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Louis Pasteur did it for us especially

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Each great discovery is inexhaustible as science itself, and is strictly addressed to those who did found his or her predestination for trying to understand it and to develop it. What was a basis for the Pasteur discovery, what is the essence of it, and what kind of consequences have been found from it, all these points are considered in this paper.

L. Pasteur (27 December 1822 – 28 September 1895)
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'If I have seen farther than others, it is because I was standing on the shoulders of giants.'

Isaac Newton, 1676

Traditions

Pasteur was standing on the shoulders of giants.[1–6] That is why it could happen in Paris 155 years ago. By those times in France, the banner of science was kept flying with passwords inserted by his preceptors: 'Crystallography is a science of all sciences' (Rome de l'Isle) and 'The principle of geometrism' – the form of a crystal should comply with the forms of atomic groups and molecules, of which it is composed (A. R. J. Haüy). F. H. Delafeses has already introduced a concept of the hemihedrism (enantiomorphism) of crystals, and Haüy revealed such an attribute in quartz. The teacher of Pasteur, J.-B. Biot, has already studied the properties of plane-polarised light; he applied it to detect the optical activity of crystals and solutions (polarimetry) and disclosed both (+)- and (–)-optical activity in the enanitomorphous crystals of natural quartz. J. W. F. Herschel has shown that (+)- or (–)-optical rotation coresponds to a mirror-opposite hemihedrism in quartz crystals (1820). In his famous first lecture (1860), Pasteur noticed that the above observations laid down to the main basis of his discovery in the course of investigating tartrates.[1]

Tartaric acid has been known since antiquity in the form of its potassium acid salt (tartar, $KHC_4H_4O_6$) obtained as a deposit from fermented grape juice. C. W. Scheele isolated the free acid (1770). P. Kestner (1818), a French manufacturer from Thann (Alsace), obtained a new form of the acid† (thannic acid, named later paratartaric acid) by overheating tartar.[3(*b*),5] Next year, J. F. John recognised it as a distinct compound, and J. L. Gay-Lussac identified it as tartaric acid in 1826 and gave it the name racemic acid. J. J. Berzelius, the leading chemist of those days, referred to both acids as isomers upon his careful studies. In a letter of May 28, 1830, he asked E. Mitscherlich (a leading crystallographer[6(*a*),7] and the discoverer of isomorphism‡ and polymorphism§) to examine tartrates with the aim of seeking differences between them. Mitscherlich started his investigations in 1831. In 1836, Biot found that tartaric acid was dextrorotatory unlike the optically inactive isomer. In 1841–1842, C. R. Fresenius, the most prominent analytical chemist, analysed the salts of both acids; at the same time, the prominent crystallographer F. H. de la Provostaye studied their crystalline forms but did not reveal isomorphism of the crystals. However, in 1844, Mitscherlich sent a note to Biot about surprising results of his studies and 'has given the means of repeating it': sodium ammonium salts of two isomeric acids possessed the same crystal form and densities, … 'but here the nature and the number of the atoms, their arrangement, and their distances are the same in the two substances compared'. Pasteur noticed (1860) that this communication was a driving force and the second important base for his own investigations.[1] Finally, in the Pasteur notebook, the observation by Hankel (1843) on hemihedral faces of (+)-tartaric salt were mentioned.[3(*b*)] The latter, undoubtedly, was the third important base for his discovery.

'Discovery consists of seeing what everybody has seen and thinking what nobody has thought.'

Albert von Szent-Györgyi, 1962

Innovations

In 1847, Pasteur has been convinced that all the tartrates studied were hemihedral but racemates have never been. Being preoccupied with an idea on the inter-relation of hemihedrism and the rotatory phenomenon, he decided to re-investigate the crystalline form of two Mitscherlich's salts. Moreover, he thought at once that Mitscherlich was mistaken and had not observed that his double tartrate was hemihedral while his paratartrate (racemate) was not. Unexpectedly, he found that the paratartrate was also hemihedral; however, its hemihedral faces were not all turned the same way, like in the tartrate, but inclined sometimes to the right and sometimes to the left. Then, he carefully separated the right and left crystals, examined their solutions separately, and saw with no less surprise than delight opposite optical rotations. As he described it in his first lecture,[1] 'the crystal hemihedral to the right deviated the plane of pola-

† The cause of such a transformation was elucidated later when Pasteur discovered the phenomenon of racemization: upon heating to 170 °C, the cinchonine salt of (+)-tartaric acid was converted into the salt of *rac*-tartaric acid.[4(*a*)]

‡ D. I. Mendeleev was interested in the isomorphism and fulfilled his first thesis on this topic (1856).

§ These phenomena are ones of prime importance in modern crystallography.[8]

rization to the right, and 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 toward the light in consequence of the neutralization of the two equal and opposite individual deviations'. Thus, Pasteur was able to recognise the smallest difference in two kinds of crystals, showed that they are isomorphous, and isomorphous with the corresponding tartrate, 'but the isomorphism presents itself with a hitherto unobserved peculiarity; it is the isomorphism of an dissymmetric crystal with its mirror image".[1] On May 15, 1848, he presented his discovery to the French Academy of Sciences. The manual sorting of left and right crystals is the first Pasteur's method for separating racemates, which crystallise as conglomerates. The latter term was introduced into practice by Jean Jacques, a successful Pasteur's follower, who left a rich heritage such as two well-known monographs on chiral chemistry[4(*a*),9] and a popular essay on Pasteur.[4(*b*)] For the curious minds, Jacques gives a methodology to repeat the Pasteur's experiment and reminds a record from his notebook: 'the crystals of salt are hemihedral often but not always', then he notes that the crystals corresponding to the drawing by Pasteur never occurred.

Two other procedures for repeating Pasteur's experiment[6] and the spontaneous resolution of a hydrobenzoin conglomerate[10] were reported.

Pasteur has found a fundamental phenomenon of the homochiral crystallization of dissymmetric organic molecules and, thereby, spontaneous resolution at the level of single crystals. Earlier, Biot has revealed a similar phenomenon of the homochiral packing of achiral SiO_2 molecules in quartz. Pasteur explained it in his second lecture (1860)[1] as follows: 'Quartz! …Imagine a spiral stair whose steps are cubes… Destroy the stair, and the dissymmetry will have vanished.' In fact, (+)-tartaric acid, the Pasteur's salt and (–)-asparagine [(–)-Asn] possess optical activity both in solution and in crystalline forms (6.1°, 0.8° and 5.9° per mm, respectively), whereas the chiral crystals of achiral compounds like quartz, $NaClO_3$ and diacetyl phenolphthalein are optically active in crystalline forms (21.7°, 3.2° and 19.8°, respectively)[11] rather than in solutions. Noteworthy, the theoretical investigations of the meanings of this fundamental phenomenon, *i.e.*, the possibility of homochiral crystal formation, were independently started by O. Bravais in France in 1848 (Bravais crystal lattices[12]) and completed by E. S. Fedorov in Russia and A. Schönflies in Germany (1890–1891).[13] Of 230 Fedorov groups, 65 are chiral; and hence, all organic compounds that crystallise in these space groups do form conglomerates. Like in Pasteur times, nowadays the interest of chemists in crystallography is roused up, and the list of chiral space groups was published recently in three journals.[14(*a*)–(*c*)]

The correct formula of tartatric acid was established by A. S. Couper in 1858.[15] As early as 1860, Pasteur has carried out the first total synthesis of this natural chiral organic compound starting from ethylene.[3(*b*),16] The absolute configuration of (*R*,*R*)-(+)-tartaric acid was determined by J. M. Bijvoet *et al.* by anomalous scattering in an X-ray diffraction study of sodium rubidium (+)-tartrate,[17(*a*)] and afterwards by chemical methods.[17(*b*),(*c*)]

Further, Pasteur supposed that combinations of an optically active base with (+)- and (–)-tartaric acids should differ in physical properties: 'Towards the two tartaric acids, quinine does not behave like potash, simply because it is dissymmetric and potash is not. Molecular dissymmetry exhibits itself henceforth as a property capable by itself, in virtue of its being dissymmetry, 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 combinations'.[3(*b*)] Indeed, *rac*-tartaric acid forms two diastereomeric salts with an alkaloid, which are readily resolved by crystallization ('We might almost believe that we were dealing with the crystallization of two distinct salts of unequal solubility'), and then the enantiomerically pure (+)- and (–)-acids can be isolated.[9] This is the second Pasteur's method for the resolution of racemates by chiral resolving reagents. This method is universal because it can be applied to both conglomerates and true racemates.

This discovery was followed up with a next one, which was a perfectly logical transition: 'the difference in properties of corresponding right and left substances when they are subjected to dissymmetric forces,¶ seems to me to be interesting in the highest degree on account of ideas which it suggests to us in regard to the mysterious cause which presides over the dissymmetric arrangement of the atoms in natural organic substances… 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 ammonium… The originally inactive liquid possesses a sensible rotative power to the left… When it is evaporated and mixed with alcohol it gives immediately a beautiful crystallization of left tartrate of ammonium… Thus we find introduced into physiological principles and investigations of the idea of the influence of the molecular dissymmetry of natural organic products … and the chemistry of living matter'.[1] This is the third Pasteur's method for separating the racemates by enzymatic resolution.

These Pasteur's methods form the basis of modern industry for the production of chiral drugs and enantiomerically pure materials.[9]

In his famous second lecture entitled 'On the molecular dissymmetry of natural organic products',[1] Pasteur raised a series of questions. Concerning the occurrence of only left amino acids and only right sugars in our living nature, he exclaimed: 'Why even right or left substances at all? Why this dissymmetry? Why the one dissymmetry rather than its inverse? Do these dissymmetric 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 current by which physicists explain the terrestrial magnetic poles?'[1] And these are actual questions: a left-handed solar system,[18(*a*)] chirality, magnetism, light[18(*d*)] and electric current.[18(*f*)]

Finally, Pasteur opened a question on the possibility of antipodal life: 'if the mysterious influence to which the dissymmetry of natural products is due should change … (into) opposite dissymmetry. Perhaps a new world would present itself to our view… These are mysteries which furnish much work for the future, and demand henceforth the most serious consideration from science'. And this is also a question of the day concerning 'mirror life'.[18(*c*)]

Being interested in fermentation studies, Pasteur is carried away from chemistry to biology, and here he throws light on many important things and discovers the biological character of fermentation and infectious diseases, vaccination, and pasteurization named after him.

'Everyone who devoted himself to sciences comes inevitably to the sensation that time is incredibly precious; each year should bring new results, and a stop is no longer possible…'

Louis Pasteur, 1860

Consequences

Conglomerates

The first Pasteur method for spontaneous resolution by conglomerate crystallization is the simplest. However, for a long time, it was considered that the conglomerates such as Pasteur's salt and Asn (*see* the photograph of crystals on the cover, and pp. 97–99 of this issue) found due to the observed hemihedry of their crystals are uncommon like rare wonders. An intense search for conglomerates began late in the 1800s.[9,19,20] F. S. Kipping and W. J. Pope have revealed that, like quartz, the achiral salt $NaClO_3$ forms chiral crystals,[21] and their optical activity can be measured directly for each separate crystal be-

¶ The difference in the energies of LL- and LD-interactions is the subject of modern theoretical[18(*a*)] and experimental[18(*b*)] studies.

cause they are isotropic (have cubic space group $P2_13$[22]). Later, it was found that many inclusion compounds of achiral urea[††] with chiral guest molecules form conglomerates and undergo spontaneous resolution by Pasteur-like crystallization.[9] According to recent estimations, the number of conglomerates amounts to 5–10% of the total number of racemates.[9,14(c)] The known list[9] counts 248 conglomerates, and their number is rapidly increasing; in this issue, 14 new conglomerates are described. The point is how to seek for them.

The simplest practice is based on the Pasteur's test: one can either observe the hemihedrism of crystals or, in case of its lack, try the optical activity of a single crystal. Using this approach, we have found 11 new conglomerates at once.[24] R. Bishop *et al*. have found 12 conglomerates among the inclusion compounds of a bicyclic diol with various guest molecules (space group $P3_121$).[25] In 1910, I. I. Ostromisslensky proposed triboluminescence as a test for conglomerate formation (see p. 99). The most reliable method is X-ray diffraction study of single crystals since conglomerates crystallise in one of 65 space groups,[8,9] though it depends critically on the crystal quality. Powder X-ray diffraction is free of this disadvantage.[8(d),(i)] Convenient tests are based on the identity of solid-state IR[9] or ^{13}C NMR spectra[8(d),26] with the latter there was revealed a striking difference between the spectra of (+)- and (±)-tartaric acid, which crystallises as a true racemate.[24] More delicate way for the search is to study isotopomeric quasi-racemates (see pp. 97–99). Recently, we found an interesting example when a compound forms a racemate (achiral space group) under normal conditions but a conglomerate (chiral space group) at elevated temperature.[27(a)] Therefore, crystallization at different temperatures is necessary in a search for conglomerates. It is obvious that the most convenient and simplest method for seeking and studying conglomerates (in terms of possible twinning[27(b)] or unbalanced packing[27(c)]) is chiral chromatography of the solutions of single crystals[27(a)] (see also pp. 106–108).

Comparative analysis of the crystal structures of enantiomers and racemates opens an opportunity to design conglomerates, as demonstrated by K. Saigo[28] and in our laboratory,[27(c),29(a)] including the preparation of a chiral drug *via* spontaneous resolution of its synthetic precursor.[29(b)] Further progress in this field is possible on the basis of predicting homochiral crystal structures.[14(c)]

Resolutions

Pasteur's discovery of the homochiral crystallization of conglomerate was followed by the results obtained by his student D. Gernez. No crystallization of a supersaturated solution of the Pasteur's (+)-salt seeded with a (–)-salt crystal was observed, whereas from a supersaturated (±)-salt solution 'seeded by a particle of (+)-salt, it yielded only (+)-crystals. A portion of the same liquid in contact of (–)-crystal produced a deposit of (–)-salt. Here then is a simple means for separating at will one or the other of the two (+)- and (–)-salts…' as he wrote to Pasteur in 1866.[30] A. Werner rediscovered the phenomenon as applied to his chiral complexes in 1914.[31] Such a procedure is called resolution by entrainment (G. Amiard, 1956) or preferential crystallization; it is used widely in industrial processes.[9] Commonly, to fulfil this procedure, an optically active seed is prepared specially. However, it follows directly from the homochiral crystallization of conglomerates discovered by Pasteur, it is possible to use as a seed either a random crystal or a single crystal of the specific sign of optical rotation taken from the totally racemic original mixture. How is it possible to make homochiral crystallization not preferential but exclusive? (±)-Tartaric acid itself is a true racemate; therefore, the conglomerate formation of the Pasteur's (±)-salt is determined by Na^+ and NH_4^+ ions, which we call conglomerators[14(a)] (the term is already accepted in the chemical literature[14(c)]). Such an algorithm is a clue to a puzzle. Indeed, this approach provides the efficient resolution of the Pasteur's salt, Werner's complexes and many other conglomerates.[14(a),20,24,32] A similar effect is reached by crystallization of conglomerates with deficiency of achiral solubilizers.[14(a),(d)]

The first examples of the conglomerate formation of racemic acid/racemic amine salts were found recently by G. Coquerel[33] and K. Saigo[28] groups, and in our and V. Schurig groups.[34] Thus, the simultaneous spontaneous resolution of both chiral acid and chiral amine can be carried out.[28,33] An interesting case was a noticeable enrichment upon crystallization from a gas phase by sublimation.[35] Recently, R. Tamura *et al*. disclosed a new unusual spontaneous resolution of pseudo-racemates (solid solutions), which was called preferential enrichment; unlike preferential crystallization, during the consequent crystallization, the mother liquor is enriched up to 100% *ee* but not the deposited crystals (up to 10% *ee*).[36] The absolute asymmetric synthesis can be regarded as an outcome of the homochiral crystallization discovered by Pasteur. When conglomerate crystallised under conditions of fast enantiomerization in a solution or melt, it would be converted completely into one enantiomer as a result of exhausting crystallization. This idea proposed by E. Havinga has received a large development effort.[20]

Resolution via *diastereomers*

This field has been developed as applied to alkaloids.[37] For example, (±)-pivalophenon cyanohydrine interacts with brucine in methanol to form a diastereomerically pure inclusion compound in a quantitative yield (the total conversion of *rac*-cyanohydrine into one enantiomer resulted from the base-catalysed enantiomerization followed by the insertion of only one enantiomer into the brucine lattice). Enantiomerically pure (+)-cyanohydrine was isolated in a quantitative yield.[38(a)] Similarly to other alkaloids, 2,2′-dihydroxy-1,1′-binaphtyl and its analogues were resolved.[38(b)] Then, F. Toda *et al*. synthesised new chiral reagents for resolution *via* inclusion, for example, TADDOLs.[38(c)] Using these reagents, preparative methods for resolving various chiral compounds were developed, and a technique for the separation of enantiomers by fractional distillation in the presence of a chiral host compound was proposed.[38(d),(e)] Note that the resolution of an important precursor (2-azabicyclo[2.2.2]hept-5-ene-3-one) in the synthesis of chiral drugs was more efficient with the use of the method by F. Toda[38(f)] instead of the preferential crystallization of the conglomerate.[39]

In classical resolution *via* diastereomers, a new method based on a combinatorial approach and called 'Dutch resolution' was developed.[40(a)] To search for the most suitable resolving reagent, the substrate is added with a whole family of the structure-similar reagents, and the first crystallising product indicates which reagent gives the less soluble derivative. The role of nucleation inhibition in a process was studied.[40(b)]

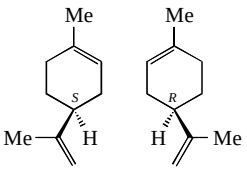
Effective complete transformation of the racemate of piperazine-2-carboxylic acid into a single enantiomer *via* diastereomers is accomplished by a continuous process of resolution–thermal epimerization–resolution.[40(c)] An alternative method for enantiomer preparation is the diastereoselective hydrogenation of pyrazine derivatives.[40(d)]

Enzymatic transformations, catalysis and biological properties of the enantiomers

The lion's share of the modern pharmaceutical production is based on the third Pasteur's method.[9,41] Note that enzymatic transformations can be carried out directly by microorganism cells with no isolation of any enzyme. Moreover, the dried cells of *Bacillus sp.* and *Rhodococcus sp*. do work in organic solvents; so, enantioselective alcoholysis of (±)-ethyl-3-hydroxybutyrate with butanol in hexane gives (*R*)-(–)- and (*S*)-(+)-enantiomers (97% and 100% *ee*, respectively) in quantitative yields.[42] The synthesis of Asp from fumaric acid and NH_3 dis-

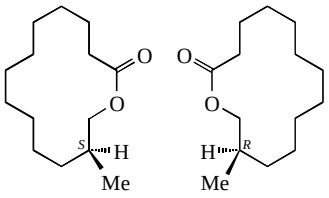
[††] According to a recognised opinion, organic chemistry has begun in 1828 when F. Wöhler synthesised urea by heating ammonium cyanate. More recently, this reaction was thoroughly re-investigated.[23]

Limonenes[47]



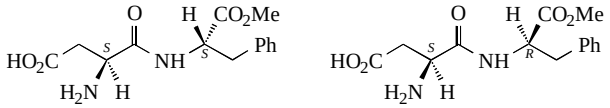
lemon odor — orange odor

12-Methyl-13-tridecanolides[48]

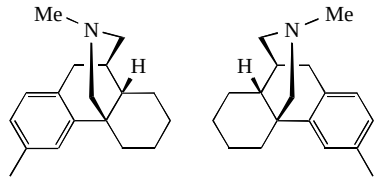


camphoraceous odor — sandal wood odor

Aspartame diastereomers[49]

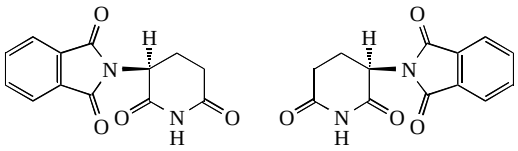


more than 100 times as sweet as sucrose — bitter



Levomethorphan — potent narcotic

Dextromethorphan[50] — common cough suppressant



(*S*)-Thalidomide — teratogen on mice and rats

(*R*)-Thalidomide[51] — non teratogenic

cussed in detail by Pasteur in his second lecture can be actually carried out either with heating or under the action of the enzyme aspartase to yield (*S*)-Asp.[43]

Asymmetric homogeneous and heterogeneous catalysis is progressing with the use of synthetic analogues of enzymes (the term chemzymes was introduced by E. J. Corey). In 2001, W. S. Knowles, R. Noyori and K. B. Sharpless became the the Nobel Prize winners.[44] Recently, a breakthrough occurred in the field of phase-transfer catalysis (intensely developed by M. Makosza[45]): new efficient chiral catalysts were created for this important and useful process.[46]

Pasteur was the first to explain a different tastes of Asn enantiomers by the dissymmetry of nerve tissues. In terms of modern pharmacy, the difference in biological effects between the enantiomers and the corresponding racemate is crucial for chiral switches.

The chiral drug thalidomide (commercially available as racemic compound) has a teratogenic effect due to its (*S*)-enantiomer, while its (*R*)-enantiomer was therapeutic. It has been withdrawn from the market but not from research. The data on the pharmacological differences of pure enantiomers are controversial; (*S*)-(–)-thalidomide is teratogenic in rats and mice,[51(*a*)] whereas both (*S*)-(–)- and (*R*)-(+)-enantiomers are teratogenic in rabbits,[51(*b*)] obviously due to their fast racemization (mean half-life of 4.7 h).[51(*b*)] Thus, resolution of thalidomide into enantiomers is no longer a panacea, any form of this drug is harmful in terms of teratoidism. Nevertheless, thalidomide was reinvented because of its usefulness in the treatment of leprosy, cancer, AIDS-related and other severe conditions.[51(*c*)]

Nerve gases have been studied by H. P. Benshop and P. A. De Jong,[52] the students of E. Havinga. It was shown that (*S*)-enantiomers of sarin, tabun, and VX are most toxic. In our laboratory, the structures of the simplest nerve gas MeO(Me)P(O)F[53(*a*)] and soman[53(*b*)] were investigated, and by comparison with the published data,[52] we found that the most toxic are soman diastereomers with the (*S*)-configuration of the phosphorous atom.

'No effective matters in the world could be done without preconceived ideas.'

Louis Pasteur, 1860

Fantasies

Many intuitive predictions by Pasteur come true. Even the fantasy on 'cosmic' forces conditioned that one dissymmetry is better than other seems to be confirmed. Like on earth, in Murchison meteorite (*S*)-amino acids predominate.[54] But why our left life is better, that still is a question. Perhaps, an answer may be found in chiral magnetism and light,[18(*c*),(*d*)] and parity-violating energy difference (PVED)[18(*f*)] (L. Keszthelyi, this issue, pp. 129–130 and R. M. Pagni, *et al*., this issue, pp. 131–132). The PVED effect on the Pasteur salt was minor[55(*a*)] whereas the effect on chiral crystals of $NaClO_3$ and $NaBrO_3$ was appreciable.[55(*b*),(*c*)] How to enhance this faint advantage? By autocatalysis, of course. K. Soai has found a remarkable autocatalytic reaction, which provides an amplification of chirality at low original enrichment[56(*a*)] or in the presence of chiral crystals such as quartz or $NaClO_3$.[56(*b*)] Recently, D. A. Singleton *et al.* have repeated it to achieve the replicative growth in enantiomeric excess from 3×10^{-5}% to 71%.[56(*c*)] Surprisingly, the authors got a similar result of autoenrichment with the same enantiomer in the absence of original enrichment, even after careful purification of the reagents, and under conditions warding off any impurities. This experiment demonstrates that an optical 'purity is a matter of degree' [see ref. 56(*c*)], and once arises the enantiomeric infection spreads like an epidemic.

The parabolic growth of nonenzymatic self-assembling model nucleotides,[57(*a*),(*b*)] lattice-controlled homochiral self-assembly and polymerization of amino acids at air–water interfaces,[57(*c*)] as well as autocatalytic self-replication of micelles[57(*d*)] were found. Probably, the day is near when the simplest mirror-life systems will be created!

Probability of the Pasteurian 'mirror life' would be cleared up by the forthcoming expeditions in solar system.[57(*e*)–(*g*)] Microbiological 'mirror life' is needed for the enzymatic synthesis of opposite enantiomers. J. Rebek, Jr. has synthesised chiral molecules capable of self-replicating and mutating.[57(*h*),(*i*)] The principle of their homochiral self-assembling reflects dipty[20] (2D) homochiral monad, yin-yang:

'Chemistry creates its own object. This creature power, similar to that of the arts, distinguishes it fundamentally from the natural and historical sciences.'

M. Berthelot, 1860

Homochirality in arts

Why the human fantasy penetrating anywhere has stopped suddenly in front of the doors of chirality? Some elements of chirality may be seen in Escher's metaphors[58(*a*)] and in dipty-chiral traceries of ancient and medieval decorations.[58(*b*)] Examples of 3D-homochirality in arts are given by J.-M. Lehn:[59(*a*)] a double

helix as found on the Cathedral of Ferrara (courtesy of F. Scandoba) and la Coupe du Roi rendered by the sculptor Max Bill. True homochiral pictures are frequently encountered in Egypt[59(*b*)] (for example, see a wonderful picture of homochiral Nefertari on the back cover).

I am grateful to Professor H. Kagan and Professor F. Toda for their assistance.

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