

CITATION FOR CHEMICAL BREAKTHROUGH AWARDS: CHOOSING PASTEUR'S AWARD-WINNING PUBLICATION

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Award paper: Louis Pasteur, "Mémoire sur la relation qui peut exister entre la forme cristalline et la composition chimique, et sur la cause de la polarisation rotatoire," *Comptes rendus hebdomadaires des séances de l'Académie des Sciences*, **1848**, 26, 535-538.

Recipient of award: École normale supérieure, Paris, France.

Year of award: 2012

The Citation for Chemical Breakthrough (CCB) awards are conferred annually by the Division of the History of Chemistry (HIST) of the American Chemical Society. According to HIST's criteria for the awards (http://www.scs.illinois.edu/~mainzv/HIST/awards/citations_chem-breakthroughs.php), "The Citation for Chemical Breakthrough award recognizes breakthrough publications, books and patents worldwide in the field of chemistry. The term 'breakthrough' refers to advances in chemistry that have been revolutionary in concept, broad

in scope, and long-term in impact." Each award is made to the department or institution where the breakthrough occurred, not to the individual scientist(s).

In some cases, several publications on a given discovery exist, and the chronologically first disclosure may not be the "breakthrough" article (1). Such a quandary had to be faced recently when the discovery of molecular chirality by Louis Pasteur (1822-1895) was considered for the CCB award (1). Pasteur's discovery is counted among the most important advances in chemistry

and constitutes the foundation of stereochemistry (2, 3). Among Pasteur's many publications on chirality (4), three (5, 6, 7) were initially deemed to be contenders for the award. This report presents the analysis that was the basis of the author's recommendation of one of the three publications as Pasteur's *breakthrough* article deserving of the CCB Award.

Introduction

Pasteur (Figure 1), a French chemist, earned a doctor-of-science degree in August 1847 (8) from the University of



Figure 1. Pasteur's official photograph as member of the Académie française. Reproduced from <http://academie-francaise.fr/immortels/index.html>, courtesy of the Académie française.

Paris based on work he carried out at the École normale supérieure (ENS) in Paris.

After earning his doctorate, Pasteur remained at the ENS until late in 1848 as *agrégé-préparateur* (a sort of laboratory or teaching assistant) in chemistry (8). For laboratory research, late in 1847 or early in 1848 Pasteur began new investigations (9) designed to expand his knowledge of crystallography; later he explained that his motivation for these studies had been his conviction that crystallography could be helpful in chemical research (10). For the new investigations he chose a substance known then as “tartaric acid” [TA], and its salts, because a great deal of crystallographic information on these compounds was available (10). Pasteur’s TA ((+)-TA by today’s nomenclature), a natural product known by then to be optically active and dextrorotatory, was obtained from the fermenting grape juice during the wine-making process. Nothing was known at the time about the arrangement of atoms in molecules, and therefore (in modern terms) the chemical structure of TA was unknown to Pasteur.

Pasteur also included in his studies a mysterious substance known then as “paratartronic acid” (PTA) or “racemic acid.” PTA had been isolated, on a single occasion around 1820, in a factory producing (+)-TA in Alsace, France. PTA was known to be optically inactive and was thought to be an “isomer” of (+)-TA (11), but the nature of its chemical/structural relationship to TA was not understood at the time.

In the spring of 1848 Pasteur found that the sodium ammonium salt of PTA crystallized as a mixture of two types of crystals that were non-superposable mirror-image forms of each other (i.e., enantiomorphous, by today’s terminology). One of the crystal types appeared identical to the crystals of the sodium ammonium salt of “ordinary” TA, i.e., (+)-TA. Pasteur manually separated the two crystal types of the PTA salt and measured their optical activity in solution, finding their rotations to be equal (within experimental error) in absolute magnitude but opposite in direction. This observation eventually led him to the realization that the molecules of TA had to be chiral and that PTA was the equimolar combination of the two enantiomers of TA (5, 6, 7, 12, 13).

Pasteur’s First Article on Molecular Chirality (*Comptes rendus*) 1848 (5)

The 25-year-old Pasteur read a memoir announcing his discovery to the *Académie des sciences* (Academy

of Sciences, Académie henceforth; translations are by the present author) in Paris on May 22nd, 1848 (5, 12). A summary of the lecture was published in the issue of the proceedings of the Académie, the *Comptes rendus hebdomadaires des séances de l’Académie des Sciences* (CR henceforth), for the May 22nd session (5). Translated into English, the title of the article in the CR is “Memoir on the relationship that can exist between crystalline form and chemical composition and on the cause of optical rotation.” After the title and the author’s name the article is indicated to be an “*extrait*” (extract, excerpt) of the memoir Pasteur read to the Académie. The *extrait* was prepared by Pasteur (14). The full text of the memoir read by Pasteur to the Académie has not been published and a verbatim transcript of Pasteur’s lecture to the Académie has not yet been uncovered, if such a transcript does exist.

The article in the CR, of which an English translation is available (15), was Pasteur’s first announcement of his discovery of the resolution of TA. It is short (slightly over three pages) and does not contain the full experimental details. Pasteur begins by pointing out that the many salts of (+)-TA he examined have crystal forms that display great similarity, which he interprets as an indication that a common molecular grouping is shared by these compounds. He then discusses the salts of PTA and points out that while there is a similarity between the (+)-tartrate and paratartrate salts in their basic crystal forms, a fundamental difference between the two series exists, namely, the presence of hemihedral facets (i.e., small surfaces replacing some of the corners or edges of the basic crystal form) in the crystals of the salts of (+)-TA and their absence in the crystals of most of the salts of PTA. He explains that he said “their absence in most of the paratartrates” for a specific reason. That is, he found that the crystals of one of the paratartrates, the sodium ammonium salt, do display hemihedral facets. However, he finds that this salt is a combination of two crystal types, with the hemihedral facets leaning in one direction in some of the crystals and in the opposite direction in the other crystals when the crystals are viewed according to an arbitrary convention. Pasteur then specifies: “Here now is the crystallographic difference between these two types of crystals. They are all hemihedral; but some are hemihedral to the right, others to the left, and the direction of [optical] rotation depends on this dissymmetry.” And then a crucial sentence in the article: “Is it not evident by now that the property of certain molecules of rotating the plane of polarization has as its cause, or at least is linked in a most intimate manner to, the dissymmetry of these molecules?”

Pasteur's use of "dissymmetry" and "dissymmetric" in the CR article is critical to the analysis. He applied these terms both to the crystal shapes and to the molecules of the TAs and his use of the terminology was in the general sense of a disruption or degradation of symmetry. He did not mention handedness or non-superposable-mirror-image relationships in the article (and we do not know whether he was more explicit in the actual lecture he delivered to the Académie) (13).

Thus, in the CR article Pasteur proposes that the molecules of (+)- and (-)-TA are *dissymmetric*, i.e., differ in some symmetry properties, the nature of which he did not specify. However, it is likely that he already had the concept of handedness in mind, since a few months later, in the next article (6) contending for the CCB award (see below), he stated that the dissymmetry of the crystals and molecules of the TAs was of the non-superposable-mirror-image type (13).

In summary, the 1848 CR article was Pasteur's first announcement of his resolution of sodium ammonium tartrate; the first recognition of the combination of the two enantiomers in a substance (in equimolar ratio, i.e., a racemate by today's terminology); the first proposal that the basis for the existence of the two optically active TAs can be sought in the differing symmetries of their molecules; and the first proposal that the cause of the optical activity of these substances is in fact the dissymmetry of the molecules. (It is also noteworthy that Pasteur's isolation of (-)-TA from PTA produced the first example (TA) of a substance both of whose enantiomers became known.)

Pasteur's Second Article on Molecular Chirality (*Annales de Chimie et de Physique*) 1848 (6)

Later in 1848, Pasteur published a full paper on the resolution of TA in the *Annales de Chimie et de Physique* (*Annals of Chemistry and Physics*, *Annales* henceforth). This journal began life as *Annales de Chimie* in 1789 (16). Pasteur's paper in the *Annales* (as his CR article, see above), was based on a memoir he presented to the Académie. The presentation took place during the session of October 9, 1848, but the issue of the CR for the session contains only the name of the author and the title of the memoir, which was, as translated into English, "Investigations on the relationships that can exist between crystalline form, chemical composition, and the direction of optical rotation" (17). Thus, instead of a

printed memoir in the CR, in this case Pasteur published a full paper in the *Annales*.

Pasteur's article appeared in the October 1848 issue of the *Annales* (18). The article is 18 pages long and consists of two parts. The first part examines the crystal properties of (+)-TA and a series of its salts as well as some salts of PTA. Pasteur finds hemihedry in (+)-TA and its salts, and first describes the hemihedral crystals as dissymmetric in that the two extremities of the crystal (along the crystal axis) are modified unequally, in violation of Haüy's law of symmetry in crystallography (19), widely believed at the time to govern crystal formation. As for the salts of PTA, Pasteur reports, as in the CR article, the absence of hemihedry in most of them.

In the second part of the article, Pasteur discusses his experiments and findings on the two crystal types of the sodium ammonium salt of PTA. He describes the two types as "dissymmetric crystals facing one another in a mirror." This then is the first time that Pasteur specifically associates the term "dissymmetric" with non-superposable-mirror-image morphology. He then goes on to indicate, also for the first time, that the two TA *molecules* corresponding to the two crystal types of sodium ammonium paratartrate must also have this mirror-image dissymmetry and he points out that the optical rotation by the two acids correlates with their molecular dissymmetry which in turn correlates with the crystal morphology. *Dissymmetry* in the connotation of handedness as specified in the *Annales* article became Pasteur's standard terminology in both the molecular and crystal-morphology contexts for what we call today *chirality*. (The latter term was coined by Lord Kelvin in 1894, nearly a half-century after Pasteur's discovery of molecular dissymmetry (20).) In fact, "dissymétrie moléculaire" (molecular dissymmetry) became the fundamental term for Pasteur's work on chirality in molecules (13).

In summary, the *Annales* article (6) contains extensive experimental details while the paper in the CR (5) contains little such information. Another important difference between the two articles is the explicit statement by Pasteur in the *Annales* paper that the two crystal types of the sodium ammonium salt of PTA (and the crystals of the corresponding free TAs) have handedness and are in fact related as the two hands, i.e., are non-superposable-mirror-image forms of each other. In addition, a critical new element in the *Annales* article is the explicit recognition by Pasteur that the *molecules* of the two optically active TAs are chiral and are related as enantiomers (by today's terminology).

Pasteur's Retrospective Article on Molecular Chirality (*Leçons de Chimie*) 1861 (7)

By the late 1850s, Pasteur had abandoned his work on chirality and embarked on his eventually celebrated work in microbiology and infectious diseases (21). However, on January 20th and February 3rd, 1860, he presented two lectures to the Société chimique de Paris (Chemical Society of Paris, CSP) in which he reviewed and analyzed his extensive work of about 10 years on molecular and crystal dissymmetry. (There were two separate lectures due to time constraints). Pasteur's lectures were published as a single article in the original French in 1861 as part of a collection of lectures to the CSP (7). An English translation (divided into two separate articles corresponding to the two lectures) was published in 1862 (22, 23).

The article based on Pasteur's two lectures constitutes an important exposition of his work on molecular chirality. In its originally published form it is 42 pages long and is divided into two sections entitled Lecture 1 and Lecture 2, respectively. Pasteur begins Lecture 1 by reviewing some of the phenomena underlying his studies of molecular dissymmetry, including polarized light, optical rotation, and crystal hemihedrism. He then describes in great detail his studies of the crystallography of the tartrates, his resolution of sodium ammonium paratartrate, and his isolation of the two (*dextro*- and *levo*-rotatory, respectively) free TAs starting from the sodium ammonium salt of PTA.

In the final section of Lecture 1, Pasteur provides a detailed and lucid interpretation of his findings. He emphasizes that the two optically active TAs are isomeric by virtue of a difference in the arrangement of the atoms in the molecules, and explains that this difference is of the non-superposable-mirror-image type. Importantly, he asks whether this mirror-image dissymmetry may be the result of a helical or a tetrahedral arrangement of the atoms in the molecules. He also states that molecular dissymmetry is the cause of the formation of dissymmetric hemihedral crystals and is also the cause of optical rotation by substances in the non-crystalline state (e.g., in solution, in the liquid phase, etc.).

In Lecture 2, Pasteur considers the presence of molecular dissymmetry in some compounds and its absence in others. He concludes that (a) all the "products of the laboratory" (i.e., wholly synthetic substances) and the inorganic compounds are not dissymmetric, and (b) the majority of the organic natural substances,

those that are essential to life, are dissymmetric. He points out that all the latter compounds are optically active in the non-crystalline state, which he states to be a necessary and sufficient property for the indication of molecular dissymmetry. Pasteur points out that molecular dissymmetry is the only known absolute demarcation between life and inanimate matter, and wonders about the universal forces that induce dissymmetry in organic natural substances in plants and animals. In the final section of Lecture 2 Pasteur extends his observations on molecular dissymmetry in substances derived from living organisms by describing his discovery that (+)-TA is metabolized with considerable preference over (-)-TA when PTA is incubated with a microorganism (21, 24).

In summary, in addition to the material also included in the two 1848 papers (5, 6), the 1861 article (7) contains an extensive discussion of the background underlying Pasteur's discovery and also includes an examination of the origins of molecular chirality in natural products; importantly, in this article Pasteur suggests that the basis of molecular dissymmetry may be a helical or tetrahedral arrangement of the atoms in the molecules.

Overall Analysis and Recommendation

Of the three contending Pasteur publications (CR (5), *Annales* (6), and *Leçons de Chimie* (7)), which is the "breakthrough" paper? All three articles are important documents of Pasteur's discovery, and all three have often been cited in the literature; only a few such citations can be mentioned here (25-31). However, all three articles also have unique aspects and elements.

Clearly, the CR article (5) was first: it appeared no later than May 29th, 1848, i.e., one week after Pasteur's lecture to the Académie (32). The CR, an important publication by a leading institution of science, the Académie, contained scientific articles from a large variety of fields and was widely distributed (33). The CR article was brief and did not go into chemical or experimental details. (Brevity was a requirement for publishing in the CR (32).) On the other hand, the succinct and uncomplicated presentation in the CR made for a focused and clear article that was understandable by readers from a variety of backgrounds. The article reported entirely new and revolutionary observations with crucial implications for molecular structure. The first formulations of molecular-structural theory appeared about 10 years after Pasteur's discovery of 1848 (34), but even at the time of Pasteur's announcement of molecular dissymmetry, the question of the arrangements of atoms

in molecules was of interest in a variety of fields, e.g., chemistry, crystallography, physics, etc. Moreover, until Pasteur's announcement in the CR (5), there had been no explanation for optical rotation by substances in the non-crystalline state.

French (Parisian) chemistry in the 19th century was troubled by certain "pathologies," including a "culture of celebrity" (35). Nevertheless, the system functioned well in many respects (35), and the novelty and importance of the discovery announced in the CR by the young and unknown Pasteur did attract the attention of Parisian scientific circles (36). He soon received significant recognition, including from renowned scientists such as the chemist Louis Jacques Thenard (1777-1857) (37) and the physicist Jean-Baptiste Biot (1774-1862) (36).

Pasteur's article (6) in the *Annales*, a respected journal of the period (16), had the great merit of containing the first written statement by Pasteur that his findings meant that the molecules of (+)- and (-)-TA must be dissymmetric (i.e., chiral, by today's terminology), and Pasteur's insight was clearly of great importance in the history of chemistry. (As we have seen, in the CR article Pasteur did refer to the TA molecules as "dissymmetric" but did not explicitly mention handedness). However, the *Annales* article described in considerable detail the crystallographic characteristics of a great many substances, material that would have been meaningful to (and readable by) only a relatively few individuals. Indeed, the large amount of such detail somewhat "dilutes" Pasteur's statements in the article concerning molecular chirality. Moreover, the readership of the *Annales* consisted primarily of chemists and physicists, and it did not have the wide interest and dissemination that the CR enjoyed (16, 33). Overall, the *Annales* article did not make the clear, stunning, and broad impact that Pasteur's concentrated first announcement in the CR achieved.

Pasteur's retrospective article of 1861 (7) has the merit of containing a detailed, well-organized, and lucid account of the background and the discovery. It also contains the suggestion of a helical or tetrahedral atomic arrangement as the potential explanation of molecular chirality, truly revolutionary insights by Pasteur that preceded van 't Hoff's (38) and LeBel's (39) proposals for the tetrahedral asymmetric carbon atom by well over a decade. Nevertheless, since the article (7) appeared 13 years after Pasteur's discovery, it did not cause the "sensation" that the CR article had produced. In addition, the 1861 article contains a great deal of material beyond the TA resolution and the concept of molecular chirality:

as mentioned above, the article deals at length with the biological origins of molecular chirality, and while this aspect is recognized today as highly important (40), the focused announcement of the CR article seems, at least to the present author, more in line with the aims and criteria of the CCB award.

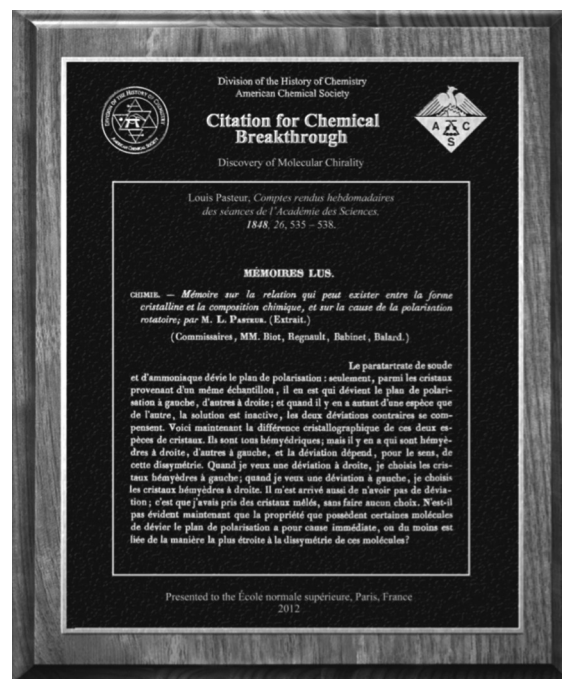


Figure 2. The plaque of the CCB award to the ENS.

Overall, then, for all the reasons laid out above, the CR article (5) was my recommendation as Pasteur's breakthrough publication (1), and was the final choice for a CCB award made to the ENS in Paris. The CCB award includes a high-quality plaque to be placed at a site selected by the recipient near the office or laboratory where the breakthrough was achieved. The plaque for the award to the ENS for Pasteur's discovery is shown in Figure 2.

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Joseph Gal, a member of the editorial board of the journal *Chirality*, has long been interested in Pasteur's work on chirality and has published a number of articles on this subject.