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Pasteur and Molecular Chirality

by Alain Sevin
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The term *chirality* is derived from the Greek *keir* (hand). It describes the fact that some figures or bodies are not superimposable to their mirror image, no matter the scale on which the phenomenon takes place. Chirality has become central to physics, chemistry and biology, and the chirality of macroscopic objects has been recognised and discussed since Ancient Greece. Nevertheless, we are indebted to Pasteur for having studied this fundamental asymmetry of nature, and for defining the link between the measurable macroscopic properties observed and the molecular structure of the bodies considered. His work has launched an ever-growing number of developments in chemistry and biology.¹

THE CONCEPT OF CHIRALITY BEFORE THE NINETEENTH CENTURY

We are indebted to Plato for the first scientific remark on chirality. In *Timaeus*, he proposes a theoretical analysis of the mechanism of vision, saying,

*As for the origin of the images given by mirrors and all the shiny and polished surfaces [...] But then what is to the left appears to the right.*²

Aristotle was the first to implicitly use chirality in his study on the movement of stars. He defines the "natural movement" as going from the bottom up, from back to front and from right to left. Chirality appears in his final criterion. Considering then the apparent movement of the sun, he deduces a logical consequence from the fact that the east is lit before the west. However, for the Greek observer, this would "seem" as if the sun had an anti-natural movement (i.e., going from left to right)! Let's save the phenomenon! (*sauzein ta phainomena*)³: the sun does not in fact have this movement. The solution is

1. Many developments can be found in *Symétrie m'était contée*, C. Dézarnaud Dandine, A. Sevin, illustrated by Piem, Ellipses, 2007.

2. Plato, *Timaeus*, 46 a-b, translation by Albert Rivaud, Les Belles Lettres, p. 163, 1985.

3. Pierre Duhem *Sauver les phénomènes. Essai sur la notion de théorie physique de Platon à Galilée. Sozein ta phainomena*, Bibliothèque des Textes Philosophiques, Paris, Vrin, 2005.

simple: the world's axis is oriented from our head to our feet. And with this convention, it is fine for us to lower our heads – since everything falls into place!

As a matter of a fact, the perpendicular of something is the starting point for local movement, and the starting point for circular movement is the area in which stars rise, in such a way that it would be to the right, and the area in which they fall to the left. Therefore, if stars begin their journey from the left, in order to go in a circular movement to the right, then the highest point has to be the invisible pole, because if it were the visible pole, the movement would be to the left – and this is not the case.⁴

Notice the perfect coherence of the reasoning that is based on the postulation of natural movement. The definition's arbitrariness is only apparent. The opposite convention would be equally arbitrary. The definition of chirality is relative to an observer who has *already* put their right hand over their left hand: for to be able to understand and transmit chirality, *you must already possess it*.

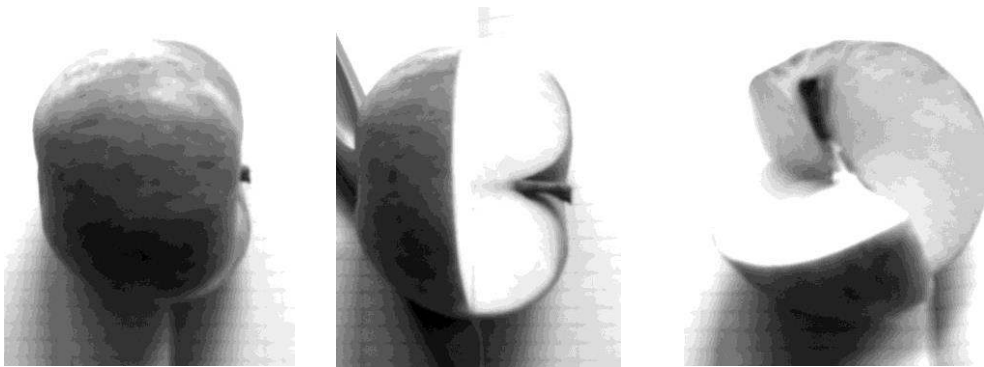


Figure 1: 1a. The apple is whole; 1b. A quarter is cut out; 1c. A second quarter is cut out. The half-apple (two quarters of the apple have been removed) in 1c is chiral (image from Dézarnaud-Dandine & Sevin, cf. NbdP 1)

Kant stresses the intuitive nature of chirality, that simple volutes are chiral:

So, we can no longer understand the difference between two things that are similar and equal and yet unlike (for example, inversely coiled volutes) by any concept, but only by the relationship between the right and left hand, which is instantly to do with intuition. [...] Thus, what is the solution? These objects are not representations of themselves, per se, and as pure understanding would know them, but are sensible intuitions, i.e., phenomena whose possibility is based on the relationship between certain unknown things, per se, and something else – namely our sensitivity.⁵

4. Aristotle, *Traité du ciel*, translation by J. Tricot, Vrin, 1998, p.72. See also: *Traité des animaux*, Book I.

5. E. Kant, *Prolégomènes à toute métaphysique future*, Pléiade, Œuvres complètes, Volume 2, §13, p. 55.

THE DISCOVERY OF MOLECULAR CHIRALITY

The basis of Pasteur's work on chirality is mainly the use of plane-polarised light for studying solutions of natural compounds. Among the forerunners are:

- Augustin Fresnel (1788-1827). He was the first to create polarised light circularly. He proposed a simple vector construction of plane-polarised light⁶.
- Jean-Baptiste Biot (1777-1862). Around 1815, he developed and used the saccharometer which employs the deflection of the plane of polarisation of light for studying and measuring sugar solutions. He formed the simple law:

$$\alpha = [\alpha_0]_{T, \lambda} \ell c$$

where α , measured in degrees, is the observed deviation of the plane of light, $[\alpha_0]$ is the specific deviation of the studied compound, ℓ the length in dm of the tank that is penetrated by light, containing the sample in solution and c its concentration in g mL^{-1} . $[\alpha_0]$ is set to temperature T and the wavelength λ is given, and, in addition, with the nature of the solvent being equally precise.

Louis Pasteur (1822-1895), Active Chemist from 1840



Figure 2: Banknote of 5 French francs, put into circulation in 1966.

Pasteur is the only scientist to have his face on a French banknote, aside from Marie Curie on the 500 French francs banknote, put into circulation in 1994. The original building of the Pasteur Institute can be seen here (founded in 1895 in Paris, 15th arrondissement), still in existence today.

The discovery of the rabies vaccine (1885) contributed to Louis Pasteur's great reputation among the people. In the national imagination, this

6. See the [BibNum](#) analysis of a Fresnel text (1822): Jeanne Crassous, "La double réfraction de Fresnel et les molécules pharmaceutiques chirales", January 2009.

popularity associates Pasteur with the Third Republic and the victory achieved by science at that time – until World War I.

And yet, Pasteur had an active scientific career in the 1840s (under the reign of Louis Philippe I). He joined the *École normale supérieure* in 1843 and completed his thesis in 1847. The first text analysed here, on molecular chirality, dates May 1848: thanks to this work, Pasteur received the prestigious Rumford Medal, from the Royal Society, 1856.

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Another image that is firmly linked to Pasteur is that of microbiology, and of the discovery of germs (or microbes). We forget that if he had indeed created this new science, he was originally by training and by practice a chemist – hence his work on the polarity of molecules. Pasteur was a student of the physicist Jean-Baptiste Biot (1774-1862).

From the 1840s, Pasteur studied the products formed in fermentation, paying particular attention to salts, which he called “paratartrates”, and which are salts of tartaric acid with several varieties, as shown in the following figure.

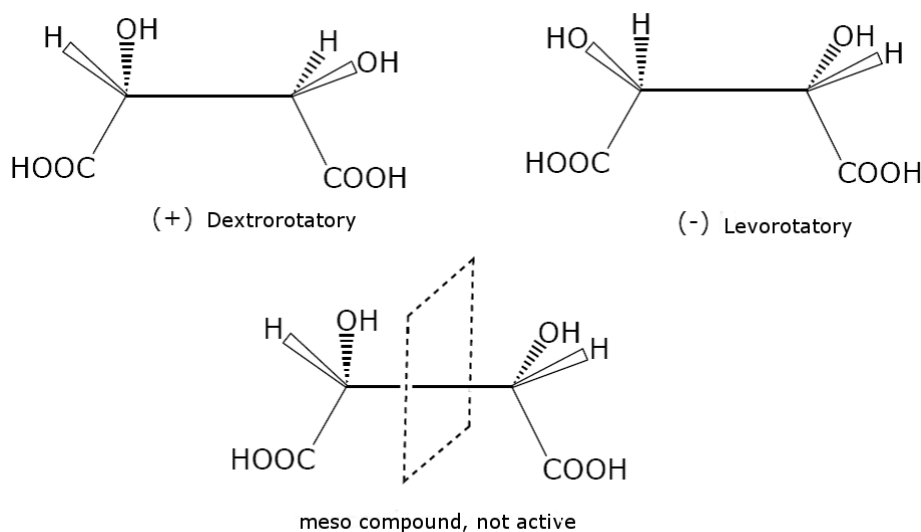


Figure 3: Tartrate isomers, or tartrate salts. Tartaric acid (with the chemical formula $C_4H_6O_6$) is an organic compound present in many plants, including grapevine; the salts that come from tartaric acid, or tartrates, are collected during the fermentation of wine.

3a (above): The first pair of tartrates, denoted (+) (dextrorotatory) and (-) (levorotatory) is composed of two enantiomers (a geometric mirror image). The third compound, known as a "meso compound", made up of a plane of symmetry, is not active when opposite polarised light. **3b (below):** The chemical formula developed of the two enantiomers (to the left: the levorotatory; and to the right: the dextrorotatory)



Pasteur managed to separate by hand two crystal forms which he identified as being enantiomer forms (geometric mirror image) of the same compound. He observed that when put in solution, each type of crystal rotated the plane of light on the same angle, but in the opposite direction. These crystals are shown here, Fig. 1 and Fig. 4 in the following diagram, from one of Pasteur's original publications⁷ (below is a modern diagram of these two crystalline configurations).

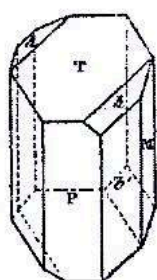


FIG. 1.

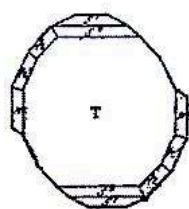


FIG. 2.

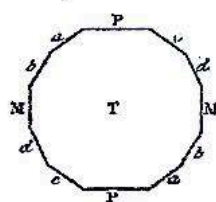


FIG. 3.

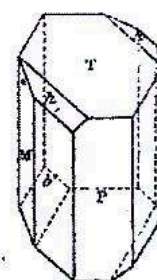
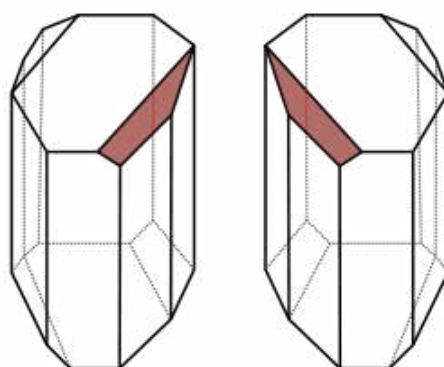


FIG. 4.



[In response to the incorrect conclusion made by Mitscherlich, and taken up by Biot]: *Well, just by pure chance, Mitscherlich was misled and Biot too in*

7. "Recherches sur les propriétés spécifiques des deux acides qui composent l'acide racémique", in *Annales de chimie et physique*, 3rd edition, XXVIII, p.56-99; printed in *Œuvres de Pasteur*, volume 1, *Dissymétrie moléculaire*, Masson (1922), online at [Gallica](http://gallica) (the figure is on p.90).

his turn. The paratartrate of soda and ammonia deviate on the plane of polarisation; it is only among the crystals that come from the same sample that some deflect the plane of polarisation to the left, and others to the right; when there are as many of one type as the other, the solution is not active, and the two complete deviations are compensated.

Pasteur deduced that the observed macroscopic property comes from a different spatial arrangement of atoms at the molecular level. This proposal is therefore of great value — this crucial discovery would be supported later on by the work of renowned scientists Joseph Achille Le Bel and Jacobus Henricus van 't Hoff, who in 1874 independently introduced the tetrahedral structure of carbon in saturated organic compounds. Thanks to their findings, Pasteur's hypothesis can quite easily be confirmed and justified, which was based on the macroscopic structure of crystals, though in the 1850s it had not yet been confirmed at the molecular level, due to a lack of essential knowledge about molecular structures.

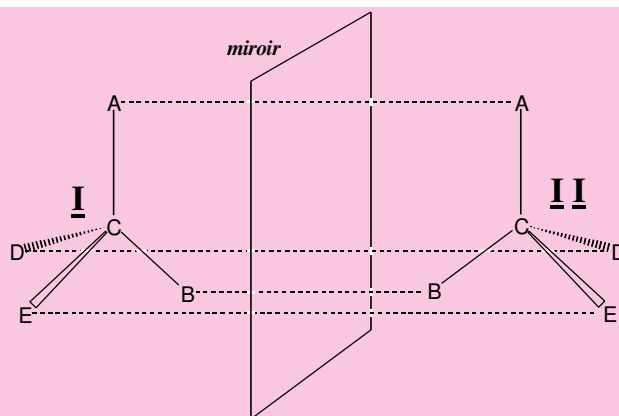
Note that the variety of tartrates, known as "meso" earlier, are not active in polarised light as they are shared by a plane of symmetry, passing through the middle of the C-C bond. This molecule is therefore superimposable to its image; you only have to place it in coincidence with the plane of molecular symmetry.

Three basic consequences ensue from the separation of crystalline forms:

- Enantiomer-type crystals correspond to molecules that have the same physical properties, and only differ by the absolute spatial configuration of their components. This arrangement produces a different behaviour for each enantiomer when opposite the polarised light;
- The mixture in equal amounts of these two forms leads to a neutralisation of properties when opposite the plane of polarised light;
- If a compound has a plane of molecular symmetry, then it is superimposable to its image and is not active in polarised light.

Explanation of Pasteur's Discovery

We shall use this fundamental result of Le Bel and van t'Hoff. A carbon atom with four different substituents (alternatively, it would have a plane of symmetry) is not superimposable to its mirror image. This is shown in the following diagram where we can see that the central carbon has four different substituents, which are marked as A, B, D, E.



I and its mirror image, II, are not superimposable. The spatial arrangement of the substituents of the central atom is called "absolute configuration". To define it without ambiguity, an observer is needed who by nature is chiral, i.e., their right hand is not superimposable to their left hand⁸. The new molecules I and II, of opposite spatial configurations are called enantiomers. Mixing them in equal amounts is what is known as a *racemix* mixture, as previously stated by Pasteur.

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It is worth distinguishing the *configuration*, with an absolute nature (which can only be changed by destroying the molecule), from its simple conformation, resulting in a free rotation around a C-C axis; these conformations do not change the molecule's nature (e.g., below).

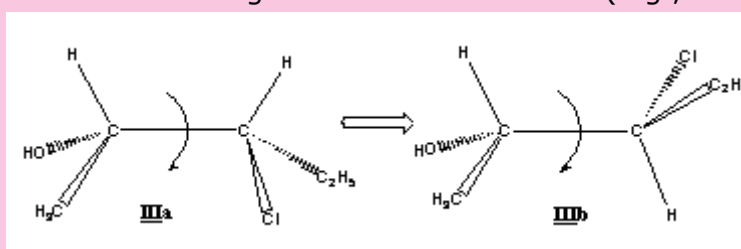


Figure 4: Conformations of the same molecule. Unlike I and II, which are two different molecules, here the same molecule, III, can adopt different geometries, such as IIIa and IIIb.

THE POSTERITY OF PASTEUR'S WORKS: THE ROLE OF CHIRALITY IN BIOLOGY

This sort of concludes a long chapter in the history of chemistry that Pasteur addressed his colleagues from the Chemical Society of Paris in a meeting, 1883:

[...] *The principles of molecular dissymmetry*⁹ were based [on polarimetric measurements]

[...] *Gentlemen, to be perfectly honest, it is understood that things are this way. Perhaps you never commented on this when I first brought it to your*

8. This definition is tautological! We cannot do anything about that.

9. Today we use the term "asymmetry".

attention. Consider any object, be it natural or artificial, of the mineral or organic kingdom, living or dead, created by life or constructed by man, a mineral, a plant, this table, a chair, the sky, the earth — which is to say, any object whatsoever. Just consider the form of all these objects, their exterior appearance and the same thing for similar objects, if they exist, and what you will discover is that all of them can be put into two major categories: the first category would include all those that have a plane of symmetry. There can be several planes of symmetry for the one object — it is a question of being able to share this plane, so that what you find to your left is also what you find to your right. [...] On the other hand, there also are bodies that have no plane of symmetry. Let a plane cross through your hand and you will see that what is to the left and what is to the right are not the same. This is the same for an eye, an ear, a spiral staircase, a helix, and a spiral shell. All these object, and others, do not have plane of symmetry; they are such that if were you to place them in front of a mirror, you would be able to see that their image is not superimposable.¹⁰

Note that in just a few words, Pasteur had extended the notion of chirality to forms that he had not found in crystals, in particular the *helix* which plays an important role in biology, be it the α -*helix* of proteins or naturally the double helix of DNA. *Actually, Pasteur not only highlighted a fundamental property of the compounds from the living world, but also the conditions of their existence!*

10. Pasteur, *La dissymétrie moléculaire*, Lecture at the Chemical Society of Paris on 22nd December 1883. Extract from *Écrits scientifiques et médicaux*, GF-Flammarion, 1994, p. 30-31 (also printed in *Œuvres de Pasteur*, vol. I, *op. cit.*)

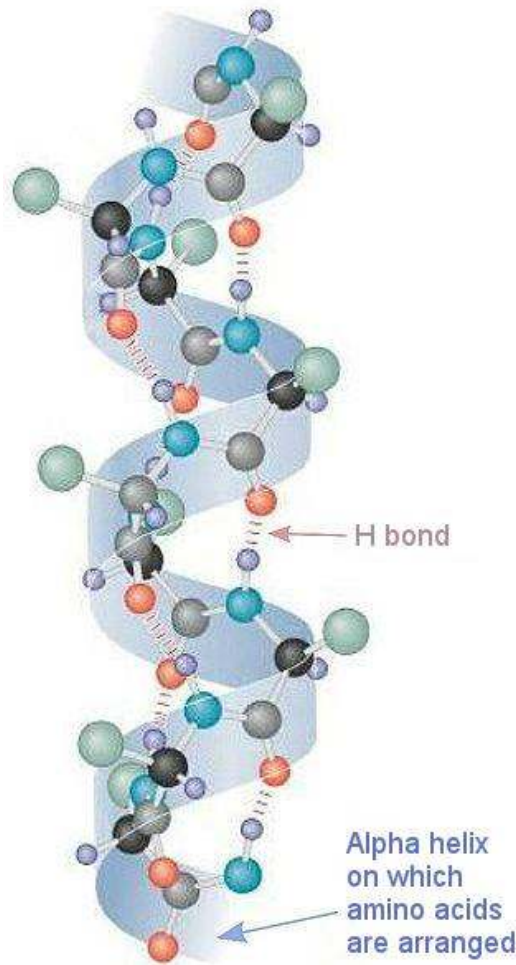


Figure 5: Common structure, α -helix, of a protein (image WikiCommons). Amino acids (combination of carboxyls-COOH and amines-NH₂) are formed in a helix, with the creation of hydrogen bonds that reduce the internal energy of the molecule, stabilising it.

CHIRALITY AND LIFE: A THOUGHT EXPERIMENT

To show that chirality is a necessary condition for the existence of the living world, we will conduct a brief thought experiment. Consider the synthesis of a protein formed by the chain of around ten amino acids, marked A, B,...J, each of which could adopt absolute configuration (*levorotatory* L) or (*dextrorotatory* D), randomly. Now form a chain of n monomers, of type A (L)-B(D)-C(L)-A(D)-D(D)-J(D)-B(L)-D(L)-E(D)...where the configuration of each component is either (L), or (D), randomly. It is easy to show that we can form different, separable¹¹ 2^n compounds, which we refer to as *diastereomers*. If, as is the case in reality, n is in the region of several hundred, the number 2^{100} is beyond our imagination. Under

11. Consider two components A, B. We can have: A(L)-B(L); A(L)-B(D); A(D)-B(L); A(D)-B(D) or distinct 2^2 compounds, known as diastereomers.

these conditions, it would be practically impossible to produce the same compound twice: duplication would be unthinkable, whatever the means considered. *There is only one way to be sure of obtaining in each duplication a compound identical to the model: using only one enantiomer of each amino acid, always the same.* This condition is scrupulously followed by the living and we see that, without chirality, life would not be able to reproduce or even simply exist.

To conclude, by laying the foundations of molecular chirality, Pasteur unveiled one of the first main discoveries in chemistry and biology. Since this pioneering work, chirality has been central to material sciences. Its applications are numerous, ranging from the synthesis of active molecules to the properties of components involved in imaging. Also worth mentioning is the recent science, astrochemistry, where research of chiral precursors of terrestrial molecules is more relevant than ever. The big question is this: in what way has nature chosen a single enantiomer form of sugars and amino acids from which we are made?



(January 2012)

(Translated in English by John Moran, published April 2015)