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PREFACE

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The suggestions made independently by Van't Hoff and Le Bel in 1874 are most appropriately celebrated in these special centennial issues of "Tetrahedron". However, it should be recognised that the great advance in our knowledge of molecular structure of carbon compounds was made in the previous 12 years, and the full explanation of the fundamental facts discovered by the founder of stereo-chemistry could not at that time be clearly related to molecular structural theory. The pioneer who recognised the existence of molecular asymmetry and in so doing laid the foundations for stereo-chemistry was Louis Pasteur, born at Döle in 1822. He became a student of natural science at the École Normale in Paris and very soon developed a habit of independent thought on current problems in physics and chemistry. In 1860 he gave a remarkable and lucid account of his work in two lectures to the French Chemical Society (Paris 1861). The citations which follow are from an English translation made by the Alembic Club, Reprint No. 14, published by William F. Clay, Edinburgh, 1897. The experimental work was carried out from 1848–1850. (Pasteur's work was accordingly carried out well before the recognition of the quadrivalence of carbon by Kekulé and by Couper in 1858).

When I began to devote myself to special work, I sought to strengthen myself in the knowledge of crystals, foreseeing the help that I should draw from this in my chemical researches. It seemed to me to be the simplest course, to take, as a guide, some rather extensive work on crystalline forms; *to repeat all the measurements, and to compare by determinations with those of the author. In* 1841, *M. De La Provostave, whose accuracy is well known, had published a beautiful piece of work on the crystalline forms of tartaric and paratartaric acids and of their salts. I made a study of this memoir. I crystallised tartaric acid and its salts, and investigated the forms of the crystals. But, as the work proceeded, I noticed that a very interesting fact had escaped the learned physicist. All the tartrates which I examined gave undoubted evidence of hemihedral faces.*

This peculiarity in the forms of the tartrates was not very obvious. This will be readily conceived, seeing that it had not been observed before. But when, in a species, its presence was doubtful, I always succeeded in making it manifest by repeating the crystallisation and slightly modifying the conditions. Sometimes the crystals bore all the faces demanded by the law of symmetry, but the hemihedry was still betrayed by an unequal development of one half of the faces. This is seen, for example, in tartar emetic. It must be admitted that a circumstance which adds greatly to the difficulty in recognising hemihedry is the frequent irregularities of the crystals, which never develop quite freely. From this cause there arise deformations, arrestments of development in one direction or another, faces suppressed by accident, etc. Unless in circumstances of an almost exceptional character, the recognition of hemihedry, particularly in laboratory crystals, demands very attentive study. To this we must add the fact that, although hemihedry may be possible in a given form, and although it is a function of the internal structure of the substance, it may not be indicated externally, any more than one finds on every crystal of a cubic species all the forms compatible with the cube.

But however these things may be, I repeat that I found the tartrates hemihedral......

.... Now if we compare the disposition of the hemihedral faces on all the prisms of the primitive forms of the tartrates, when they are oriented in the same manner, this disposition is found to be the same.

Here follows an explanation of the geometric method used to give the sense of the hemihedry.

These results, which have been the foundation of all my later work, may be summed up in two words: *the tartrates are hemihedral, and that in the same sense.*

Guided then on the one hand by the fact of the existence of molecular rotatory polarisation, discovered by Biot in tartaric acid and all its compounds, and on the other by Herschel's ingenious correlation, and yet again by the sagacious views of M. Delafosse, with whom hemihedry has always been a law of structure and not an accident of crystallisation, I believed that there might be a relation between the hemihedry of the tartrates and their property of deviating the plane of polarised light.

It is important thoroughly to grasp the development of the conceptions:- *Haüy and Wëiss observe that quartz possesses hemihedral faces and that these faces incline to the right on some specimens and to the left on others. Biot on his part finds that* *quartz crystals likewise separate themselves into two sets, in relation to their optical properties, the one set deviating the plane of polarised light to the right, the other to the left, according to the same laws. Herschel in his turn supplies to these hitherto isolated facts the bond of union, and says: plagihedra of one kind deviate in the same sense; plagihedra of the other kind deviate in the opposite sense.*

For my own part I find that all tartrates are plagihedral, if I may so express myself, and that in the same sense; so that I might presume that here, as in the case of quartz, there was a relation between the hemihedry and the circular polarisation. At the same time the essential differences to which I have just referred between circular polarisation in quartz and in tartaric acid must not be neglected.

Thanks to the above discoveries, and to the relations which I have just enumerated, we are now in possession of a preconceived notion (for it is still nothing more than that) as to the possible interrelation of the hemihedry and the tartrates.

Being very anxious to find by experiment some support for this still purely speculative view, my first thought was to see whether the very numerous crystallisable organic products which possess the molecular rotative property, have hemihedral crystalline forms, an idea which had not previously occurred to any one in spite of Herschel's correlation. This investigation met with the success which I anticipated.

I also occupied myself with the examination of the crystalline forms of paratartaric acid and its salts. These substances are isomeric with tartaric compounds, but had all been found by Biot to be inactive towards polarised light. None of them exhibited hemihedry.

Thus the idea of the inter-relation of the hemihedry and the molecular rotatory power of natural organic products gained ground.

I was soon enabled to establish it clearly by a wholly unexpected discovery.

The correlation due to Sir John Herschel, and mentioned in the course of the lecture, referred to plagihedra such as quartz. He related the sense of the hemihedry of the quartz crystals to the direction of their rotations of the plane of polarisation of light. Pasteur found this a very helpful idea though, as he pointed out, it was not directly concerned with the concept of molecular asymmetry.

I must first place before you a very remarkable note by Mitscherlich which was communicated to the Academie des Sciences by Biot. It was as follows:

The double paratartrate and the double tartrate of soda and ammonia have the same chemical composition, the same crystalline form with the same angles, the same specific weight, the same double refraction, and consequently the same inclination in their optical axes. When dissolved in water their refraction is the same. But the dissolved tartrate deviates the plane of polarisation, while the paratartrate is indifferent, as has been found by M. Biot for the whole series of those two kinds of salts. Yet, adds Mitscherlich, here the nature and number of the atoms, their arrangement and distances, are the same in the two substances compared.

This note of Mitscherlich's attracted my attention forcibly at the time of its publication. I was then a pupil in the Ecole Normale, reflecting in my leisure moments on these elegant investigations of the molecular constitution of substances, and having reached, as I thought at least, a thorough comprehension of the principles generally accepted by physicists and chemists. The above note disturbed all my ideas. What precision in every detail! Did two substances exist which had been more fully studied and more carefully compared as regards their properties? But how, in the existing condition of the science, could one conceive of two substances so closely alike without being identical? Mitscherlich himself tells us what was, to his mind, the consequence of this similarity:

The nature, the number, the arrangement, and the distances of the atoms are the same. *If this is the case what becomes of the definition of chemical species, so rigorous, so remarkable for the time at which it appeared, given by Chevreul in 1823?* In compound bodies a species is a collection of individuals identical in the nature, the proportion, and the arrangement of their elements.

In short, Mitscherlich's note remained in my mind as a difficulty of the first order in our mode of regarding material substances.

You will now understand why, being preoccupied, for the reasons already given, with a possible relation between the hemihedry of the tartrates and their rotative property, Mitscherlich's note of 1844 should recur to my memory. I thought at once that Mitscherlich was mistaken on one point. He had not observed that his double tartrate was hemihedral while his paratartrate was not. If this is so, the results in his note are no longer extraordinary; and further, I should have, in this, the best test of my preconceived idea as to the inter-relation of hemihedry and the rotatory phenomenon.

I hastened therefore to re-investigate the crystalline form of Mitscherlich's two salts. I found, as a matter of fact, that the tartrate was hemihedral, like all the other tartrates which I had previously studied, but, strange to say, the paratartrate was hemihedral also. Only, the hemihedral faces which in the tartrate were all turned the same way, were, in the paratartrate inclined sometimes to the right and sometimes to the left. In spite of the unexpected character of this result, I continued to follow up my idea. I carefully separated the crystals which were hemihedral to the right from those hemihedral to the left, and examined their solutions separately in the polarising apparatus. I then saw with no less *surprise than pleasure that the crystals hemihedral to the right deviated the plane of polarisation to the right, and that those hemihedral to the left deviated it to the left; and when I took an equal weight of each of the two kinds of crystals, the mixed solution was indifferent towards the light in consequence of the neutralisation of the two equal and opposite individual deviations.*

Thus, I start with paratartaric acid; I obtain in the usual way the double paratartrate of soda and ammonia; and the solution of this deposits, after some days, crystals all possessing exactly the same angles and the same aspect. To such a degree is this the case that Mitscherlich, the celebrated crystallographer, in spite of the most minute and severe study possible, was not able to recognise the smallest difference. And yet the molecular arrangement in one set is entirely different from that in the other. The rotatory power proves this, as does also the mode of asymmetry of the crystals. The two kinds of crystals are isomorphous, and isomorphous with the corresponding tartrate. But the isomorphism presents itself with a hitherto unobserved peculiarity; it is the isomorphism of an asymmetric crystal with its mirror image. This comparison expresses the fact very exactly. Indeed, if, in a crystal of each kind, I imagine the hemihedral facets produced till they meet, I obtain two symmetrical tetrahedra, inverse, and which cannot be superposed, in spite of the perfect identity of all their respective parts. From this I was justified in concluding that, by the crystallisation of the double paratartrate of soda and ammonia, I had separated two symmetrically isomorphous atomic groups, which are intimately united in paratartaric acid. Nothing is easier than to show that these two species of crystals represent two distinct salts from which two different acids can be extracted. Using the treatment always employed in such cases, the purpose is served by precipitating each salt with a salt of lead or baryta, and then isolating the acids by means of sulphuric acid.

The study of these acids is of immense interest. I do not know any that is more interesting.

But before enlarging on it allow me to introduce here some recollections in connection with their discovery.

The announcement of the above facts naturally placed me in communication with Biot, who was not without doubts regarding their accuracy. Being charged with giving an account of them to the Academy, he made me come to him and repeat before his eyes the decisive experiment. He handed over to me some paratartaric acid which he had himself previously studied with particular care, and which he found to be perfectly indifferent to polarised light. I prepared the double salt in his presence, with soda and ammonia which he had likewise desired to provide. The liquid was set aside for slow evaporation in one of his rooms. When it had furnished about 30 to 40 grams of crystals, he asked me to call at the Collège de France *in order to collect them and isolate before him, by recognition of their crystallographic character, the right and the left crystals, requesting me to state once more whether I really affirmed that the crystals which I should place at his right would deviate to the right, and the others to the left. This done, he told me that he would undertake the rest. He prepared the solutions with carefully measured quantities, and when ready to examine them in the polarising apparatus, he once more invited me to come into his room. He first placed in the apparatus the more interesting solution, that which ought to deviate to the left. Without even making a measurement, he saw by the appearance of the tints of the two images, ordinary and extraordinary, in the analyser, that there was a strong deviation to the left. Then, very visibly affected, the illustrious old man took me by the arm and said:-*

"My dear child, I have loved science so much throughout my life that this makes my heart throb."

You will pardon me, gentlemen, these personal recollections which have never been effaced from my mind. In our day, and with our habits, they would offend in a scientific memoir, but they have seemed to me not out of place in an oral account; and perhaps the biographical interest of such recollections will constitute one of the advantages of the kind of instruction which the Societe Chimique *inaugurates today.*

Indeed there is more here than personal reminiscences. In Biot's case the emotion of the scientific man was mingled with the personal pleasure of seeing his conjectures realised. For more than thirty years Biot had striven in vain to induce chemists to share his conviction that the study of rotatory polarisation offered one of the surest means of gaining a knowledge of the molecular constitution of substances.

Let us return to the two acids furnished by the two sorts of crystals deposited in so unexpected a manner in the crystallisation of the double paratartrate of soda and ammonia. I have already remarked that nothing could be more interesting than the investigation of these acids.

One of them, that which comes from crystals of the double salt hemihedral to the right, deviates to the right, and is identical with ordinary tartaric acid. The other deviates to the left, like the salt which furnishes it. The deviation of the plane of polarisation produced by these two acids is rigorously the same in absolute value. The right acid follows special laws in its deviation, which no other active substance had exhibited. The left acid exhibits them, in the opposite sense, in the most faithful manner, leaving no suspicion of the slightest difference.

That paratartaric acid is really the combination, equivalent for equivalent, of these two acids, is *proved by the fact that, if somewhat concentrated solutions of equal weights of each of them are mixed, as I shall do before you, their combination takes place with disengagement of heat, and the liquid solidifies immediately on account of the abundant crystallisation of paratartaric acid, identical with the natural product.**

In accord with their chemical and crystallographic properties, all that can be done with one acid can be repeated with other under the same conditions, and in each case we get identical, but not superposable products; products which resemble each other like the right and left hands. The same forms, the same faces, the same angles, hemihedry in both cases. The sole dissimilarity is in the inclination to right or left of the hemihedral facets and in the sense of the rotatory power.

From these results, as a whole, it is evident that we have to do with two isomeric substances, whose general relations as regards similitude and molecular dissimilarity we know.

Now recall the definition of a chemical species which I gave a few minutes ago:- the aggregate of individuals identical in the nature, *the* proportion, *and the* arrangement *of the elements. All the properties of substances are functions of these three terms, and the object of all our work is to pass, by investigation of the properties, to the knowledge of these three things.*

In isomeric bodies, the nature and proportion are the same. The arrangement alone differs. The great interest of isomerism has been to introduce into the science the principle that substances may be, and are, essenially different solely because the arrangement of the atoms is not the same in their chemical molecules.

But no isomeric bodies existed whose relations in respect to molecular arrangement could be known. This desideratum was supplied for the first time by the discovery of the constitution of paratartaric acid, and of the constitution relations of the right and left tartaric acids. We know, on the one hand, that the molecular structures of the two tartaric acids are asymmetric, and on the other, that they are rigorously the same, with the sole difference of showing asymmetry in opposite senses. Are the atoms of the right acid grouped on the spirals of a dextrogyrate helix, or placed at the summits of an irregular tetrahedron, or disposed according to some particular asymmetric grouping or other? We cannot answer these questions. But it cannot be a subject of doubt that there exists an arrangement of the atoms in an asymmetric order, having a non-superposable image. It is not less certain that the atoms of the left acid realise precisely the asymmetric grouping which is the inverse of this. Lastly, we know that paratartaric acid results from the juxtaposition of these two inversely asymmetric atomic groupings.

Henceforth observation of the chemical and physcal resemblances and differences, corresponding to these arrangements whose relations are known to us, offers especial interest, and gives solid foundations to molecular mechanics. It enables us to establish the connection of the physical and chemical properties, with the molecular arrangement which determines their very existence, or conversely it enables us to pass from the properties to their primary cause.

A resume *of these general relations between the properties and corresponding atomic arrangements may be given as follows:*

(1) *When the elementary atoms of organic products are grouped asymmetrically, the crystalline form of the substance manifests this molecular asymmetry in non-superposable hemihedry.*

The cause of the hemihedry is thus recognised.

(2) *The existence of this same molecular asymmetry betrays itself, in addition, by the optical rotative property.*

The cause of rotatory polarisation is likewise determined.†

(3) *When the non-superposable molecular asymmetry is realised in opposite senses, as happens in the right and left tartaric acids and all their derivatives, the chemical properties of these identical and inverse substances are rigorously the same.*

However, Pasteur said this at the end of a lecture, this statement must be qualified by a manner which he will explain in the next lecture. It then appeared that this was of the utmost importance and was to the effect that a substance composed of asymmetric molecules would differ from one composed of the mirror image of those molecules in its behavior towards any one-handed asymmetric substance or any one-handed asymmetric agent or force which can in any way affect the behavior of a collection of asymmetric molecules. Put in another way, Pasteur enunciated a proposition that an asymmetric entity cannot be recognised and used as such by symmetrical entities, but that one asymmetric entity of any kind may recognise and perhaps make use of an asymmetry of another such entity, not necessarily in the same class. The separation of the sodium ammonium racemate (paratartrate) into the salts of

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**This beautiful experiment called forth applause from the audience.*

†*Fresnel, with one of those flashes of genius, of which he had so many, had a sort of presentiment of this cause of rotatory polarisation.*

He expresses himself thus, in one of his memoirs, in Vol. XXVIII, of the Annales de chimie et de physique, 1825:- *Rock crystal shows optical phenomena which cannot be reconciled with complete parallelism of the molecular lines, and which would seem to indicate a progressive and regular deviation of these lines, in the passage from one layer of the medium to the next.*

the dextro- and levo rotatory tartaric acids, was an example of this type of special interaction. Pasteur being an asymmetrical organism was able to recognise the two types of hemihedral crystals from sodium ammonium racemate. It will be impossible to devise a symmetrical machine which could bring about this separation. At about this stage in his lecture Pasteur found it necessary to adopt some words to describe the principle which we now call enantiomorphism. He spoke of objects especially molecules, which have superposable images and others which have non-superposable images when examined, in fact or in imagination, in a mirror. We now resume his actual words.

..... *All bodies (I here imply the expression in the chemical sense) fall into great classes, bodies with superposable images and bodies with non-superposable images,—bodies with asymmetric atomic arrangement and those with homohedral atomic arrangement.*

Here we encounter a fact which would be worthy of our attention, even if we considered it alone and separate from the set of considerations which follow. It is this:

All artificial products of the laboratory and all mineral species are superposable on their images. On the other hand, most natural organic products (I might even say all, if I were to name only those which play an essential part in the phenomena of vegetable and animal life), the essential products of life, are asymmetric, and possess such asymmetry that they are not superposable on their images.

Before going further, I wish to remove some objections which will not fail to arise in your minds.

Quartz! you will say at once. We saw in the last Lecture that quartz possesses the two characteristics of symmetry—hemihedry in form, observed by Haüy, and the rotative phenomenon discovered by Arago! Nevertheless, molecular *asymmetry is entirely absent in quartz. To understand this, let us take a further step in the knowledge of the phenomena with which we are dealing. We shall find in it, besides, the explanation of the analogies and differences already pointed out between quartz and natural organic products.*

Permit me to illustrate roughly, although with essential accuracy, the structure of quartz and of the natural organic products. Imagine a spiral stair whose steps are cubes, or any other objects with superposable images. Destroy the stair and the asymmetry will have vanished. The asymmetry of the stair was simply the result of the mode of arrangement of the component steps. Such is quartz. The crystal of quartz is the stair complete. It is hemihedral. It acts on polarised light in virtue of this. But let the crystal be dissolved, fused, or have its physical structure destroyed in any way whatever; its asymmetry is suppressed and with it all action on polarised light, as it would be, for example, with a solution of alum, a liquid formed of molecules of cubic structure distributed without order.

Imagine, on the other hand, the same spiral stair to be constructed with irregular tetrahedra for steps. Destroy the stair and the asymmetry will still exist, since it is a question of a collection of tetrahedra. They may occupy any positions whatsoever, yet each of them will none the less have an asymmetry of its own. Such are the organic substances in which all the molecules have an asymmetry of their own, betraying itself in the form of the crystal. When the crystal is destroyed by solution, there results a liquid active towards polarised light, because it is formed of molecules, without arrangement, it is true, but each having an asymmetry in the same sense, if not of the same intensity in all directions.

Quartz is therefore not molecularly asymmetric, and up to the present we have not any example of a mineral possessing molecular asymmetry. I have remarked that this proposition must be extended to the artificial compounds of the laboratory. Here again some scruples may be felt. It might be objected, for instance, that natural camphor, which is asymmetric, gives, artificially, camphoric acid, which is likewise asymmetric; that aspartic acid derived from asparagine by a laboratory reaction is asymmetric in the same way as asparagine, and I might cite many other similar examples. But no one can doubt that camphoric and aspartic acids owe their own asymmetry to camphor and to asparagine. This existed in the original products, and is handed on, more or less modified by substitution, from the original substances to their derivatives. In fact, a better proof of the conservation of the primitive type, in a series of products united together by a common origin, than that given by the permanence of the optical property, could not be adduced.

When I affirm that no artificial substance has yet shown molecular asymmetry, I refer to artificial substance properly so called, made entirely of mineral elements or derived from substances not themselves asymmetric. Thus, alcohol is not asymmetric. Its molecule, if we could isolate and study it, when placed before a mirror would give a superposable image. Now not a single derivative of alcohol is asymmetric. I could multiply ad infinitum *examples of this kind. More than this: take any asymmetric substance whatever, and, if you submit it to fairly energetic chemical reactions, you may confidently expect to see the asymmetry of the primitive group disappear. Thus, tartaric acid is asymmetric. Pyrotartaric acid is not so. Malic acid is asymmetric. The maleic and paramaleic acids of Pelouze are not. Gum is asymmetric, mucic acid is not.*

Artificial products have, therefore, no molecular asymmetry: and I could not point out the existence of any more profound distinction between the products formed under the influence of life, and all *others. Let us enforce this point more strongly, for you will find the physiological side of these researches become more and more prominent in the remainder of this Lecture. Let us pass in review the principal classes of natural organic products.*

Cellulose, starches, gums, sugars,—tartaric, malic, quinic, tannic acids,—morphine, codeine, quinine, strychnine, brucine,—essences of turpentine, of citron,— albumen, fibrin, gelatin. All these immediate principles are molecularly asymmetric. All these substances in the state of solution possess the rotative power, a characteristic necessary and sufficient to establish their asymmetry, even when, crystallisation being impossible, hemihedry is lacking as a means of recognising this property.

All the substances most essential in the animal or vegetable organism appear in this list.

There are many natural substances which are not asymmetric. But are they natural in the same sense as the others? Must we not regard bodies like oxalic acid, hydride of salicyle, fumaric acid, etc., as derivatives of natural substances properly so called, formed by interactions analogous to those of the laboratory? These products appear to me to be, in the vegetable organism, what urea, uric acid, creatine, glycocoll, etc., are in the animal organism—excretions rather than secretions, if I may so speak. It would be very interesting to follow up this point of view experimentally.

Let us add that many substances which are apparently not asymmetric, may be like paratartaric acid. *We still want a word in chemical language to express the fact of a double molcular asymmetry concealed by the neutralisation of two opposite asymmetries, the physical and geometrical effects of which rigorously compensate each other.*

The double proposition to which we have been led, on the habitual asymmetry of immediate organic principles, and on the absence of this character in all the products of inorganic nature, will permit us to enlarge and render more definite our mode of regarding the subject of this remarkable molecular property.

In 1850 M. Dessaignes, whose ingenuity and skill are known to all chemists, announced to the Academy that he had succeeded in transforming bimalate of ammonia into aspartic acid. This was an advance which confirmed the important results obtained by Piria some years before. Piria had succeeded in transforming asparagine and aspartic acid into malic acid. M. Dessaignes, in turn, showed that conversely we could return from malic acid to aspartic acid.

So far everything connected with M. Dessaignes' observation was perfectly natural, even from the optical point of view. For, on my side, I had found that asparagine, aspartic acid and malic acid were active towards polarised light. The passage chemically from one to the other of these bodies had nothing astonishing about it.

A few months later M. Dessaignes took a further step. He announced that not only bimalate of ammonia, but also fumarate and maleate of ammonia had likewise the property of being transformed by heat into aspartic acid.

Here I saw an impossibility; or, if the facts were as M. Dessaignes stated, this skilful chemist had made a discovery which he did not suspect. I had in fact observed that fumaric and maleic acids and all their salts were without action upon polarised light. If, therefore, M. Dessaignes had succeeded in transforming their ammonia salts into aspartic acid, he would have accomplished for the first time the production of an asymmetric substance by the aid of compounds which are not so. But it seemed to me more reasonable to suppose that the aspartic acid of M. Dessaignes differed from natural aspartic acid in the absence especially of the molecular rotatory property. M. Desaignes, it is true, had carefully compared the properties of the artificial acid with those of the natural acid, and stated that he had found them identical. After the example of Mitscherlich, of which I spoke in last Lecture, I knew better than anyone else what delicate things were the demonstrations of the identity of chemical species, in investigations where the greatest similarity in properties often conceals profound differences. I had therefore no hesitation in believing that the new fact reported by M. Dessaignes required confirmation.

Attaching so much importance to the elucidation of this question, and indeed foreseeing the results which I am about to have the honour of explaining to you, I immediately set out for Vendome, where I related my suspicions to M. Dessaignes, and he hastened to supply me with a specimen of his aspartic acid. As a matter of fact I found, as soon as I reached Paris, that M. Dessaignes' acid was only an isomer of natural aspartic acid, that is of the acid from asparagine. It differed from it, as I had foreseen, in the rotatory property, which was quite absent in the artificial acid and indubitable in the natural acid. Yet all the other chemical and physical properties showed the greatest analogies, so great that M. Dessaignes, not being put on his guard by any preconceived idea, had decided that the two substances were really identical.

What charmed me most in the examination of the new compound (which in itself shows no remarkable crystallisable compounds), was its transformation into malic acid. It is known indeed, I mentioned the fact a moment ago, that Piria long since showed how to pass from asparagine and aspartic acid to malic acid, and I had assured myself by the most rigid proofs that this malic acid was identical with that from the mountain ash, from apples, from the grape, and from tobacco.

I therefore applied to the new acid the treatment discovered by Piria and actually transformed it into a new malic acid, very similar to the natural acid. It *was so nearly allied to the latter that a chemist would have had difficulty in distinguishing them, even if he had been warned of their real disparity. Only, this malic acid had no action on polarised light, and the same was true of all its salts.*

There are certain derivatives of these two malic acids which, on comparison, do not exhibit very clearly the real mutual dependence of the molecular arrangements of these curious isomers; but there are others in which it exhibits itself to its full extent. Let us consider, for example, the ordinary active bimalate of lime, and the corresponding inactive bimalate. Their chemical composition is exactly the same and their crystalline forms are alike, with the difference that the active one has four small hemihedral faces which are always absent in the inactive one. The result is that, when the active one is placed before a mirror, the image cannot be superposed on it, while the image of the inactive one is absolutely identical with and superposable on the reality which produces it. But in all that does not concern the hemihedral faces, the resemblance of the two forms is perfect.

Who could doubt, after that, the relation of the molecular arrangements in the two salts? Is it not evident that we have here to deal with a malic acid identical with the natural one, except for the simple suppression of its molecular asymmetry?

It is natural malic acid untwisted, if I may so express myself. The natural acid is a spiral stair as regards the arrangement of its atoms, this acid is the same stair made of the same steps, but straight in place of being spiral.

It might be asked whether the new acid is not the paratartaric member of the series, that is, the compound of the right malic acid with the left malic acid. That is improbable, for then not only would we have made an active body from an inactive one, we would have made two, a right and a left.

Besides, I have found that, just as there exists an inactive non-asymmetric malic acid, there is likewise an inactive non-asymmetric tartaric acid quite different from paratartaric acid, which cannot be resolved into a right tartaric acid and a left tartaric acid. It is impossible to doubt that we have here to do with right or left tartaric acid rendered non-symmetric.

I have likewise discovered inactive amyl alcohol which gives rise to a whole series of inactive products corresponding to the series from active amyl alcohol.

We are now, thanks to the discovery of inactive substances, in possession of a fertile idea. A substance is asymmetric, right or left; by certain artifices of isomeric transformation, which must be sought and discovered for each particular case, it may lose its molecular asymmetry, become untwisted, to use a rough metaphor, and assume in the arrangement of its atoms a disposition with superposable image. In this way each asymmetric substance offers four varieties, or, better, four distinct sub-species: the right body, the left body, the combination of the right and the left, and the substance which is neither right nor left nor formed by the combination of the right and the left.

This general conclusion from the above-mentioned investigations throws a new light on our ideas of molecular mechanics. We discover that if the natural products elaborated under the influence of vegetable life are, as a rule, asymmetric, contrary to what we find in the case of artificial and mineral products, this disposition of the elementary particles is not a condition of the existence of the molecule,—that the twisted organic group can be untwisted, and so assume the ordinary character of artificial and mineral substances. Conversely, it seems to me logical to regard the latter as capable of exhibiting an asymmetric arrangement of their atoms after the manner of the natural products. The conditions for their production have still to be discovered.

To sum up what has been said, the groups of elementary atoms which constitute compound matter can assume two distinct states corresponding to the two general types under which every material object can be classified. The form of the group has either a superposable or a non-superposable image; but the latter type is double, for its inverse can exist equally well with itself. We must add the case of the association of these two inverse types, recalling the union by pairs of identical and non-superposable members in the higher animals. There are therefore in reality four remarkable arrangements for the groups of atoms which constitute matter. All our efforts should be bent to produce them for each particular species.

Almost all these conclusions are so rigorous that it is practically impossible to call them in question.

Thus, how can we refuse to admit that a right body has a possible left form, knowing as we do the significance of the right or left character? We might as well doubt that an irregular tetrahedron has its inverse, that a right helix has its left form, that a right hand has a possible left.

And consequently, if the mysterious influence to which the asymmetry of natural products is due should change its sense or direction, the constitutive elements of all living beings would assume the opposite asymmetry. Perhaps a new world would present itself to our view. Who could foresee the organisation of living things if cellulose, right as it is, became left; if the albumen of the blood, now left, became right? These are mysteries which furnish much work for the future, and demand henceforth the most serious consideration from science.

Possibly, since chemistry has been up to the present time powerless to prepare asymmetric substances, one might fear that we should remain for ever in ignorance of a way of making the inverse forms of natural organic substances. Happily this *fear is exaggerated. In fact I have discovered that ordinary chemical processes, such as the action of heat, enable us to pass from a right to a left substance, and* vice versa. *Thus, when right tartaric acid is heated under certain fixed conditions which it would take too long to specify here, it is transformed into left tartaric acid, or rather into paratartaric acid. And conversely under the same conditions precisely, the left tartaric acid becomes right.*

Here are ten or twelve grams of perfectly pure left tartaric acid, which have been obtained in this manner. Their preparation has cost me much trouble. But M. Biot was particularly anxious to study the dispersive properties of this left tartaric acid of such remarkable origin. He wished himself to defray the cost of the operation, which was very expensive, for the transformation depends on the employment of tartrate of cinchonine or of quinine, and the base is lost because the tartrate has to be heated to a temperature which destroys it. By this means I prepared paratartaric acid enough to yield twelve grams to left tartaric acid, which exhibited, in the inverse sense, absolutely the same optical characters as tartaric acid.

We must always consider every transformation like this of a natural asymmetric body into its inverse as a great advance of organic chemistry.

At the conclusion of our former meeting I referred to some observations to which it is now time that we devoted the attention which they deserve. These observations are connected with the comparison of the physical and chemical properties of the corresponding right and left isomers. I have already insisted on the perfect identity of all their properties, excepting always the inversion in their crystalline forms and the opposite sense of their optical deviations. The physical aspect, lustre of the crystals, solubility, specific weight, simple or double refraction, all these things are not merely alike, similar, nearly allied, but identical in the strictest sense of the word.

This identity is all the more remarkable since we shall see it replaced by general and noteworthy contrast of the properties of the same substances when they are subjected to special conditions which I am about to indicate.

We have seen that all artificial or natural chemical compounds, whether mineral or organic, must be divided into two great classes: non-asymmetric compounds with superposable image and asymmetric compounds with non-superposable image.

Taking this into account, the identity of properties above described in the case of the two tartaric acids and their similar derivatives, exists constantly, with the unchangeable characters which I have referred to, whenever these substances are placed in contact with any compound of the class with superposable image, such as potash, soda, ammonia, lime, baryta, aniline, alcohol, ethers,—in a word, with any compounds whatever which are non-asymmetric, non-hemihedral in form, and without action on polarised light.

If, on the contrary, they are submitted to the action of products of the second class with non-superposable image,— asparagine, quinine, strychnine, brucine, albumen, sugar, etc., bodies asymmetric like themselves,—all is changed in an instant. The solubility is no longer the same. If combination takes place, the crystalline form, the specific weight, the quantity of water of crystallisation, the more or less easy destruction by heating, all differ as much as in the case of the most distantly related isomers.

Here, then, the molecular asymmetry of a substance obtrudes itself on chemistry as a powerful modifier of chemical affinities. Towards the two tartaric acids, quinine does not behave like potash, simply because it is asymmetric and potash is not. Molecular asymmetry exhibits itself henceforth as a property capable by itself, in virtue of its being asymmetry, of modifying chemical affinities. I do not believe that any discovery has yet made so great a step in the mechanical part of the problem of combination.

Let us try to illustrate the cause of these identities and differences. Let us imagine a right screw and a left screw separately penetrating two identificial blocks of wood with the grain straight. All the mechanical conditions of the two systems will be the same. This will no longer be so from the moment that the same screws are associated with blocks which are themselves twisted in the same sense or in the opposite sense.

Here is a very interesting application of the facts which have just been explained.

Seeing that the right and left tartaric acids formed such dissimilar compounds simply on account of the rotative power of the base, there was ground for hoping that, from this very dissimilarity, chemical forces might result, capable of balancing the mutual affinity of the two acids, and thereby supply a chemical means of separating the two constituents of paratartaric acid. I sought long in vain, but finally succeeded by the aid of two new bases, quinicine and cinchonicine, isomers of quinine and cinchonine, which I obtained very easily from the latter without the least loss.

I prepare the paratartrate of cinchonicine by neutralising the base and then adding as much of the acid as was necessary for the neutralisation, I allow the whole to crystallise, and the first crystallisations consist of perfectly pure left tartrate of cinchonicine. All the right tartrate remains in the mother liquor because it is more soluble. Finally this itself crystallises with an entirely different aspect, since it does not possess the same crystalline form as the left salt. We might almost believe that we were dealing with the crystallisation of two distinct salts of unequal solubility.*

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*("Right" in original.)

But the difference in properties of corresponding right and left substances when they are subjected to asymmetric forces, seems to me to be interesting in the highest degree on account of the ideas which it suggests to us in regard to the mysterious cause which presides over the asymmetric arrangement of the atoms in natural organic substances. Why this asymmetry? Why the one asymmetry rather than its inverse?

Carry yourselves back with me in thought to the time when, having recognised the absolute identity of the chemical and physical properties of the corresponding right and left substances, I had not any idea, not even the suspicion, of possible differences between these substances. It was, in fact, after an interval of several years that I recognised these similarities and differences.

It was then impossible for me to understand how nature could make a right substance without at the same time making the left substance. For the same forces which are at work at the moment at which the molecule of right tartaric acid is elaborated, must, it seemed, yield a left molecule also, and there would have been nothing but paratartaric *compounds.*

Why even right or left substances at all? Why not simply non-asymmetric substances; substances of the order of inorganic nature?

There are evidently causes for these curious manifestations of the play of molecular forces. To indicate them in a precise manner would certainly be a difficult matter. But I believe that I am not deceived when I say that we know one of their essential characters. Is it not necessary and sufficient to admit that at the moment of the elaboration of the primary principles in the vegetable organism, an asymmetric force is present? For we have just seen that there is only a single case in which the right molecules differ from the left, the case where they are submitted to influences of an asymmetric character.

Do these asymmetric actions, possibly placed under cosmic influences, reside in light, in electricity, in magnetism, or in heat? Can they be related to the motion of the earth, or to the electric currents by which physicists explain the terrestrial magnetic poles? It is not even possible at the present time to express the slightest conjecture in this direction.

But I regard as necessary the conclusion that asymmetric forces exist at the moment of the elaboration of natural organic products; forces which would be absent, or ineffectual, in the reactions of our laboratories either on account of the violent course of these phenomena, or because of some other unknown circumstance.

We now reach a final experiment which does not yield in interest to any of those which precede, in respect to the manifest proof which it will give us of the influence of asymmetry in the phenomena of life. We have just seen asymmetry intervening to modify chemical affinities; but the reactions involved were purely inorganic, artificial, and we know all the prudence that must be observed in the application of the results of the laboratory to the phenomena of life. On this account I kept to myself almost all the views expressed in this Lecture till the moment that I recognised in the most certain manner that molecular asymmetry exhibited itself as a modifier, no longer of the reactions of inorganic nature, but of those of physiological character, in fermentations.

Here is the remarkable phenomenon to which I refer.

It had long been known, from the observation of a German manufacturer of chemical products, that the impure tartrate of lime of the works, mixed with organic matters, when left under water in summer, could ferment, giving various products.

Knowing this, I set the ordinary right tartrate of ammonia to ferment in the following manner. I took the very pure crystallised salt, dissolved it, adding to the liquor a clear solution of albumenoid matter. One gram of dry albumenoid matter was sufficient for one hundred grams of tartrate. Very often it happens that the liquid ferments spontaneously when replaced in an oven. I say very often; but it may be added that this will always take place if we take care to mix with the liquid a very small quantity of one of those liquids with which we have succeeded in obtaining spontaneous fermentation.

So far there is nothing peculiar; it is a tartrate fermenting. The fact is well known.

But let us apply this method of fermentation to paratartrate of ammonia, and under the above conditions it ferments. The same yeast is deposited. Everything shows that things are proceeding absolutely as in the case of the right tartrate. Yet if we follow the course of the operation with the help of the polarising apparatus, we soon discover profound differences between the two operations. The originally inactive liquid possesses a sensible rotative power to the left, which increases little by little and reaches a maximum. At this point the fermentation is suspended. There is no longer a trace of the right acid in the liquid. When it is evaporated and mixed with an equal volume of alcohol it gives immediately a beautiful crystallisation of left tartrate of ammonia.

Let us note, in the first place, two distinct things in this phenomenon. As in all fermentation properly so called, there is a substance which is changed chemically, and correlatively there is a development of a body possessing the aspect of a mycodermic growth. On the other hand, and it is this which it is important to note, the yeast which causes the right salt to ferment leaves the left salt untouched, in spite of the absolute identity in physical and chemical properties of the right and left tartrates of ammonia as long as they are not subjected to asymmetric action.

Here, then, the molecular asymmetry proper to organic substances intervenes in a phenomenon of a *physiological kind, and it intervenes in the role of a modifier of chemical affinity. It is not at all doubtful that it is the kind of asymmetry proper to the molecular arrangement of left tartaric acid which is the sole and exclusive cause of the difference from the right acid, which it presents in relation to fermentation.*

Thus we find introduced into physiological principles and investigations the idea of the influence of the molecular asymmetry of natural organic products, of this great character which establishes perhaps the only well marked line of demarcation that can at present be drawn between the chemistry of dead matter and the chemistry of living matter.

Such, gentlemen, are in co-ordinated form the investigations which I have been asked to present to you.

You have understood, as we proceeded, why I entitled my exposition, "On the Molecular Asymmetry of Natural Organic Products." It is, in fact, the theory of molecular asymmetry that we have just established, one of the most exalted chapters of the science. It was completely unforeseen and opens to physiology new horizons, distant, but sure.

I hold this opinion of the results of my own work without allowing any of the vanity of the discoverer to mingle in the expression of my thought. May it please God that personal matters may never be possible at this desk. These are like pages in the history of chemistry which we write successively with that feeling of dignity which the true love of science always inspires."

It will be recognised from this account that Pasteur did far more than simply discover the underlying theory of molecular asymmetry; he foresaw most of the main consequences of that theory and made special experiments to confirm the predictions which he saw should follow from it. He understood the principle of a transference of the asymmetric property from one set of molecules to another, and he discovered the phenomena of racemisation. He also had a clear understanding of internal compensation as in meso-tartaric acid. He realised that, theoretically, it should be possible to effect an optical resolution of a racemic mixture by combination with an asymmetric substance, the molecules of which are single-handed and gave an excellent example of the practical use of the method in the resolution of racemic acid by an optically active base. Finally, he clearly understood the biological implications of the discovery of asymmetry. His nearest approach to the structural explanations of Van't Hoff and Le Bel, which we now celebrate, was that the group with non-superposable images would include irregular tetrahedron.

A further precedent of Van't Hoff and Le Bel's generalisation was the determination of the structure of optically active natural products on the basis of Kekule/Couper's hypothesis of quadrivalent carbon atoms. The earlier investigations in this group were, however, interpreted in terms of the theory of mixed types, including the marsh gas type.

Dr. M. J. T. Robinson (see p. 1499) has contributed a careful study of the rather involved development of our knowledge of the molecular structure of tartaric acid and related substances.

The above translation of parts of Louis Pasteur's Lectures to the French Chemical Society have been selected for inclusion in this Van't Hoff–Le Bel Centerary Volume in order to demonstrate the fundamental nature of the observations of Pasteur in 1860 and their relation to the important generalisations put forward by Van't Hoff and Le Bel in 1874.

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