantiomers present in a racemate; Moss, 1996*a*,*b*) whereas the other salts and the free acid of *rac*-tartrate crystallize as *racemic compounds* (*i.e.* a crystalline racemate in which the two enantiomers are present in equal amounts in a well defined arrangement within the lattice of a homogeneous crystalline addition compound; Moss, 1996*a*,*b*). Fig. 4 shows Pasteur's own cork models of a pair of crystals of sodium ammonium (2*R*,3*R*)-tartrate and sodium ammonium (2*S*,3*S*)-tartrate. In the real crystals, observation of the minor faces is more difficult than in the models.

Figure 4
Pasteur's own cork models of a pair of crystals of sodium ammonium (2*R*,3*R*)-tartrate and sodium ammonium (2*S*,3*S*)-tartrate. In real crystals of these compounds, observation of the minor faces is more difficult than in the cork models. Courtesy of l'Institut Pasteur, Paris.

Pasteur (1848*f*,*g*) made several deductions and claims (all correct) as a result of the experiments he described. Firstly, he had unequivocally established the existence of molecular chirality. Secondly, he was the first person to be able to explain one particular form of isomerism. The (2*R*,3*R*)- and (2*S*,3*S*)-tartrates are isometric and related one to another as non-superposable mirror images. Of course, at this stage he had neither any stereochemical theory of the chirality of these molecules nor any theory to explain the formation of a racemic conglomerate by spontaneous resolution. Thirdly, he had made a synthesis of chemical, physical (optical) and crystallographic evidence. By chance he had stumbled on the perfect system to study.

3.2. Early (auto)biographical reports

The main source of the information for this section is Pasteur's first biography (Vallery-Radot, 1922), which was authored anonymously and distributed by his son-in-law René during Pasteur's lifetime. It is generally recognized to have been produced under Pasteur's control (Gal, 2008*b*; Geison, 1995) and may to some extent be considered autobiographical. Some reminiscences are also to be found in Pasteur's (1860) lectures to the Chemical Society in Paris. In the opening paragraph of §3, we have already noted that such reports are not purely scientific in nature. For example, the fact that the date (22 May) of the first oral presentation of the discovery of spontaneous resolution has been reported erroneously in many works as being 15 May is perhaps associated with the contemporaneous death of Pasteur's mother on 21 May. This has been discussed in detail by Gal (2008*b*).

The story goes that Pasteur had seen Mitscherlich's note on the enantiomerically pure and racemic sodium ammonium tartrate (Biot, 1844) and had pondered it deeply. It did not seem to make sense. One would hardly expect two compounds with different properties to have the same crystal structure. At that time he was an undergraduate student and had no time to follow up this enigma, but he had talked about it with his friend Chappuis during their walks around the garden of the Luxembourg palace and he was able to recite Mitscherlich's note by heart (Vallery-Radot, 1922). With his Dr ès sciences theses finished, Pasteur became *agrégé préparateur* at the Ecole Normale and was free to follow up the work on the tartrates. The story continues, presenting the work as following the same logical development as used in Pasteur (1848*f*,*g*) and in §3.1. It is said that on making the major discovery Pasteur rushed out of the laboratory into the corridor, where on seeing Bertrand he embraced him and said '*Je viens de faire une grande découverte! J'ai séparé le paratartrate double de soude et d'ammoniaque en deux sels de dissymétrie inverse et d'action inverse sur le plan de polarization de la lumière. Le sel droit est de tout point identique au tartrate double. J'en suis si heureux que j'éprouve un tremblement nerveux qui m'empêche de remettre de nouveau l'oeil à l'appareil de polarization*' (Frankland, 1897).

Biot was sceptical about Pasteur's results and required to see the experiments performed for himself. Frankland (1897) provides the following description in English, certainly taken from Pasteur's (1860) own and Vallery-Radot's (1922) versions in French:

> He (J.-B. Biot) sent for me to repeat before his eyes the several experiments. He gave me racemic acid which he had himself previously examined and found to be quite inactive to polarized light. I prepared from it in his presence the sodium ammonium double-salt, for which he also desired himself to provide soda and ammonia. The liquid was set aside for slow evaporation in one of the rooms of his own laboratory, and when 30–40 grams of crystals had separated he again summoned me to the Collège de France, so that I might collect the dextro- and laevo-rotatory crystals before his eyes, and separate them according to their crystallographic character, asking me to repeat the statement that the crystals which I should place on his right hand would cause the deviation to the right, and the others to the left. This done, he said that he himself would do the rest. He prepared the carefully weighed solutions, and, at the moment when he was about to examine them in the polarimeter, he again called me into the laboratory. He first put the more interesting solution, which was to cause rotation to the left, into the apparatus. Without making a reading, but already at the first sight of the colour-tints presented by the two halves of the field in the Soleil saccharimeter, he recognized that there was a strong laevo-rotation. Then the illustrious old man, who was visibly moved, seized me by the hand, and said '*Mon cher enfant, j'ai tant aimé les sciences dans ma vie que cela me fait battre le coeur!*'.

3.3. Pasteur's laboratory notebook report

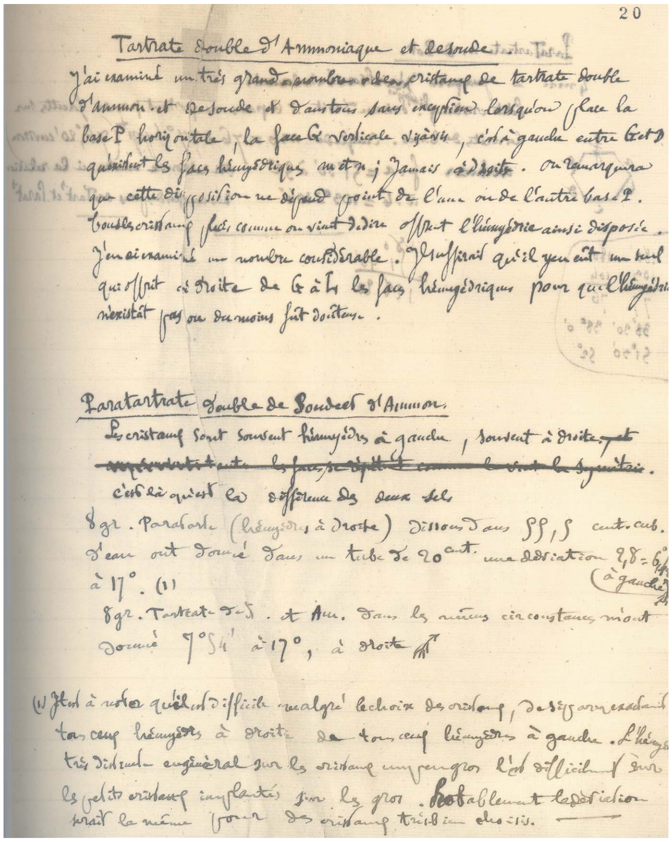
Pasteur kept handwritten laboratory notebooks of his daily work. Many of them are now at the Bibliothèque nationale de France. They came into the public domain for study by scholars in the 1970s. A few studies have been undertaken of the relevant notebooks (Pasteur, 1847/48). Bernal (1953), a crystallographer, made a brief study prepared in 24 hours as a complement to a lecture he presented in 1946 at the Congress of Commemoration of the Fiftieth Anniversary of the Death of Pasteur. There followed studies by the historians Mauskopf (1976) and more recently by Geison (1995). Balibar (1995) studied in detail those parts of the notebooks in which Pasteur prepared one of the early manuscripts on dimorphism prior to the chirality work. Of particular interest in her study are the reservations that Pasteur had about explicitly invoking the atomic theory of matter. The trouble was that he was stuck between the very powerful and highly influential Jean-Baptiste Dumas, an anti-atomist, and the brilliant, young and persuasive but ill-established Auguste Laurent, who was an atomist, one of Pasteur's potential rivals and politically undesirable to Dumas.

Concerning the discovery of molecular chirality and spontaneous resolution we follow Geison (1995). In brief, Pasteur's laboratory notebook clearly shows that the research leading to the discovery of molecular chirality and spontaneous resolution was *not* motivated by the enigma presented in Mitscherlich's note (Biot, 1844) and was not carried out in the clear logical way described in §§3.1 and 3.2. Moreover, the use of optical-activity measurements did not occur until the final stages of this work and then only as a means of characterizing the enantiomerically pure and racemic tartrates. The scientific problems that Pasteur wished to resolve were entirely a continuation and extension of his work on isomorphism and dimorphism of crystals originating from his interaction with Laurent. At the outset there was no real component either of chirality or optical activity in this research. The scientific value of the initial studies on isomorphism and dimorphism is minimal in comparison to the discovery to which they lead. It will thus come as no surprise that there is no mention of them, nor of Laurent, in the reports of §§3.1 and 3.2. The latter tend to stress and flatter the scientific establishment in Paris with whom Pasteur wished to enter into a fruitful relationship.

Pasteur's (1848*d*) first short publication on dimorphism, following Laurent's approach, was presented orally to the Académie des sciences on 20 March 1848. It contains work on well known $CaCO_3$ polymorphs. He also made the rather bold announcement that he had experimental proof that a set of eight enantiomerically pure tartrate salts could form mixed crystals (solid solutions). Some of these belonged to the orthorhombic and others to the monoclinic (but pseudo-orthorhombic) system. In the full version of the work (Pasteur, 1848*e*) this assertion is omitted and the notebook reveals that Pasteur had serious doubts about his precipitous statement. He gathered together information on the eight tartrate salts. As Laurent's theory required isomorphous compounds to have the same number of solvent (water) molecules, Pasteur paid particular attention to the published, and often discrepant, values of the composition of the tartrate salts. These data were a muddle, as some salts having identical numbers of water molecules crystallized in different crystal systems. Pasteur also used available data to calculate something akin to a molecular volume under the premise that the latter was a necessary criterion for isomorphism. But two of his tartrate salts with equal molecular volume (within experimental error) did not form a continuous range of solid solutions. Subsequently Pasteur studied a set of sulfate salts and returned to the tartrates in the second half of April. He started on a systematic study using as many methods as possible. In particular he attempted to form solid solutions by cocrystallizing pairs of tartrate salts. He projected to do density measurements. The number of waters of crystallization was always in question. In this confused situation, he proceeded by making a list (chemical composition, crystal morphology, isomorphism) of what he knew about the eight tartrate salts and developed a plan of work to resolve the different points. The anomalies were legion and could have arisen by any of the listed properties having been observed incorrectly. The compositions of some of the compounds were redetermined and further studies of solid-solution formation were projected. Sodium ammonium (2*R*,3*R*)-tartrate and the isomorphous sodium potassium (2*R*,3*R*)-tartrate were reported as having eight molecules of water of crystallization. The value now accepted for sodium ammonium (2*R*,3*R*)-tartrate is four at 323 K (Jacques *et al.*, 1981). Only enantiomerically pure tartrates had been considered up to this point.

It is at this point that Pasteur considered the *rac*-tartrate salts for the first time. He noted that the number of waters of crystallization had not been reported in the literature for sodium ammonium *rac*-tartrate, but Pasteur supposed that it must be similar to sodium potassium tartrate, although it is not clear whether the (2*R*,3*R*)- or *rac*- salt was intended. Mitscherlich's famous note (Biot, 1844) came to his mind, but from the context in the notebook the relation to optical activity is clearly incidental. What Pasteur wished to resolve was only the crystallographic problem of the reported isomorphism of the enantiomerically pure and racemic compound in view of a report by Gerhardt that there were two molecules of water of crystallization in sodium ammonium *rac*-tartrate. He realized that the composition of these compounds needed to be redetermined. All considerations in Pasteur's mind at this stage concerned the relationship between the number of waters of crystallization and the crystal morphology to confirm or disprove the purported isomorphism. Another anomaly in composition and morphology between dipotassium (2*R*,3*R*)-tartrate and diammonium (2*R*,3*R*)-tartrate reminded Pasteur that measurement of the pyroelectricity of these salts could be useful to establish the chirality of the crystals in the absence of clear morphological indications. Furthermore, a note at the end of his list of anomalies of the eight enantiomerically pure tartrates and the few *rac*-tartrates mentioned the question of the chirality of the morphology of the crystals. It is reasonable to deduce that Pasteur was beginning to suspect that the chirality of the tartrate crystals would provide the key to the isomorphism, and from late April 1848 he would pay increased attention to minor details of morphology and less to the number of molecules of water of crystallization.

On 29 April Pasteur was examining sodium ammonium (2*R*,3*R*)-tartrate, systematically comparing it to sodium potassium (2*R*,3*R*)-tartrate. He soon discovered that crystals of sodium ammonium (2*R*,3*R*)-tartrate were chiral, noting that although de la Provostaye had observed chiral crystals of four other (2*R*,3*R*)-tartrate salts, he had not studied this particular compound. For some unidentified cause, Pasteur also undertook to arrange a large number of the crystals of sodium ammonium (2*R*,3*R*)-tartrate according to a common morphological criterion to observe that they were all right-handed. Armed with these very significant results on the enantiomerically pure sodium ammonium (2*R*,3*R*)-tartrate, Pasteur approached the case of its racemate. What he expected to find can only be a matter of conjecture but one must recall that the reported compositions for the number of molecules of water of crystallization for the enantiomerically pure and racemic compound were incorrectly different. He found the results on the crystals of sodium ammonium *rac*-tartrate were confusing: 'The crystals are frequently chiral to the left, frequently to the right' and in a crucial passage that he later crossed out 'and sometimes all the faces repeat themselves according to the laws of symmetry' (*i.e.* were achiral). See Fig. 5. With the crucial deleted passage taken as true, one has the 'obvious' but wrong solution, *i.e.* the crystals of enantiomerically pure sodium ammonium (2*R*,3*R*)-tartrate are chiral, all of the same hand and contain eight molecules of water of crystallization, whereas the crystals of racemic sodium ammonium *rac*-tartrate are achiral and those of the racemic compound containing two molecules of water of crystallization. Note yet again that at this stage of the investigations the optical activity, or lack of it, had played no part at all. The observation of the formation of a racemic conglomerate came first and the relationship of the chiral crystals to their optical activity in solution followed very rapidly in its wake, as the notebook shows.



20

Tartrate double d'Ammoniaque et de soude.

J'ai examiné un très grand nombre de cristaux de tartrate double d'ammon. et de soude et d'autres sans exception lorsqu'on place la base P horizontale, la face G verticale vis-à-vis, c'est à gauche entre G et D qu'existent les faces hémiédriques m et n ; jamais à droite. On remarquera que cette disposition ne dépend point de l'une ou de l'autre base P. Tous les cristaux placés comme on vient de dire offrent l'hémiédrie ainsi disposée. J'en ai examiné un nombre considérable. Il suffirait qu'il y en eût un seul qui offrît à droite de G à D les faces hémiédriques pour que l'hémiédrie n'existât pas ou du moins fût douteuse.

Paratartrate double de Soude et d'Ammon.

Les cristaux sont souvent hémiédres à gauche, souvent à droite ~~et [illegible] les faces se répètent [illegible] la symétrie~~.
C'est là qu'est la différence des deux sels

8 gr. Paratartr. (hémiédres à droite) dissous dans 55,5 cent. cub. d'eau ont donné dans un tube de 20 cent. une déviation 9,8 = 6° (à gauche) à 17°. (1)

8 gr. Tartrate d. S. et Am. dans les mêmes circonstances m'ont donné 7°54' à 17°, à droite

(1) Il est à noter qu'il est difficile malgré le choix des cristaux, de séparer exactement tous ceux hémiédres à droite de tous ceux hémiédres à gauche. L'hémiédrie très distincte en général sur les cristaux un peu gros l'est difficilement sur les petits cristaux implantés sur les gros. Probablement la déviation serait la même pour des cristaux très bien choisis.

Figure 5

Note in Pasteur's laboratory notebook recording the results on sodium ammonium *rac*-tartrate. Reproduced with permission from the Bibliothèque nationale de France N.a.fr 19774 f° 20.

4. Pasteur's work on molecular chirality and crystallography

This section is arranged by theme, each of which is developed chronologically. Some items are relevant to several themes and appear several times, at least in outline. The information is taken from Pasteur's publications in the scientific literature. All of the latter, together with some unpublished material, were collected together and republished by Pasteur's grandson Louis Pasteur Vallery-Radot (1922, 1939) in a seven-volume series *Oeuvres de Pasteur* itself arranged by theme.[1] Pasteur Vallery-Radot (1946) also edited and published selected items of Pasteur's correspondence, which have also been consulted in the preparation of this paper.

4.1. Tartrates and tartaric acid

Pasteur (1848*f*,*g*) followed up on his initial experiments as these had provided only minute quantities of the enantiomerically pure sodium ammonium (2*R*,3*R*)- and (2*S*,3*S*)-tartrates. He made larger quantities of these two compounds by crystallization of sodium ammonium *rac*-tartrate from aqueous solution and sorting the racemic conglomerate as described in §3.1. He compared their chemical composition, optical rotation, density, solubility, birefringence and crystal morphology with the (2*R*,3*R*)-tartrates and acid from wine (Pasteur, 1849*a*,*b*, 1850*a*). The compounds are identical apart from the optical rotation, which is of the same absolute value but of opposite sign. He was aware that spontaneous resolution was a rare event and amongst the tartrates that he had studied only sodium ammonium and sodium potassium *rac*-tartrates form racemic conglomerates. Pasteur (1849*b*) also observed that crystals of three salts of the racemate show an achiral morphology. He even studied the pyroelectricity of the tartrate crystals. He also synthesized *rac*-tartaric acid by mixing (2*R*,3*R*)- and (2*S*,3*S*)-tartaric acids and compared this with the *rac*-tartaric acid obtained from Kestner (Pasteur, 1849*a*,*b*, 1850*a*). The formation of *rac*-tartaric acid is exothermic, which lead Pasteur to conclude that there was real chemical combination (Pasteur, 1850*a*). By heating (2*R*,3*R*)-tartaric acid in the presence of a base, Pasteur (1853*e*) discovered that he could both produce *rac*-tartaric acid (see §4.5.1) and another optically inactive isomer which is now known to be *meso*- or (2*R*,3*S*)-tartaric acid.

In the summer of 1852 Pasteur was informed by Mitscherlich that a German manufacturer of tartaric acid from Saxony had produced a quantity of *rac*-tartaric acid (Pasteur, 1853*b*; Vallery-Radot, 1922). In September 1852 Pasteur undertook a journey around Europe (Zwickau, Leipzig, Freiberg, Vienna, Prague) to uncover sources of *rac*-tartaric acid. As a result of this journey, he came to the conclusion that Kestner's production of *rac*-tartaric acid was a chance event brought about by the use of crude tartar coming from Naples. In general the first treatment of tartar in the industrial process gets rid of the racemate and factories received deliveries of treated tartar free of *rac*-tartrate (Pasteur, 1853*b*). He hence deduced that the origin of the *rac*-tartrate in tartar was of natural origin, the quantity present being dependent on the place and source of production. Is this deduction justified? Many authors attribute the occurrence of *rac*-tartaric acid to bad control of temperature in the industrial processes leading to prolonged overheating (see *e.g.* Derewenda, 2008). As mentioned above, Pasteur himself managed to racemize (2*R*,3*R*)-tartaric acid but in conditions that one would not find in the industrial process. However, in 1873 E. Jungfleisch discovered that (2*R*,3*R*)-tartaric acid could be racemized by heating it in 10–15% water for 30–48 h, confirming the opinion of Kestner's son-in-law, in a letter dated 9 February 1873 to Jungfleisch, on what had happened in the Thann factory (Jacques, 1986). The presence of *rac*-tartrate in tartar is hence not of biochemical origin as Pasteur thought. Moreover, we shall see in §5 that Jungfleisch turned out to be somewhat of a thorn in Pasteur's side.

4.2. Aspartates and malates

The work on this series of compounds was spurred by Dessaignes' synthesis of aspartic acid from ammonium hydrogen fumarate (Pasteur, 1852*a*). Pasteur observed, what he had certainly expected, that whereas the chemical and most of the physical properties of naturally occurring and synthetic aspartic acids were identical, the first is optically active and the latter optically inactive. However, these series of compounds gave rather confusing results both concerning the optical activity and the crystal morphology compared to the very clear picture which emerged from the tartrates (see §3). In this section alone, in order to avoid any confusion in view of the (false) conclusions that Pasteur drew from his observations, the naturally occurring optically active (2*R*)-aspartates and (2*R*)-malates will be referred to as optically active aspartates and malates, and the synthetic optically inactive *rac*-aspartates and *rac*-malates will be referred to as optically inactive aspartates and malates.

The optical activity of aspartic acid was observed to depend on pH (Pasteur, 1852*a*), dextrorotatory at high pH and laevorotatory at low pH. The crystals were too small and bad to be able to observe whether their morphologies were chiral or achiral. Optically inactive aspartic acid had different unit-cell dimensions and belonged to a different crystal system from the optically active acid. This is typical of a racemic compound. The aspartic acid hydrochlorides also gave bad crystals with those of the optically active compound being morphologically chiral and those of the optically inactive compound morphologically achiral. For the sodium aspartates, the crystals of the optically active salt are morphologically chiral whereas those of the optically inactive compound are so heavily twinned it was not possible to determine their state of chirality. Pasteur studied a few other aspartate salts but no

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[1] Details of Louis Pasteur's family and background, quotations about the universal chiral force, and a crosslink between the primary literature and the *Oeuvres de Pasteur* are available from the IUCr electronic archives (Reference: SH5092) as Appendices A1, A2 and A3, respectively. In addition to work cited in the main text, these appendices also cite Nicolle (1969), Pasteur Vallery-Radot (1956, 1968), Salomon-Bayet (1995) and Vallery-Radot (1987). Services for accessing these appendices are described at the back of the journal.

clear conclusions could be drawn. He stated that the optically active and inactive salts have identical chemistry and similar solubilities, and that any differences reside in the crystal morphology and the optical activity, properties that he recommended all chemists to study for the compounds they synthesize.

Pasteur (1852*a*) observed that the chemical and physical properties of the naturally occurring and synthetic malic acids are identical apart from one being optically active and the other inactive. He also observed that the optical activity of malic acid changed sign depending on the pH but he did not report any crystallographic data for the malic acids. In general for the optically active malate salts and acid Pasteur observed that:

(i) the optical activity of some was dextrorotatory and others laevorotatory, and

(ii) the morphology of the crystals was such that for some compounds the minor faces were to the right and in others to the left.

Pasteur provided a detailed comparison of two optically active and inactive malate salts:

(i) Ammonium hydrogen malate was weakly optically active but the crystals were in general of achiral morphology (Pasteur, 1851*a*), although by changing conditions he did manage to obtain crystals of chiral morphology (Pasteur, 1852*a*). Crystallization of optically inactive ammonium hydrogen malate gave two sorts of crystals. The first to come out of solution were identical '*ont exactement la forme et la composition du bimalate actif*' (Pasteur, 1852*a*) to those of the optically active compound but, in striking contradiction to the above statement of identity, (*a*) were striated, an effect not observed with the optically active compound (the striations may be an indication that the crystals are twinned by inversion) and (*b*) were morphologically achiral with no minor faces. The crystals of the second sort to come out of solution were very nice and of a morphology and unit-cell dimensions not seen with the optically active compounds. In this form the compound has three molecules of water of crystallization compared to one molecule of water for the optically active compound. Pasteur (1852*a*) provided a small *notum* describing the crystallization of an equi-molar mixture of the optically active and inactive compound. He also studied the action of heat on the optically active ammonium hydrogen malate. Part of the product turned out to be identical to optically inactive malic acid. This is the first mention of a thermal racemization in his work.

(ii) Calcium bis(hydrogen malate) was weakly optically active but the crystals were in general morphologically achiral (Pasteur, 1851*a*). The morphologies of the crystals of the optically inactive compound seemed to be very similar to those of the optically active compound and were achiral.

The crystal symmetry and unit-cell dimensions of some optically active and inactive malate salts were quite distinct and incompatible, as usually happened. However for others, *e.g.* ammonium hydrogen malate and calcium bis(hydrogen malate), the unit-cell dimensions of the optically active and inactive salts were identical but the crystals of the optically active compound were morphologically chiral, whereas those of the optically inactive compound were morphologically achiral (Pasteur, 1851*b*, 1852*a*) and remained so even if the experimental conditions were changed. Pasteur stressed that in his view an important difference between the malates and the tartrates was that the amount of water of crystallization in the optically active and inactive compounds was different. Pasteur (1851*b*) (incorrectly) deduced that these optically inactive malate salts were *not* racemates. His explanation was that the crystals contained a molecular structure which was symmetrical and not superposable on the molecules of the optically active compound. It was described as being just like the optically active malic acid but whose chirality had been suppressed. Initially he used the term *symmetrical* to describe this molecular structure but later Pasteur (1860) preferred the term *détordu*. The closest translation in English is 'untwisted' but even this does not do justice to the term. Pasteur wrote that he regretted that the work was incomplete and a fuller study of the malates and the acid was promised for a later date. Evidently he was under pressure to publish. Pasteur (1861*a*) later wondered whether the optically inactive malic acid was not *détordu* but after all a racemate.

4.3. Optical activity

Pasteur (1849*b*) reported that calcium (2*R*,3*R*)-tartrate in HCl solution was laevorotatory in contrast to all the other (2*R*,3*R*)-tartrates and the acid, which were dextrorotatory. This result was the first of those breaking the strict correspondence between the chirality of the molecule and the sign of its optical activity that Pasteur had observed in the tartrates. Further observations weakened this relationship further. The optical activity of (2*R*,3*R*)- and (2*S*,3*S*)-tartaric acids is strongly dispersive (*i.e.* the specific rotation changes with the wavelength of the light) and is not the only property of tartaric acid which is unusual (Pasteur, 1851*b*). Its activity also increases with the amount of water present, with temperature, and with the presence of boric acid. Malic acid is similar (Pasteur, 1851*b*). Asparagine, aspartic, malic and tartaric acids have optical activities which depend on pH (Pasteur, 1850*b*, 1851*a*), some of them even changing sign. Pasteur (1850*b*, 1851*a*) found a time-dependent decreasing optical activity in the compound glucose·NaCl and later in glucose and lactose (Pasteur, 1856*a*). When the crystals of chiral morphology of these compounds are dissolved, the optical activity is high and this gradually decreases to a medium value. Some malate salts are dextrorotatory whilst others are laevorotatory (Pasteur, 1851*a*) and Pasteur also found that some have such a weak optical activity that it was even difficult to establish the sign of the rotation. Pasteur (1873) comments on some optical-activity measurements which needed a polarimeter with a tube 4 m long.

As his studies advanced, Pasteur (1849*b*, 1850*b*, 1851*a*, 1854) expressed the wish to be able to carry out optical-activity measurements on various crystals of low symmetry. He attempted such measurements, and later Pasteur (1857*c*)

Table 1
Pasteur's (1853*a*) results showing crystallization conditions of enantiomerically pure compounds to give crystals of achiral and chiral morphology.

Compound	Achiral crystals	Chiral crystals
Calcium bis[hydrogen (2*R*)-malate]	Aqueous solution	Nitric acid solution
Ammonium hydrogen (2*R*)-malate	Aqueous solution	Impure† aqueous solution
(2*R*,3*R*)-Tartramide	Aqueous solution	Dilute aqueous NH_4OH solution
Ammonium hydrogen (2*R*,3*R*)-tartrate	Aqueous solution	Aqueous solution with sodium hydrogen (2*R*,3*R*)-tartrate
Diammonium (2*R*,3*R*)-tartrate		Form 1: aqueous or dilute NH_4OH solution
Diammonium (2*R*,3*R*)-tartrate		Form 2: aqueous solution with ammonium hydrogen (2*R*,3*R*)-tartrate
Diammonium (2*R*,3*R*)-tartrate		Form 3: aqueous solution with antimony (2*R*,3*R*)-tartrate
Sodium ammonium (2*R*,3*R*)-tartrate‡	Aqueous solution (minority of crystals)	Aqueous solution (majority of crystals)
Sodium potassium (2*R*,3*R*)-tartrate‡	Aqueous solution (majority of crystals)	Aqueous solution (minority of crystals)
Sodium potassium (2*R*,3*R*)-tartrate‡		Aqueous solution with either potassium hydrogen (2*R*,3*R*)-tartrate or ammonium hydrogen (2*R*,3*R*)-tartrate – mixture of right- and left-handed crystals
Sodium potassium (2*S*,3*S*)-tartrate		Aqueous solution with either potassium hydrogen (2*S*,3*S*)-tartrate or ammonium hydrogen (2*S*,3*S*)-tartrate – mixture of right- and left-handed crystals

† Impurity produced by heating the compound. ‡ Sodium potassium and sodium ammonium (2*R*,3*R*)-tartrates are isomorphous.

stated that optical activity was hidden by the birefringence in biaxial crystals such as strontium diformate and the tartrates, a statement which was confirmed by an unpublished text of Pasteur (1878*a*,*b*).

4.4. Chirality of crystals

From 1850 the focus of some of Pasteur's (1850*b*) work was resolving two important converse questions. We shall call these Pasteur's first and second questions and we shall deal with them separately.

4.4.1. Pasteur's first question: Do all compounds which are optically active in solution form chiral crystal structures? In the quest to find an answer to this question, a systematic study (Pasteur, 1853*a*) showed that many enantiomerically pure compounds have chiral crystal structures. In this study, enantiomerically pure compounds observed to give crystals with a chiral morphology were: (2*R*,3*R*)- and (2*S*,3*S*)-tartramide, (2*R*,3*R*)- and (2*S*,3*S*)-tartramic acid, morphine valerianate, papaverine·HCl, and cinchonine (2*R*,3*R*)-tartrate, while those giving an achiral morphology were: malamide, disodium (2*R*,3*R*)-tartrate, codeine (from ether) and calcium (2*R*,3*R*)-tartrate. These results confirmed Pasteur's (1848*g*) very first studies, consistently confirmed later (Pasteur, 1850*a*, 1852*b*), that according to the crystallization conditions used an enantiomerically pure compound does not necessarily produce crystals showing a chiral morphology. He used several kilogrammes of disodium (2*R*,3*R*)-tartrate trying to find a crystal of chiral morphology. He stated clearly that in these cases although the morphology of the crystal was achiral, the crystal structure was chiral. Pasteur (1851*a*) stated that if in these cases crystals of an achiral morphology appeared, all that had to be done was to change the conditions of crystallization and in the end crystals of chiral morphology would be produced. Pasteur's (1853*a*) results are given in Table 1. Pasteur (1853*a*) then stated that since his study was based on a random selection of compounds for all of which he managed in the end to obtain crystals of chiral morphology, it must in general be true that on finding suitable experimental conditions crystals of chiral morphology can be grown for enantiomerically pure compounds.

Pasteur (1854) hypothesized on the case of two identical chiral molecules (of the same chirality) combining to form an *achiral* dimer, and the achiral dimers then solidifying to give a *chiral* crystal structure of either hand. Were such a process to be possible, a chiral crystal structure of either hand could result from the crystallization of an enantiomerically pure compound. Pasteur's seemingly outrageous suggestion of an enantiomerically pure compound forming a chiral crystal structure of either hand is most interesting. The formation of the achiral dimer from two identical enantiomers of the same chirality brings to mind the *Coupe du Roi* discussed by Flack (2003).

Pasteur (1856*b*) found a case of a series of enantiomerically pure compounds where despite changing the crystallization conditions, he never found crystals of chiral morphology. These compounds were various derivatives of (*S*)-2-methyl-1-butanol (Gal, 2008*a*). The latter compound occurred in an optically active natural product called 'amyl alcohol' which Pasteur (1855) established to be a mixture, in varying proportions according to source, of two isomers, one chiral, (*S*)-2-methyl-1-butanol, and one achiral, 3-methyl-1-butanol (Pasteur, 1856*b*; Gal, 2008*a*). The crystals of these two isomers were strictly isomorphous, both always showing an achiral crystal morphology. He stated that the molecular structure was different but the morphology was identical. He also stated that it was not possible to have association or combination of two isomers, one chiral and one achiral, which had isomorphous crystal structures. To prove this point he had tried crystallizations of mixtures of two isomers, one enantiomerically pure and one achiral, of various unspecified compounds and observed that in all cases the two compounds never crystallized together but formed crystals of the individual compounds. Pasteur's conclusion based on the isomorphism of the crystals of the enantiomerically pure and achiral amyl alcohol was that the crystal structures of the derivatives of the enantiomerically pure isomer were in fact achiral: '*Je conclus de cet isomorphisme absolu des dérivés amyliques actif et inactif que la structure hémihédrique n'existe pas dans les produits actifs*'. Even so he still had some doubts: '*Mais cette preuve ne suffit pas encore*', and tried crystallization experiments of derivatives of the chiral and achiral isomers to force the crystals to be chiral by using an enantiomerically pure derivatizing group. In practice Pasteur used the enantiomerically pure and achiral sulphamylates combined with enantiomerically pure cinchonine. He did not obtain the results he wanted. He found that the crystals of these new pairs of compounds were always isomorphous and chiral, the crystals always showing the same chirality sense. He stated that the chirality was clearly due to the cinchonine alone. In conclusion he thought it was remarkable that one could find identical crystals from different isomers. By 1860 his interpretation appeared to have changed, as it was stated that there was an achiral form of amyl alcohol described as being *détordu* (Pasteur, 1860). Concerning Pasteur's suggestion for amyl alcohol, in 2008 there is no known well established example of an enantiomerically pure compound with an achiral crystal structure. This case has been discussed by Flack (2003).

Sometimes Pasteur found it advantageous to measure some other chiral-dependent physical property to establish the chiral nature of the crystal structure. For example, in the studies of candied sugar (Pasteur, 1848*f*,*g*) the chiral morphology of the crystals was only really observed after measurement of the pyroelectricity proved the crystals to be chiral.

4.4.2. Pasteur's second question: Are crystals of chiral morphology necessarily optically active? It is unspecified in this second question whether initially Pasteur had the optical activity of the solution or the crystal in mind.

The key compounds used by Pasteur to answer his own second question were quartz (see §2.2) and strontium diformate. Pasteur (1849*a*) carried out his first crystallizations of strontium diformate and later completed them in Pasteur (1850*b*, 1851*a*). Aqueous solutions of the compound were optically inactive but the morphology of the crystals was chiral and they could be sorted out into batches of left-handed and right-handed crystals. A solution of entirely right-handed (or left-handed) crystals of strontium diformate was optically inactive and on recrystallization gave a mixture of right- and left-handed crystals. No wonder Pasteur was surprised and perplexed, and was reported as saying '*Ah! formiate de strontiane, si je te tenais*'! (Vallery-Radot, 1922). This remark was repeated with ironic glee by his Strasbourg friend Bertin to anyone who cared to listen. By 1851 he had also observed that unlike the sodium ammonium *rac*-tartrate, the proportion of right- and left-handed crystals of strontium diformate was not fixed to 50:50 but was variable from batch to batch. Indeed in one batch he found almost entirely left-handed crystals. He made the correct deduction, stating that the chirality of the crystals was not due to the arrangement of the atoms in the molecule but due to the arrangement of the molecules in the crystal (Pasteur, 1850*b*, 1851*a*). He made the parallel with quartz and pointed out that as crystals of quartz were optically active, crystals of strontium diformate should also display this property. Another compound he knew to be like strontium diformate was $MgSO_4$ and he also observed that the cell dimensions of these compounds were near to special values (*e.g.* either two cell lengths approximately equal or a cell angle close to 90°), which would make the crystals morphologically achiral.

Pasteur (1854) stated very clearly that chiral crystal structures may be formed both by enantiomerically pure compounds and by a wider class of achiral molecules. He was clear that for crystals formed of achiral molecules or building units the chirality of the crystal was due to the crystalline arrangement and not due to the molecular structure, and that the liquid or solution phase was not optically active. He was also very well aware that in the crystallization of a compound in this class the ratio of right- to left-handed crystals was not fixed by molecular structure. He stated that in quartz and strontium diformate he had obtained a mixture of crystals of both chiralities, whereas in $MgSO_4$ and $KHSO_4$ he had obtained only crystals of one chirality sense. Pasteur (1856*c*, 1857*c*) gave further consideration to this matter. For quartz he took some naturally occurring mineral samples where there were a large number of chiral quartz crystals together and counted the number of left- and right-handed crystals. He found a spread around 50% for five independent samples. He also stated that he never found a sample in the various collections in Paris that he examined of a batch of quartz crystals all of the same chirality. Quartz had the disadvantage that the batches of crystals of identical chirality can not be recrystallized easily. He proposed to use strontium diformate for a further systematic study which was never published. In fact, later workers all used $NaClO_3$ in this type of study (Kipping & Pope, 1898). Pasteur (1856*b*) referred for the first time to $NaClO_3$ as a compound having achiral ions with a chiral crystal structure. $NaClO_3$ had been identified as such by Rammelsberg (1855) and Marbach (1856). The crystal structure of $NaClO_3$ is cubic and consequently the crystals are not birefringent. Moreover, the tabular shape of the crystals makes for easy identification of their chirality under the polarizing microscope by way of the sign of their optical activity.

4.4.3. Crystal growth. Pasteur (1856*c*, 1857*c*) undertook crystallization experiments on ammonium hydrogen (2*R*)-malate from pure aqueous solution, giving crystals of achiral morphology, and impure aqueous solution, giving crystals of chiral morphology. The impurity was created by adding a small amount of the product of heating the compound. If a crystal of chiral morphology obtained from the impure solution was allowed to grow further in pure aqueous solution, the crystal morphology became achiral. Likewise, a crystal of achiral morphology, grown from pure aqueous solution, became chiral when the growth was continued in impure aqueous solution. Pasteur also observed the behaviour of regrowth of cleaved, broken or filed-down crystals in slightly or just supersaturated aqueous solution. He observed that the broken crystal grew on all faces but that growth on the broken part was much faster until the crystal had attained its unbroken morphology. He also undertook kinetic studies of crystal growth from pure and impure aqueous solution and found that crystals from the former were much wider and from the latter were longer than the other. He roughly measured the rates of growth of the main faces and came to the hypothesis that the growth rates were responsible for the disappearance of the minor faces showing the chirality of crystals grown from pure aqueous solution. As a consequence he undertook the regrowth of broken crystals of achiral morphology in pure aqueous solution and was able to observe the minor faces indicating the chirality in the regrowth zone. Of course, when the crystal was fully regrown the minor faces had disappeared. He also undertook the experiment of covering the side faces and cutting off the end faces of a crystal of achiral morphology and letting it continue its growth in pure aqueous solution. As he had expected, after a few hours the crystal morphology had become chiral.

In an unpublished manuscript note Pasteur (1870) has further ideas for growth experiments on broken and repaired crystals. Most unfortunately this note was not reproduced by Pasteur Vallery-Radot (1939).

4.4.4. Dimorphism, pseudosymmetry and twinning. In his early work on dimorphism in crystals of various compounds, Pasteur (1848*a*,*b*,*c*,*d*,*e*) observed that there was a relationship between the symmetries and the unit-cell dimensions of the two phases. Often one of the structures could be obtained from the other by the unit-cell dimensions taking special values giving an increase in symmetry. Typical examples are a low-symmetry crystal in the monoclinic system with a unit-cell angle β close to 90° becoming orthorhombic with $\beta = 90°$, or a crystal in the orthorhombic system with unit-cell lengths $a \simeq b$ becoming tetragonal with $a = b$. Later even individual phases were observed to display pseudosymmetry. The optically inactive (in solution) compounds with chiral crystal structures, strontium diformate and $MgSO_4$, have almost special unit-cell dimensions which would make the morphology of the crystals achiral. Some crystals of quartz were observed to be twinned by inversion (*i.e.* a Brazil twin). In crystals of ammonium hydrogen (2*R*,3*R*)-tartrate the unit-cell dimensions were near to a specialized value, leading the morphology to show a symmetry higher than that of the crystal system. There were indications that the crystals were twinned (Pasteur, 1853*a*). Crystals of dipotassium (2*R*,3*R*)-tartrate and potassium ammonium (2*R*,3*R*)-tartrate were isomorphous, had special unit-cell dimensions and apparently twinned crystals (Pasteur, 1853*a*).

Pasteur (1854) considered and studied dimorphism in enantiomerically pure compounds using diammonium (2*R*,3*R*)- and (2*S*,3*S*)-tartrates as test cases. Form 1 of these compounds was obtained by crystallization from an aqueous solution of the free acid saturated with ammonia. The anhydrous crystals of the two compounds were enantiomorphous. Form 2 was obtained by adding a small quantity of diammonium (2*R*)-malate to the solution. Form 2 had a different crystal structure from form 1 but was also chiral and anhydrous, although the crystals were tetartohedral rather than hemihedral, and were enantiomorphous for the two compounds (see §6 for a short explanation of the term tetartohedral). Under the above conditions it was much easier to produce form 2 of the (2*R*,3*R*)- than the (2*S*,3*S*)-tartrate. Pasteur stated that this was to be expected due to his work described in §4.5.1. If instead of diammonium (2*R*)-malate, its racemate was used, form 2 continued to form equally well for both the (2*R*,3*R*)- and the (2*S*,3*S*)-tartrate. Nevertheless the crystallization of form 2 was capricious. Taken into solution, crystals of the two forms have the same absolute value of the specific rotation, its sign depending on the enantiomer chosen. Pasteur also observed in one crystallization experiment that both forms of crystals appeared, but by the following day the crystals of form 2 had disappeared. In conclusion he postulated that there were perhaps two different ways that dimorphism could manifest itself in such compounds. The dimorphism might arise either due to small changes in the arrangement of the atoms in the molecules or due to the same molecules being arranged in different manners in the crystal. For the diammonium tartrates he opted for the first hypothesis.

4.5. Properties of enantiomers

4.5.1. Chemical. Pasteur's major contribution to the chemistry of molecular chirality was in the discovery of diastereoisomers and thermal racemization. Starting from the known fact (Pasteur, 1852*b*, 1853*a*) that the compounds formed between an achiral compound and either (2*R*,3*R*)- or (2*S*,3*S*)-tartaric acid have the same chemical and physical properties apart from the sign of the optical activity, he wondered what would happen if instead of the achiral compound an enantiomerically pure one was used. His studies confirmed that the compounds formed in this way were different. The results are presented in Table 2.

This experimental evidence allowed Pasteur to deduce that diastereoisomer formation was a general phenomenon. Moreover Pasteur (1853*e*) observed differences in thermal stability between diastereoisomers made with (2*R*,3*R*)- and (2*S*,3*S*)-tartrates.

Pasteur (1850*a*) thought that it only needed the attention of chemists to be drawn to the problem of the formation of *rac*-tartrates in tartar for someone to discover a laboratory procedure to racemize (2*R*,3*R*)-tartaric acid. On the basis of an observation by Biot that the optical rotation of tartaric acid diminishes with temperature, Pasteur (1850*a*) attempted the racemization of (2*R*,3*R*)-tartaric acid by cooling in aqueous solution. The experiment was unsuccessful as on cooling the solution froze, which according to Pasteur resulted in a limitation of molecular movement: '*et l'on conçoit que le mouvement moléculaire n'est plus guère possible*' (Pasteur, 1850*a*). He then tried the cooling of tartaric acid in sulfuric acid because such a solution had a lower freezing point and it was known that the specific rotation of tartaric acid in sulfuric acid was much reduced. In 1852 Pasteur thought that one could not racemize (2*R*,3*R*)-tartaric acid in the laboratory.

Pasteur (1852*a*) studied the action of heat on ammonium hydrogen (2*R*)-malate. Part of the product turned out to be

Table 2
Pasteur's (1853*a*) results on compound formation between pairs of enantiomerically pure compounds.

The second reactant T_R or T_S was always based on the tartrate anion and was available as the two enantiomers T_R = (2*R*,3*R*) and T_S = (2*S*,3*S*). *X* and *Y* are various sets of cations unspecified by Pasteur (1853*a*). A blank entry means that Pasteur (1853*a*) stated that the experiments had been performed but no results were reported. As an example an entry such as $C_RT_R = C_R + T_R$ under optical activity means that the optical activity of the product was equal to the sum of the optical activities of the reactants.

First reactant C_R	Second reactant T_R or T_S	Product	Solubility	Optical activity
Ammonium hydrogen (2*R*)-malate	Ammonium hydrogen tartrate	C_RT_R, no C_RT_S	$C_RT_R \neq C_R$ or T_R	$C_RT_R = C_R + T_R$
(2*R*)-Malamide	Tartramide	C_RT_R	$C_RT_R \neq C_R$ or T_R	$C_RT_R = C_R + T_R$
		C_RT_S	$C_RT_R < C_RT_S$	$C_RT_S = C_R + T_S$
X (2*R*)-malate	*Y* or *Y* hydrogen tartrate			
Cinchonine	*Y* or *Y* hydrogen tartrate	C_RT_R		
		C_RT_S		
Brucine	*Y* or *Y* hydrogen tartrate	C_RT_R or $C_R(T_R)_2$		
		C_RT_S or $C_R(T_S)_2$		
Strychnine	*Y* or *Y* hydrogen tartrate	C_RT_R or $C_R(T_R)_2$		
		C_RT_S or $C_R(T_S)_2$		
Quinine	*Y* hydrogen tartrate	C_RT_R	$C_RT_R \neq C_RT_S$	Heating
		C_RT_S		$C_RT_R \neq C_RT_S$

rac-malic acid. Only by raising the temperature did he manage to racemize (2*R*)-malic acid. Pasteur (1853*a*) observed that the two diastereoisomers of hydrogen (2*R*,3*R*)- and (2*S*,3*S*)-tartrates with enantiomerically pure quinine behave differently on heating and had different solubilities. Consequently, after much experimentation, Pasteur (1853*d*,*e*) found conditions leading to the thermal racemization of (2*R*,3*R*)-tartaric acid. This was achieved by heating the (2*R*,3*R*)-tartaric acid in the presence of a base, *e.g.* cinchonine for several hours at 443 K. To prove the identity of the product, he resolved it into (2*R*,3*R*)- and (2*S*,3*S*)-tartaric acids. He also proved that (2*S*,3*S*)-tartaric acid could be racemized by the same procedure. In fact, he stated that his motivation in these experiments was to try to produce an optically inactive tartaric acid similar to the *détordu* malic acid that he thought erroneously to have been observed previously (see §4.2). In the first instance, rather than finding a *détordu* tartaric acid (*i.e.* achiral) he had found the racemate. However, Pasteur (1853*e*) also found another optically inactive tartaric acid as a reaction product [it was in fact *meso*- or (2*R*,3*S*)-tartaric acid]. No evidence was presented to prove that this new form of tartaric acid was indeed a single achiral molecule rather than a racemate, although later Pasteur (1860) stated that the *meso*-tartaric acid could not be resolved into (2*R*,3*R*)- and (2*S*,3*S*)-tartaric acid.

4.5.2. Biochemical. Pasteur (1853*a*) made some comments relating the activity of diastereoisomers to the biosphere and (Pasteur, 1857*a*) announced his discovery that certain microorganisms consumed one enantiomer of tartaric acid far more rapidly than the other on fermentation. He also applied the same fermentation process to *rac*-tartaric acid and found that one of the enantiomers in the racemate was consumed and the other was left unaltered. The description of the fermentation of *rac*-tartaric acid constitutes the first published observation of enantioselectivity in a biological process. Later Piutti (1886) had observed that D- and L-asparagine have a different taste. Pasteur (1886) interpreted this as being due to the molecular receptors in the body being enantiomerically pure and having very different interactions with the D- and L-asparagine.

4.5.3. Thermochemical. The formation of *rac*-tartaric acid is exothermic, which lead Pasteur (1850*a*) to conclude that there was a real chemical combination. Measurement of thermochemical properties was used sparingly in Pasteur's work. The principal technique he used was solubility measurement. Melting temperatures were very rarely reported. Indeed, these techniques provided more useful information for the differentiation of isomers and diastereoisomers rather than enantiomers and racemates. We give a few examples.

rac-Aspartic acid·HCl was more soluble in water than (2*R*)-aspartic acid·HCl, whereas sodium *rac*-aspartate is slightly less soluble in water than sodium (2*R*)-aspartate (Pasteur, 1852*a*). In his study of amyl alcohols (a mixture of two isomers, see §4.4.1) purification (*e.g.* by fractional distillation, the two isomers have very similar boiling points) was a terrible problem and he achieved separation by fractional crystallization of barium sulphamylate, measuring differences in the solubility. One compound had a solubility 2.5 times greater and a higher density than the other. Pasteur (1861*c*) stated that for compounds with a low specific rotation it was sometimes useful to measure the difference in solubility of the compound in solutions of opposite enantiomers of another compound, *e.g.* (2*R*,3*R*)- and (2*S*,3*S*)-tartaric acid.

Lead (2*R*)- and *rac*-malates had the same melting temperature of less than 273 K. Pasteur measured differences of melting temperature between the enantiomerically pure and the two forms of the racemate of ammonium hydrogen malate (see §4.4.3).

4.5.4. Structure. As a result of his thermal racemization experiments (see §4.5.1), Pasteur (1853*e*) concluded that there were four tartaric acids: (i) (2*R*,3*R*)-tartaric acid, (ii) (2*S*,3*S*)-tartaric acid, (iii) *rac*-tartaric acid, being a combination of (2*R*,3*R*)- and (2*S*,3*S*)-tartaric acids, and (iv) *meso*-tartaric acid, which was described as being neither right- nor left-handed nor the combination of right- and left-handed molecules but as being *détordu*.

Pasteur (1850*b*, 1851*a*, 1852*a*) undertook a comparison of the optical activity of the enantiomerically pure malates and tartrates in part to reveal the similarities and differences of their molecular structures. He came to the conclusion that there were common molecular groups in the tartrates and malates. Moreover, he incorrectly deduced (Pasteur, 1851*a*) that both tartaric and malic acids had two chiral groups in the molecule and it was this which gave the variable optical activity. Pasteur (1853*c*) used the same argument in attempting to rationalize the optical activity of several alkaloid bases derived from quinquina.

Pasteur (1853*a*) concluded that it was:

(i) very probable that every right-handed chiral molecule should have a left-handed opposite and *vice-versa*, and

(ii) very probable that every chiral molecule also had an achiral isomer, giving the same relationships as seen in the optically active and inactive malic and aspartic acids, but no mention was made of *meso*-tartaric acid.

He hence deduced that for a chiral molecule T combined with a chiral molecule C there would be nine diastereoisomers, as illustrated in Fig. 6 (taken from the original publication). Pasteur also stated that he was soon to publish a work showing that in a large number of organic compounds one could easily remove the optical activity. This publication never appeared. Pasteur (1855) wondered whether the arrangement of the atoms in optically active malic acid was in the form of a chiral tetrahedron and the optically inactive *détordu* form was an achiral octahedron. If so, it would hence be a general concept that a chiral molecule could shift around its atoms to become achiral whilst conserving its stability. Pasteur (1860) stated that there was an achiral form of amyl alcohol described as being *détordu*.

Pasteur (1861*a*), using succinic acid as an example, wondered whether *all* molecules had four isomers: *i.e.* a left-handed molecule, a right-handed molecule, a racemate and an achiral *détordu* molecule. Pasteur (1861*b*) considered several optically inactive compounds (*e.g.* succinic acid) which on oxidation gave *rac*-tartaric acid. As he still had in mind that by synthetic means one could not transform achiral molecules into chiral molecules (in many places he expresses the view that such a transformation may only be achieved in the biosphere), he suggested that optically inactive succinic acid may be achiral in some special way by analogy with *rac*-tartaric acid. He again stated that for the latter, (2*R*,3*R*)- and (2*S*,3*S*)-tartaric acids combined exothermally to form a racemic *compound*, but wondered about the nature of the bond between the two enantiomers. He postulated that *rac*-tartaric acid might be an achiral molecule in its own right and that perhaps succinic acid was in the same situation. Clearly he was still trying to understand the identities of racemates and achiral molecules.

4.6. Resolution of racemates

The discovery of spontaneous resolution of sodium ammonium *rac*-tartrate also represented the very first method of resolving a racemate. Pasteur (1853*e*) himself stated that a very rare set of circumstances was necessary to achieve a resolution by this means and thought that sodium ammonium *rac*-tartrate was an unique example. The second recorded spontaneous resolution was reported nearly 40 years later by A. Piutti (1886) with the amino acid asparagine (Jacques, 1986).

Pasteur (1853*e*) discovered a second and more practical method of resolving racemates. This followed from Pasteur's (1852*b*, 1853*a*) study of the properties of enantiomers and the formation of diastereoisomers (see §4.5.1). This method of resolution is frequently known as the classical method of resolution and consists of forming a salt between a racemic acid A(L) + A(D) in solution with a suitable enantiomerically pure base B(L), assumed arbitrarily here to be laevorotatory. If the base B(L) has been chosen properly, the two salt diastereoisomers A(L)B(L) and A(D)B(L) have different solubilities and may be separated. Pasteur reported only one practical example of this method, that of *rac*-tartaric acid. He never managed or tried to resolve *rac*-malic acid. Use of this method was slow to develop. From a study of the references given in Jacques *et al.* (1981), it seems that Bremer (1880) was the next person to achieve a resolution by formation of a diastereoisomer.

As presented in §4.5.2, some microorganisms consume one enantiomer over the other in a racemate upon fermentation (Pasteur, 1857*a*, 1858). Fermentation with a suitable microorganism thus constitutes a viable method of resolution of a racemate, albeit providing only one of the enantiomers.

The final method of resolution is due to Gernez (1866), one of Pasteur's co-workers. Gernez's technique is a kinetic resolution based on seeding a supersaturated solution of the racemate with crystals of one of the enantiomers. When the conditions are correct, enantiomerically pure crystals of the same chirality as the seed will be deposited.

4.7. Universal chiral force

For this topic there are very few written reports, published or unpublished by Pasteur. The most complete description of Pasteur's thinking and experimentation (proposed or achieved) on this matter is to be found in the available original texts in French, which have been collected together in Appendix A2 in the supplementary material for ready reference.

Pasteur pondered the possible causes of the spontaneous resolution of sodium ammonium *rac*-tartrate. In Pasteur (1850*a*, 1853*e*) he admitted to having no idea of the cause of spontaneous resolution, although a few sentences in a letter (Pasteur, 1850*c*) to Chappuis suggested that he thought he

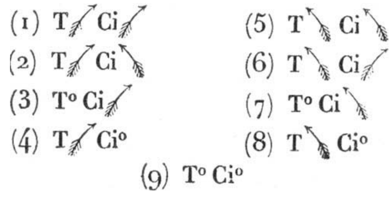

Figure 6
Pasteur's 1853 scheme of diastereoisomers of combinations of chiral molecules T and C.

might be about to make a breakthrough on this topic. He later came to formulate the existence of a universal chiral influence or force. Vallery-Radot (1922) gives an account of this preliminary theory placing it during Pasteur's years in Strasbourg, but this text is in part identical to that of Pasteur (1874), see Appendix A2. The first published account from Pasteur's own hand is in his conference to the Chemical Society of Paris (Pasteur, 1860). On our planet he hypothesized that this force might arise through the agency of the terrestrial magnetic field or the rotation of the Earth. In his time at Strasbourg and Lille in the early 1850s, according to his own later account (Pasteur, 1884*a*), Pasteur had powerful magnets built by Rhumkorff. He performed crystallization experiments in a magnetic field on compounds normally displaying an achiral crystalline morphology. He hoped that crystals of chiral morphology would result. He also attempted (or, perhaps more correctly, proposed) to invert the optical activity of natural products by growing plants in an artificial environment, produced by means of a heliostat, in which the sun rose in the west and set in the east. Mason (1984) stated that Pasteur also undertook plant-growing experiments in a centrifuge. We have been unable to identify the source of this information. In Pasteur (1870) one finds manuscript propositions for experiments related to this topic. Some of them are very closely related to the experiments that Pasteur (1884*a*) stated had been undertaken in his years in Lille (1854–1857). We have been unsuccessful in finding the location or any drawing or pictorial representation of the crystallization magnets or the plant-growing heliostat. The equipment might still be lurking in some dusty cellar in Strasbourg or Lille. From the sources available to us, it is very hard to be sure what in fact was undertaken. The potentially most informative source must be Pasteur's handwritten laboratory notebooks archived in the Bibliothèque nationale de France. For the years 1849–1857 these have not yet been the subject of an in-depth historical study and as of April 2009 they are not yet available online.

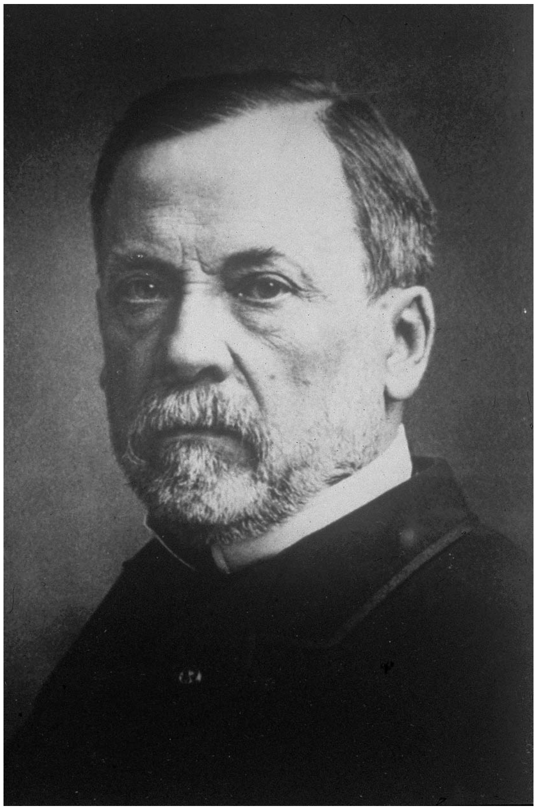

Figure 7
Portrait of Pasteur in 1884 in Copenhagen by Petersen, courtesy of l'Institut Pasteur, Paris.

Our reading of the texts in Appendix A2 confirms the conclusions of Geison (1995) that Pasteur had come to the conclusion that enantiomerically pure chiral molecules only appear in the presence of a chiral influence. This follows from his work with diastereoisomers and bacterial resolution. The chiral influences mentioned in these texts were not only his 'universal chiral force' but localized chiral influences. However, within the Pastorian mindset it was difficult to reconcile this theory with some simple cases for which experimental observations were in fact available. One example of these was the synthetic transformation of succinic acid (achiral, see Fig. 2) into *rac*-tartaric acid in which chiral molecules are created in the laboratory from achiral ones. Pasteur waivered between models in which succinic acid was naturally an (unresolvable) racemate or was some sort of a *meso* compound. Another example is Pasteur's own starting problem, the formation of a racemic conglomerate by spontaneous resolution. As we shall see in §5 Pasteur never accepted that chiral influences were unnecessary for the formation of a racemic conglomerate.

5. Pasteur's post-1858 views on his early work

In September 1854 Pasteur was appointed Professor and Dean of the new faculty of sciences in Lille. This marks the beginning of the end of his active interest in molecular chirality and crystallography (Gal, 2008*a*), which was effectively terminated in 1858. In 1860, then installed at the Ecole Normale in Paris, Pasteur (1860) presented two lectures to the Chemical Society of Paris which were essentially a review of his past work on molecular chirality spiced with a few personal reminiscences. The only new element was the presentation of his views on the universal chiral force, but this was without any account of the experiments on crystallization in a magnetic field or growing plants in an inverted environment (see §4.7).

On 22 December 1883 Pasteur (1884*a*) spoke a final time on molecular chirality to the Chemical Society of Paris, some 25 years after he changed direction in his research and ten years after the publications of Le Bel (1874) and van't Hoff (1874). Viewed as a scientific review in 1883 of molecular chirality, the written report of this talk is a disgrace. The content is out of date and the author (see Fig. 7) is out of touch. There was a single very short reference to the consequences of Le Bel and van't Hoff's work to molecular chirality, '... *ayant dans leurs formules ce qu'il appelle du carbone asymétrique* ...', and Pasteur presented no attempt to apply the theory to his own results. There is in fact no incompatibility between Pasteur's experimental observations and the Le Bel and van't Hoff theory. As concerns the formation of a racemic conglomerate by sodium ammonium *rac*-tartrate Pasteur clearly stated that he was convinced that this only occurred during crystallization due to the presence of some chiral force which, if it was not due to light or magnetism, must be due to some chiral organic dust on the surfaces of the crystallization dish. He further stated that nothing would be simpler than to crystallize an aqueous solution of sodium ammonium *rac*-tartrate in an environment free of organic dust in order to observe the formation of crystals of the racemic compound. On presenting his notion of the universal chiral force, he published for the only time in his life some short details of his experiments to establish its presence (see §4.7 and Appendix A2).

Criticism of Pasteur's opinion on these matters had already or soon appeared. Indeed the Chemical Society of Paris published a series of comments by others with answers by Pasteur on his presentation. The most poignant comments are those of Wyrouboff and Jungfleisch (Wyrouboff *et al.*, 1884). In the opinion of these two chemists the production of the racemic conglomerate is just a matter of differences of solubility, and changes thereof with temperature, of the various salts. Wyrouboff stated that the experiment suggested above by Pasteur had already been carried out and published by Scacchi (1864/5[2], 1865), who found that above 301 K sodium ammonium *rac*-tartrate crystallizes as a racemic compound. Pasteur (1884*b*) was both uncompromising ('*Il m'est impossible de trouver raisonnable l'opinion qui place la cause de ce dédoublement dans une influence de solubilité*') and impolite ('*Voilà ce que M. Jungfleisch n'a pas compris, pas plus que M. Wyrouboff*'). The modern view of the formation of racemic conglomerates and compounds, as presented in the exemplary monograph of Jacques *et al.* (1981), is exactly the thermochemical (thermodynamic) viewpoint of Jungfleisch and Wyrouboff. Another criticism was to be found in Lord Kelvin's (1904) Baltimore lecture, which contained the following concerning the Faraday (1846) experiments: 'The magnetic rotation has neither left-handed nor right-handed quality (that is to say, no chirality). This was perfectly understood by Faraday and made clear in his writings, yet even to the present day we frequently find the chiral rotation and the magnetic rotation of the plane of polarized light classed together in a manner against which Faraday's original description of his discovery of the magnetic polarization contains ample warning.' This criticism is apposite to Pasteur's experiment on crystal growth in a magnetic field.

It is of interest to note that in Pasteur's collected correspondence (Pasteur Vallery-Radot, 1946), there is no communication with Le Bel, Bravais, Curie, Faraday, van't Hoff, Jungfleisch, Lord Kelvin, Roozeboom and Wyrouboff. There is, however, a single letter to W. H. Miller (famous for his invention of Miller indices for indexing crystal faces) dated 24 February 1857, in which Pasteur urgently requests a letter of reference for his 1857 (failed) attempt to become a member of the Académie des sciences.

6. Concluding remarks

Pasteur was a master of observation and an adroit experimenter. Although he planned his research based on theoretical considerations he made no attempt to develop a structural theory of molecular stereochemistry or molecular chirality. From the time of the discovery of spontaneous resolution and the consequent introduction of molecular chirality in 1848, 25 years had to elapse before Le Bel (1874) and van't Hoff's (1874) notion of the asymmetrical tetrahedral carbon atom came to the fore with its evident clarification of the basis of molecular chirality. Pasteur's discovery of molecular chirality did nothing to stimulate the development of molecular stereochemistry.

There is a huge mass of literature concerning Pasteur but much of it concerns his work and life post-1857, with little of direct relevance to his early chemical and crystallographic studies. Nevertheless, we find it of interest to compare some of the *modi operandi* of the established, internationally renowned, future national French hero with the young Pasteur pre-1857. Much of this information is drawn from Latour (1986). Pasteur's fits of bad temper were legendary. He was highly secretive. In discussion he was merciless (see §5). He much preferred a single high-impact demonstration to a large set of experimental observations. The demonstration of spontaneous resolution is of this kind. Likewise as part of the 1860 lecture to the Chemical Society of Paris the formation of *rac*-tartaric acid was demonstrated by mixing together separate aqueous solutions of enantiomerically pure (2*R*,3*R*)- and (2*S*,3*S*)-tartaric acids. There was immediate precipitation to huge applause. (This experiment proves that *rac*-tartaric acid is less soluble than the separate enantiomerically pure compounds. Whilst enjoying the applause, Pasteur should have pondered what would have happened had the *rac*-tartaric acid been the more soluble compound!) At about the time of the final lecture to the Chemical Society of Paris in 1883, a polemic was underway pitting Peter and Koch against Pasteur. Peter was an eminent old-style French medical doctor. The underlying basis of Peter and Koch's justifiable criticism was that Pasteur tended to generalize over-hastily based on only a few experimental observations whose validity was not fully established. In this vein we have seen in §4.2 his deduction of a *détordu* molecule of malic acid, in §4.1 the erroneous deduction of the source of *rac*-tartaric acid in Kestner's production, in §4.4.1 his deduction that isomers never form solid solutions and in §4.7 his deduction and continuing defence of the 'universal chiral force'.

Gal (2008*a*) amongst others has discussed the reasons for Pasteur abandoning the molecular-chirality and crystallography line of research in favour of the study of fermentations around 1857. From the information provided in the current paper, some further reasons come to mind. The concept of the universal chiral force was quite wrong. The experiments on crystallization in a magnetic field or plant

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[2] Scacchi published the same article twice. There is some ambiguity about the date of one publication, which although in a journal dated 1864, starts '*letta nella tornata del di 8 agosto 1865*'.

growth with the heliostat and in the centrifuge were never undertaken or were unsuccessful. Only in 1894 did Curie (1894) provide the necessary theoretical basis for satisfactorily understanding the subtle relationships which control these situations. Moreover, in the 1850s organic stereochemistry was not really in a state for further developments in the field of molecular chirality. Series of compounds such as the tartrates were exceedingly hard to come by. As we have seen in §4.2, the work on the malates was a flop. Dimorphism and polymorphism of crystals did not fit into the accepted views of structure. Morphological studies of crystals were not powerful enough. What was really needed was the analysis of molecular and crystal structure. This only appeared on the scene through the X-ray diffraction of crystals in 1913. In short, the molecular-chirality work had become confusing and was not giving enough results. There was also a certain mindset of Pasteur as we have seen in the 1883 lecture to the Chemical Society of Paris that he seems neither to have embraced the notion of the tetrahedral asymmetric carbon atom nor the developments in thermodynamics that were crucial to advancing the topic. It is, however, fair to say that by 1860 he had discovered more or less all the important information in this field with the techniques available at the time and the state of scientific knowledge. Pasteur was not only the founder, discoverer and master of molecular chirality, he was also the same for crystalline chirality. It is further worth pointing out that Pasteur was capable of changing interests and directions without turning back and without any real regret. At age 20 he stopped painting, never to recommence, although in 1863 he accepted a Professor's post at the *Ecole des Beaux-Arts* (Pasteur Vallery-Radot, 1954).

In his publications Pasteur frequently used the word *hémiédrie* (hemihedry in English) and from time to time *homoédrie* (holohedry in modern English) and *tétartoédrie* (tetartohedry in English). Pasteur well understood the meaning of these terms, which were not of his own invention. They are still used today in crystallographic texts, albeit rarely, with the same meaning which is obscure to chemists. Some words of explanation are called for. The largest or main faces of a crystal may be used to define a point symmetry, known as the holohedry, which in fact is now known to be the point symmetry of the translation lattice. There are only seven holohedral classes and these are used to give names to the corresponding seven lattice systems as follows: $\bar{1}$ (C_i) triclinic or anorthic; $2/m$ (C_{2h}) monoclinic; mmm (D_{2h}) orthorhombic; $4/mmm$ (D_{4h}) tetragonal; $\bar{3}m$ (D_{3d}) rhombohedral; $6/mmm$ (D_{6h}) hexagonal; $m\bar{3}m$ (O_h) cubic (Hahn, 2002). In practice, a study of all faces on a crystal or crop of crystals may show that the point symmetry of the crystals is lower than that of its holohedry. For example, within the orthorhombic system, the crystal may have the holohedral symmetry mmm (D_{2h}) or the lower symmetries $mm2$ (C_{2v}) or 222 (D_2); the latter two are index-2 subgroups of mmm and are called hemihedral classes. In other lattice systems subgroups of index 2 (hemihedry), 4 (tetartohedry) and 8 (ogdohedry) are possible. Crystals in the holohedral class mmm and the hemihedral class $mm2$ are achiral, whereas crystals in the hemihedral class 222 are chiral. Delafosse and Pasteur knew very well that a necessary but not sufficient condition for a crystal to be chiral is that it should occur in a hemihedral or lower class, a notion which has not been fully understood by others, who take hemihedral as being synonymous with chiral (Pasteur, 1850*a*,*b*). Pasteur (1849*b*) quotes the case of boracite, amongst others, to illustrate crystals which are achiral and hemihedral.

Pasteur also extensively used the word *dissymétrie* (dissymmetry in English), although he never provided a formal definition of it and there is no indication who coined it. The most likely persons are Delafosse, Pasteur, Laurent or Biot, in that order, although Delafosse (1840) in his work on crystallization uses *hémièdrie* but does not use *dissymétrie*. As of April 2009 a search on the electronic content of the Bibliothèque nationale de France is incomplete, as early publications were only available as unsearchable bitmap images. Lowry (1935), and Barron (2002) following him, have analysed Pasteur's (1848*g*) use of dissymmetric and come to the conclusion that it describes handed figures and handed molecules generally. Our understanding of Pasteur's (1848*g*) text is different. His use of dissymmetric was always qualified by a reference to non-superposable mirror-related (*i.e.* enantiomorphous) objects as he well knew that a hemihedral crystal may be chiral or achiral, and he needed to distinguish between the two cases. We quote two examples from his publications: '*. . . qui possède réellement dans sa constitution intime cette dissymétrie spéciale que nous voyons accusée par le caractère de l'hémiédrie cristalline . . .*' (Pasteur, 1850*a*) and '*et d'une dissymétrie à image non superposable*' (Pasteur, 1860). We hence deduce that in using dissymmetric he is referring to any symmetry reduction between a high-symmetry parent and a lower-symmetry child. For crystals the high-symmetry parent is the holohedry and the lower-symmetry child is the crystal point group, a hemihedry if the group–subgroup relation is index 2. Pasteur (1854, 1857*b*) was also well aware of symmetry reductions of higher index in crystals, as he mentioned and dealt with cases of a tetartohedry, being an index-4 symmetry reduction. In relation to molecules, the use of dissymmetry is less clear as there is no evident parent to serve as a reference high-symmetry state in any group–subgroup relationship. Post-1848, Pasteur's use of dissymmetry evolves to the usage identified by Lowry (1935) and Barron (2002). We also note that Curie (1894) in his groundbreaking paper on the use of symmetry in physics uses dissymmetry in the same way as Pasteur (1848*g*). True, the physical situation analysed in detail by Curie (1894), *i.e.* a parallel magnetic and electric field, is (falsely) chiral but the essence of his analysis is the derivation of the common subgroup of two causes, which in general is not confined to being chiral.

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