thesis

Pasteur and the art of chirality

Louis Pasteur was a scientific giant of the nineteenth century, but, as **Joseph Gal** asks, was his most famous contribution to the understanding of chemistry — chirality — influenced more by his artistic talents?

Discoveries made by Louis Pasteur (1822–1895) in microbiology and infectious diseases have been of great benefit in a diverse range of fields, including human health, veterinary medicine and agriculture[1]. But Pasteur was also a chemist and he made one of the most important discoveries in chemistry: that of molecular chirality[2]. In 1847, he earned his Doctor of Science degree from the University of Paris and shortly thereafter he undertook studies of the crystallography and optical activity of natural tartaric acid (TA) and related substances. It was during his work on the tartrates that the concept of molecular chirality originated.

Pasteur's discovery has been described as the logical outcome of groundbreaking work in crystallography, optics and structural theory during the first half of the nineteenth century[3]. Yet there were considerable odds against him, considering that he was young and relatively inexperienced when he made the discovery — at age 25 — just eight months after earning his doctorate. Moreover, his identification and rationalization of a structural element in molecules, chirality, was made when very little was known about the structures of organic compounds. Furthermore, several other accomplished scientists had studied the tartrates before him but, curiously, they had all missed what he later saw and thus failed to anticipate his discovery.

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Figure 1 | Altin Vercel. Pastel by Pasteur, 1840.

When Pasteur began his experiments, the structural theory of organic molecules was still many years away from being formulated and thus the molecular structure of TA was unknown. However, natural TA was recognized at the time as optically active and dextrorotatory in solution, that is, plane-polarized light rotates clockwise on passing through solutions of it. Pasteur found[2] that the crystals of TA and its salts displayed small surfaces called hemihedral facets, which appeared as modifications to some of the edges of the crystals[2]. These facets degraded the symmetry of the basic crystal form and he recognized that the resulting external crystal morphology was chiral.

Pasteur also studied paratartaric acid (PTA) and some of its salts. Paratartaric acid had been discovered during the production of natural TA around 1819 and was thought at the time to be isomeric with TA, but the nature of the relationship was not understood at the time. When examining crystals of sodium ammonium paratartrate (SAP) not only did he identify[2] that there were two distinct types — present in a 1:1 ratio — but he also crucially recognized that they were non-superposable-mirror-image forms of each other, that is, enantiomorphous by today's terminology. Pasteur then manually separated the two different forms of the SAP crystals and found both substances to be optically active in solution, with equal rotations in absolute magnitude (within experimental error) but opposite in direction. He then liberated the two free acids from the PTA salts and found that one of the acids was dextrorotatory and identical to natural TA ((+)-TA) in all respects. The other acid thus obtained was also optically active and its optical rotation was identical in absolute value to the rotation of the dextrorotatory acid but the opposite in direction, that is, levorotatory. This finding led Pasteur to the realization that the molecules of these acids were chiral and that PTA was simply a 1:1 combination of the two. He understood that (+)-TA and (−)-TA were non-superposable-mirror-image molecular forms of each other, and this was the discovery of molecular chirality[2,4]. Here, once again, the odds should have been against him. Only a small minority of racemates crystallize such that mirror-image crystals each made up of only one enantiomer are formed (known today as conglomerate crystallization). Fortunately for Pasteur, SAP is one of the substances that does crystallize in this fashion — if this was not the case, the discovery of molecular chirality may have had to wait yet longer.

Among the several prominent scientists who had studied the tartrates before Pasteur was Jean-Baptiste Biot (1774–1862), a distinguished French physicist, mathematician and astronomer who made the pioneering discovery that certain organic natural products, including TA and its salts, were optically active in solution or in the liquid or gas phase[5]. Biot did not mention hemihedrism or chirality in the crystals of the TA/PTA-related substances he studied. He also missed the conglomerate crystallization of SAP. Frédéric-Hervé de la Provostaye (1812–1863) was a French professor of physics who published a detailed investigation of the crystals of natural TA, PTA, and several of their salts[6], but did not mention the chirality of tartrate crystals. Wilhelm Gottlieb Hankel (1814–1899) was a German professor of physics who also studied the crystals of tartrates[7,8], but he too did not comment on their chirality.

In 1844, the eminent German chemist and crystallographer Eilhard Mitscherlich (1794–1863) reported the then-puzzling observation that although SAP and the corresponding sodium ammonium (+)-tartrate were identical in chemical composition, crystalline form, and other physical properties, the tartrate salt was optically active whereas the paratartrate was not[9]. Mitscherlich did not comment on hemihedrism or chirality in the crystals, nor did he recognize the conglomerate composition of SAP[9]. Despite their detailed studies of tartrates before Pasteur, these eminent scientists did not identify key aspects of the crystals, such as their chirality and conglomerate composition.

The question is then, what enabled Pasteur to recognize what his eminent predecessors had missed?

Pasteur was a talented artist who, as a teenager, created approximately 40 portraits of friends, relatives and dignitaries in pastel, charcoal, pencil or lithography[10,11]. They showcase his meticulous observation, precision, realism and attention to detail (see Fig. 1, for example). Several artists of the day, such as the respected Finnish painter Albert Edelfelt (1854–1905)[12], spoke highly of his artistic abilities.

I suggest that Pasteur's artistic sensibilities and experience were instrumental in his discovery of molecular chirality and, in particular, his use of lithography is intriguing in this regard. In traditional lithography an initial image is drawn onto the surface of a smooth limestone plate using a fatty substance, such as oil or wax. The stone surface is then acidified, resulting in the etching of the areas that are not protected by the lipid-based image. When the stone is subsequently hydrated, these etched areas retain water. When an oil-based dye is then applied, it is repelled by the water and adheres only to the original drawing. The dye is then transferred to a sheet of paper pressed against the stone to produce the final printed image. Given the nature of the transfer process, the final print on the paper is the mirror image of the original on the stone.

At the age of 18, Pasteur produced a lithographic portrait of his high-school classmate Charles Chappuis (Fig. 2). As he was finishing the portrait, he wrote a letter to his parents, stating[13]: "I think I have not previously produced anything as well drawn and having as good a resemblance. All who have seen it find it striking. But I greatly fear one thing, that is, that on the paper the portrait will not be as good as on the stone; this is what always happens; therefore I have been very careful while making it, by frequently looking at it in the mirror. It has just as good a resemblance."

It is clear that the teenage artist was keenly aware of the effects of mirror inversion in 1841, and it follows that the young chemist in 1848 was already sensitized to non-superposable-mirror-image reflection. His prior lithographic work may have thus facilitated his recognition of the chirality of the PTA crystals, that is, that the mirror image was not superposable on the original crystal. Was this the factor that differentiated him from his predecessors who missed this observation? Of course, we cannot be certain, but the history makes for

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Figure 2 | Pasteur's lithograph[21] of Charles Chappuis. The text under the image: "Portrait of my philosophy classmate Ch. Chappuis made in Besançon in 1841 L. Pasteur".

a compelling argument and it is not unreasonable to conclude that his artistic experience may have played an important role in his discovery of molecular chirality.

At the age of 20, Pasteur stopped producing works of art, yielding to his father's disapproval of art as a career. As a scientist, however, he drew figures for his scientific publications: initially representations of crystals, and later images for his microbiological work. He also created models of crystals by cutting them from cork or wood. As such, he continued working as an artist of sorts, albeit as a medical-scientific illustrator.

For the rest of his life, Pasteur remained closely connected to the fine arts[14,15,16]. He became a patron of the arts, maintained close friendships with eminent artists, and taught scientific aspects of art in the Ècole des Beaux Arts (School of Fine Arts) in Paris; he regularly attended the annual Salons (celebrated art exhibitions in Paris) and promoted some of the artwork displayed there. He also actively participated in the creation of the by-now-iconic painting by Edelfelt, depicting him in his laboratory[14].

Pasteur's sharp scientific mind undoubtedly underpinned the leap he made from crystal chirality to molecular chirality. However, he may have been aided here too by an unexpected element. In the 1820s, Sir John Frederick William Herschel (1792–1871), an eminent English astronomer and physicist, presciently suggested molecular asymmetry as the cause of optical rotation in the non-crystalline state[17]. Pasteur was, in general, familiar with literature pertinent to his own studies[17] and there is specific evidence suggesting that he was aware of Herschel's earlier proposal[18]. It seems, therefore, that in conceiving of molecular chirality Pasteur may have been inspired by Herschel's idea of molecular asymmetry[17].

Pasteur was far ahead of his time: the first explanation for molecular chirality — the tetrahedral asymmetric carbon atom — emerged only in 1874, a quarter of a century after his discovery[19,20], a discovery that is considered to be the foundation of stereochemistry. Pasteur's experimental and intellectual processes were undoubtedly remarkable, but there were clearly unpredictable and serendipitous elements to this story. For example, his artistic side, the fact that one of the substances he was studying crystallized as a conglomerate, and Herschel's prescient proposal of molecular asymmetry all probably contributed significantly to Pasteur overcoming the considerable odds against him. ❐

Joseph Gal is in the Departments of Medicine and Pathology at the University of Colorado, School of Medicine, Aurora, Colorado 80045, USA
e-mail: Joe.Gal@ucdenver.edu

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Acknowledgments

The author thanks the following individuals for valuable help: B. Hansen at the City University of New York; J. Seeman at the University of Richmond; and D. M. Weil at the University of Colorado.

Published online: 29 May 2017