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BIOMOLECULAR HANDEDNESS

ORIGINS AND SIGNIFICANCE

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The chemical sciences developed a theory of molecular structure only after 1874, when Le Bel [1] and van't Hoff [2] independently proposed that the four valencies of the carbon atom are directed towards the vertices of an atom-centred tetrahedron. The new proposal gave precision and a predictive potential to the earlier idea of molecular dissymmetry, due to Pasteur (1848), referring to the overall left- or right-handed shape of the molecule. Pasteur's conception of dissymmetry [3] was based upon the general morphological principle of the crystallographer, Haüy [4], who postulated in 1809, from crystal cleavage observations, that a crystal and each constituent molecule are "images of each other" in overall shape.

MOLECULAR DISSYMMETRY

The extension of Haüy's morphological analogy to the physical and chemical properties of substances led to Mitscherlich's (1819) law of isomorphism [5], which linked a similarity of crystal shape to an equivalent stoichiometry in chemical composition, and to the connection made by Herschel [6] in 1822 between the morphological handedness of quartz crystals and the sign of the optical activity of the crystals. Quartz crystals divide into two enantiomorphous sets distinguished by the right- or the left-handed screw sequence of hemihedral facets which reduce the crystal symmetry from hexagonal to trigonal. Herschel found that all crystals of the left-handed morphological set are laevorotatory, while those of the right-handed set are dextrorotatory, producing a respective anticlockwise or clockwise rotation of the plane of polarized light propagated along the trigonal crystal axis. Herschel supposed that the particular morphological chirality of a quartz crystal and the sign of its optical activity had a common molecular basis, the supposition being developed and generalised by Fresnel in 1824. Fresnel [7] showed that optically-active substances have a circular birefringence, $(n_L - n_R)$, positive for dextrorotatory and negative for laevorotatory media, where n_L and n_R refer to the refractive indices for left- and right-circularly polarized light, respectively, and he proposed that the molecules of an optically-active medium have a left- or right-handed helical form or arrangement, like the envelope traced out by the oscillating vector of a circularly-polarised light wave.

The work of Herschel and Fresnel enabled Pasteur to resolve the apparent paradox, reported by Mitscherlich [8] in 1844, that the sodium ammonium salts of active (+)-tartaric acid and inactive racemic or paratartaric acid appear to be isomorphous and identical in all respects save optical activity. Repeating the crystallisation of the inactive racemic salt, Pasteur [3] obtained two sets of hemihedral crystals, related morphologically as non-superposable mirror-image forms, like the two sets of quartz crystals. One set proved to be truly isomorphous with the crystals of the corresponding natural (+)-tartrate and to have an identical specific optical rotation in solution, positive in sign. In addition to the enantiomorphous crystal facets, the other set possessed a specific optical rotation of the same magnitude but negative in sign. From Haüy's morphological principle, Pasteur inferred that the individual molecules of (+)- and (−)-tartaric acid are stereochemically dissymmetric, related as non-superposable mirror image forms, like the macroscopic crystals of the corresponding sodium ammonium salts.

Optically-active substances in Pasteur's time were confined to natural products and their derivatives. Laboratory syntheses of chiral compounds from achiral starting materials invariably produced racemic mixtures of enantiomers, Pasteur supposed, because chemists had not yet identified and employed the chiral forces of nature which operate in both the organic and the inorganic world [9]. The solar system as a whole is dissymmetric, Pasteur observed, for it is not superposable on its mirror image, and so spin and orbital rotational forces may provide a basis for chiral structures; or magnetism, since Faraday [10] had shown in 1846 that a magnetic field induces optical activity in glass and other isotropic transparent media. In his 1883 address to the Paris Chemical Society, Pasteur [9] described the several unsuccessful attempts he had made earlier to harness the chiral forces of nature.

CHIRAL SYNTHESIS

Pasteur's conjecture that chiral forces are inherent to the physical and organic world found few early supporters, and the work of Emil Fischer on the sugar series in the 1890s appeared to show that such forces are not needed to account for the homochirality of natural products. Fischer tested, and came to use as a guide [11, 12], van't Hoff's predictions [2] of the number and type of stereoisomers expected for a chain of n chiral carbon atoms, R-$(Cab)_n$ − R′, with a tetrahedral orientation of the four bonds to each carbon atom, both for R = R′ with n even and for R ≠ R′ for any integral value of n. Fischer himself supplied the expectation for

R = R′ with n odd [11]. On increasing the value of n in the step-wise ascent of the aldose sugar series through the cyanohydrin reaction, Fischer found the synthesis to be stereoselective, the yields of the two diastereomers produced from a given lower sugar being markedly unequal. The action of enzyme preparations proved to be stereospecific. Maltase and emulsin cleave only the α- and the β-methyl-D-glucoside, respectively, and both enzymes are without effect on either of the corresponding L-glucosides.

Such observations led Fischer to propose his stereochemical "key and lock" hypothesis, designed to provide "a simple solution to the enigma of natural asymmetric synthesis" [12]. Starting with a single enantiomer or even with an enantiomeric excess in a mixture of optical isomers, synthetic reactions lead inevitably to a dominant diastereomeric product favoured by the steric congruence of the reaction intermediates. Neither a *vis vitalis* nor Pasteur's physical chiral force of nature exter ıl to the organism are required to account for the predominance, characterised by Fischer, of the D-series of sugars and the L-series of α-amino acids in the homochiral biochemistry of living organisms. Chiral homogeneity is the precondition for an economic and efficient metabolic turnover and biosynthesis in stereochemical "key and lock" terms, like the universal adoption of right-handed nuts and bolts or screws in the engineering industry for efficiency and economy of operation.

CHIRAL FIELDS

The "key and lock" hypothesis left unexplained the origin of the initial prebiotic substance or enantiomeric excess, as Fischer himself appreciated [12]. One solution, still influential [13], relegated the initial choice to chance, regarding the particular selection of the D-sugars and the L-amino acids during the course of biochemical evolution to a "frozen accident", propagated by the "common ancestor effect". Another approach went back to Pasteur, re-examining the forces of nature which he had presumed to be dissymmetric. Pierre Curie showed in 1894 that while both an electric field and a magnetic field have a mirror plane of symmetry individually, these planes are eliminated in collinear combinations of the two fields [14]. There are two enantiomorphous chiral combinations, one in which the electric and the magnetic field are parallel, and the other where the component fields are antiparallel. If the electric and the magnetic field oscillate at the same frequency, the two chiral combinations represent right- and left-handed circularly polarized electromagnetic radiation. Curie's analysis rationalised the earlier surmise of Le Bel [1] that circularly polarized light provides a chiral force "which favours the formation of one of the dissymmetric isomers" in photochemical reactions, and it supported a model of the relationship between the handedness of a chiral molecule and its optical activity put forward by Drude [15].

Drude proposed that the interaction of a chiral molecule with the electromagnetic radiation field gives rise to a helical charge displacement in the molecule. Dependent upon the handedness of the molecular structure, the oscillatory charge displacement has a right-handed helical form in one optical isomer, and left-handed in the enantiomer, at a resonance radiation wavelength. The electric and the magnetic dipole moments induced in the molecule are parallel for the right-handed helical charge displacement, or antiparallel for the corresponding enantiomeric displacement, resulting in a respective positive or negative circular dichroism light absorption ($\Delta\varepsilon = \varepsilon_L - \varepsilon_R$) at the resonant light wavelength, and a corresponding circular birefringence (respective dextrorotation or laevorotation) at longer wavelengths in the transparent spectral region. Circular dichroism, the differential absorption of left- and right-circularly polarized light by chiral substances, was first observed in amethyst quartz crystals [16] and subsequently (1895) in solutions of copper(II) and chromium(III) (+)-tartrate by Cotton [17].

Le Bel's early surmise, strengthened by Drude's theory of optical activity, Curie's characterisation of chiral fields, and Cotton's discovery of circular dichroism in fluid phases, led Byk [18] to suggest in 1905 that biomolecular chiral homogeneity had a photochemical origin. It was assumed by Byk, and by a number of others over the following half-century [19], that there is a natural predominance of one of the two circularly polarized components of the solar radiation reaching the Earth's surface, generally the right-circular component. Recent measurements show that the solar radiation has indeed a circular polarization of up to 0.5% over the visible, near infrared and near ultraviolet regions at twilight, owing to multiple aerosol scattering [20, 21]. There is no net effect; however, the right-circular component in excess at sunrise being equal in magnitude but opposite in sign to the left-circular component in excess at sunset.

On a time and a space average, the electromagnetic and other classical chiral fields characterised by Curie are even-handed, and it is necessary to postulate a particular time or place for the origin of biomolecular chiral homogeneity through their agency. Thus a racemic pool of α-amino acids located on an east-facing slope, and so exposed preferentially to the right-circular excess of solar radiation at sunrise, over the whole quartz ultraviolet region before the development of an ozone layer, would be expected to undergo enantio-selective photolysis, leaving the L-isomer in excess, from reports of the asymmetric photolysis of racemic amino acids with circularly polarized radiation in the 200–230 nm region [22, 23].

PARITY AND ITS NON-CONSERVATION

The apparent even-handedness of the established forces of nature was generalised as the principle of the conservation of parity by Wigner [24] in 1927. All physical causes and the laws linking them to the effects produced, Wigner proposed, are invariant to space-inversion (the parity operation) or, what is equivalent, to mirror-plane reflection. For the following thirty years it was maintained that the principle of parity conservation applied not only to the classical gravitational and electromagnetic inter-

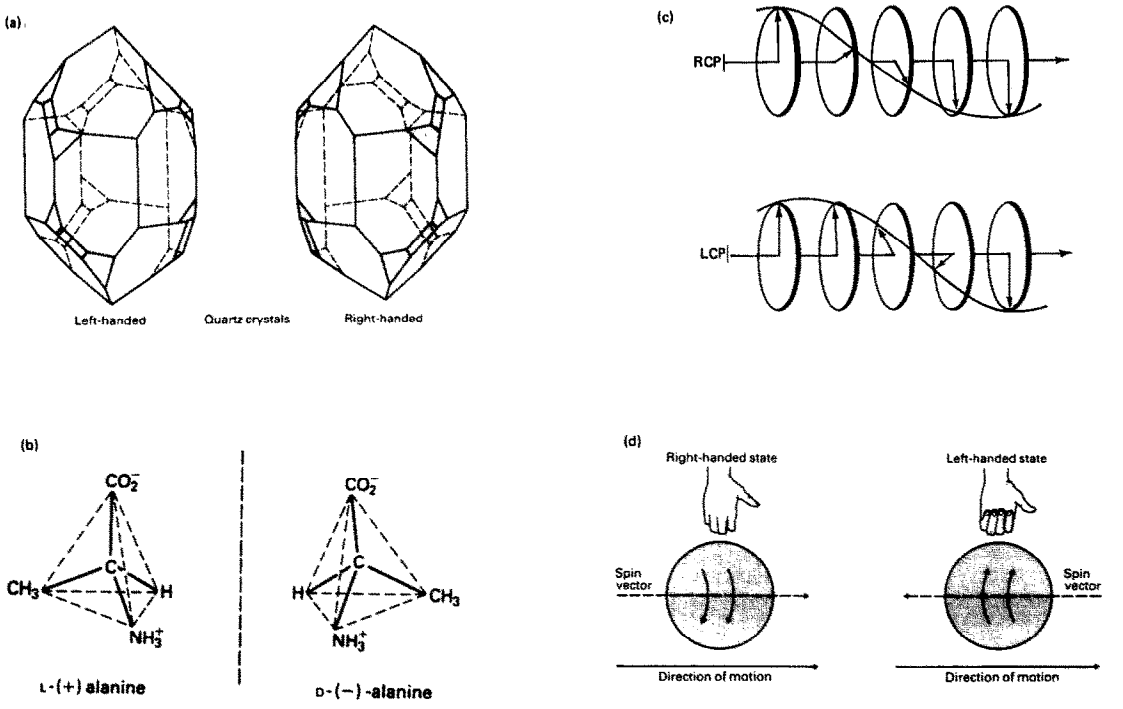

Fig. 1. Handed domains: (a) Enantiomorphous crystals; the minor facets of (−)- and (+)-quartz crystals follow a respective left-handed or right-handed screw sequence, viewed along the direction of the three-fold crystal symmetry axis. (b) Molecular enantiomers; the NH_3^+, CO_2^- and CH_3 groups follow a left-handed (anticlockwise) and a right-handed (clockwise) sequence in the L- and the D-enantiomers, respectively. (c) The chiral electromagnetic field of left (LCP) and right (RCP) circularly polarized radiation in which the transverse field vector rotates around the direction of propagation to trace out spatially an envelope of left-handed (LCP) and right-handed (RCP) helical form. (d) Fundamental particles; the left- or right-handedness follows from the respective antiparallel or parallel alignment of the spin axis and the direction of the translatory motion.

action but also to the new strong and weak nuclear interaction, mediating α- and β-radioactivity, respectively. The use of β-emitting radionucleides as beam sources for electron polarization and scattering studies (1928–30) gave results which, at least in retrospect, provided evidence for parity violation in the weak interaction [25]. But these results were set aside and were forgotten until the accumulation of other anomalies led Lee and Yang [26] to conclude in 1956 that parity is not conserved in the weak interaction.

The observation of the parity-violating effects predicted by Lee and Yang showed that the fundamental particles have an intrinsic handedness or helicity. In the β-decay of radionucleides, the electrons emitted are inherently left-handed, with their spin-axis preferentially orientated antiparallel to the direction of their linear momentum, while positrons emitted in β-decay are intrinsically right-handed, with a parallel alignment of spin-axis and momentum direction [27]. Although parity itself is not conserved in the weak interaction, the combination of parity (P) with charge-conjugation (C), the conversion of a particle into the corresponding antiparticle, e.g. the conversion of an electron into a positron, is conserved in good approximation (strictly, time-reversal (T) must be included to give the more exact principle of CPT conservation). According to the principle of CP conservation, the electron and the positron are CP mirror-image forms, and a chiral molecule composed of electrons and other particles, L-alanine, say, has a true CP mirror-image D-enantiomer, with equivalent properties, made up of positrons and other anti-particles in a counter-world of antimatter. But the natural enantiomer, i.e. D-alanine with the standard particle composition, has properties dependent upon the weak interaction which are inequivalent.

The first inequivalence investigated was the differential decomposition of the two enantiomers in a racemic mixture expected from β-irradiation, due either to the direct competitive radiolysis of the optical isomers by the β-electrons, or to the indirect differential photolysis arising from the left-circularly polarized braking radiation (Bremsstrahlung) produced as the β-electrons slow down from their initial relativistic velocities on emission in the β-decay [28]. As yet, no reproducible enantioselective reactions have been reported from such investigations, or from the use of spin-polarized electrons, positrons, or protons produced by particle accelerators [29, 30].

The expected effect is small. It is estimated that the enantiomeric excess [(L − D)/(L + D)] produced

prebiotically by the action of natural terrestrial β-radioactivity on racemic mixtures of organic substances has, at most, a 10^{-12} order of magnitude [31]. The effect is small because the handedness of a β-electron is substantial only at high energies ($>10^6$ eV) where the velocity of the electron approaches the speed of light. The handedness (helicity) of a β-electron and the circular polarization of the associated braking radiation are vanishingly small at the energies (2–5 eV) of the molecular valency electron changes involved in stereoselective chemical reactions.

THE ELECTROWEAK INTERACTION

The β-decay of radionucleides, involving charge changes, is dependent upon the weak charged current (WCC) mediated by the charged massive bosons, $W^{\pm}$, of the weak interaction, and WCC parity-violating effects vanish in the non-relativistic limit of low energies. During the 1960s, the electromagnetic and the weak nuclear interaction were unified into the electroweak interaction, dependent upon the weak neutral current (WNC) mediated by the massive neutral boson, Z^0, which was detected, along with its charged counterparts, $W^{\pm}$, at CERN in 1983 [32–34]. The parity-violating effects of the electroweak WNC interaction, in contrast to those of the WCC interaction, remain finite in the low-energy non-relativistic limit, and they have significance for even the normal or stationary electronic states of atoms and molecules.

From the electroweak viewpoint, a spherically-symmetric atom, composed of particles, is a chiral system with a CP enantiomer made up of the corresponding antiparticles, and a free atom is expected to exhibit optical activity. The optical activity, although small, increases as Z^6, where Z is the atomic number, the nuclear charge of the atom. Measurements of the optical rotation of heavy metal vapours, bismuth, lead, thallium and caesium, give an optical activity in agreement with the calculated sign and magnitude, which is smaller by some 10^{-4} than that typical of a chiral molecule [35, 36]. Since the natural enantiomers of a chiral molecule differ only in the spatial arrangement of the atoms they possess in common, the electroweak optical activity of the constituent atoms produces an optical molecular inequivalence, adding to the molecular optical activity of one enantiomer and subtracting from that of the other. Thus a minor enantioselection is expected in the photolysis of a racemate, even with radiation lacking a net polarization (equal numbers of left- and right-circularly polarized photons).

Similarly the electroweak interaction discriminates between binding energy of the corresponding electronic states, stationary or transitional, of the two mirror-image forms of a chiral molecule. A small electroweak energy increment, E_{ew}, is added to the binding energy of a given electronic state in one enantiomer and subtracts from that of the corresponding state in the other, giving an electroweak binding energy difference between the two optical isomers ($\Delta E_{ew} = 2|E_{ew}|$). The inclusion of the electroweak interaction in *ab initio* calculations of the ground state electronic binding energy of salient biomolecules indicates that the particular enantiomers selected during the course of biochemical evolution are, in fact, those which are preferentially stabilised relative to their mirror image forms by the WNC interaction.

The peptide unit of a L-polypeptide in either the regular α-helix or the pleated β-sheet conformation, and the parent L-α-amino acids with the conformation preferred in aqueous solution, are slightly more stable than their respective D-enantiomers in the ground state [37, 38]. Similarly, it turns out that the parent D-aldotriose, in the form of hydrated D-(+)-glyceraldehyde with its preferred solution conformation, is energetically stabilised relative to its L-enantiomer in the ground state [39], and so too is the biologically important furanose, D-ribose, in either of its preferred envelope conformations, C_2-endo or C_3-endo [40]. In all of these cases, the electroweak enantiomeric energy difference, ΔE_{ew}, amounts to no more than $\sim 10^{-14}$ J mol^{-1}, corresponding to an excess of about 10^6 molecules of the stabilised enantiomer per mol of racemate in thermodynamic equilibrium at Earth-surface temperature. The ratio of the enantiomeric energy difference to the thermal energy at 300 K ($\Delta E_{ew}/kT \sim 10^{-17}$), provides a measure of the enantiomeric energy advantage relative to ambient thermal fluctuations.

CHIRAL AMPLIFICATION

Although small, the electroweak interaction has provided a universal and uniform background bias throughout the history of the Earth, constant in time and equivalent in the two hemispheres, unlike the classical chiral fields with a handedness dependent upon particular times and places. To a degree, Pasteur's conjecture is now vindicated [41], although the chiral force of nature has not the magnitude he envisaged. Fischer's "key and lock" mechanism for stereochemical discrimination between alternative products in diastereomer formation could well account for the long-term development of biomolecular chiral homogeneity, given a sufficient initial enantiomeric excess, but it appears unlikely that the small enantiomeric advantage ratios provided by the electroweak interaction or selective β-radiolysis are adequate without some preliminary enhancement.

Two main types of chiral amplification have been proposed, involving either a sudden catastrophic change from racemic to homochiral chemical kinetics or a gradual cumulative evolution to chiral homogeneity. A general mechanism of the former type was first put forward by Frank [42] in 1953 and it has been developed in detail recently in order to assess the significance of the electroweak enantiomeric energy difference for chiral biomolecules [43]. The mechanism is Darwinian in conception with each enantiomer acting as "a catalyst for its own production and an anticatalyst for the production of its optical antimer" [42].

An open flow-reactor system is envisaged, such as a lake, fed by an input of achiral substrates, A and B, with a steady state maintained in the flow-reactor by an output of the enantiomers X_L and X_D

produced, together with inactive products, P. Each optical isomer autocatalyses its own production from the achiral substrates and inhibits the production of its enantiomer by combining with the latter irreversibly to form the inactive products. The dynamic steady state in the reactor remains stable so long as the input concentration of the substrates remains small, and the output of the chiral products is racemic, equimolecular in X_L and X_D, with an equal contribution from each of the two competing autocatalytic reaction processes. As the input concentration of the substrates increases, a critical point is reached where the steady state becomes metastable and hypersensitive to minor inequalities between the activation parameters, or between the stationary concentrations, of corresponding enantiomeric intermediates in the two homochiral reaction branches. Under the critical conditions producing metastability, the system switches to the chirally-homogeneous reaction branch favoured by the minor inequalities, unless the thermal fluctuations are large enough to damp out the transition, or to adventitiously reverse it to the disfavoured homochiral reaction channel.

In the original Frank mechanism [42], formulated before the discovery of parity non-conservation in the weak interaction, the activation parameters and stationary concentrations of corresponding enantiomeric intermediates in the two reaction sequences were taken to be equal, and the choice of the particular homochiral reaction branch adopted under the critical conditions of hypersensitive metastability was accordingly a matter of chance, with an equal probability for each of the two sequences. The particular handedness of biochemical chiral homogeneity, the L-amino acids and the D-sugars, thus appeared to be a "frozen accident", following the consolidation of the initial random choice by subsequent chemical elaboration of the open flow-reactor system from autocatalysis to membrane-enclosed self-replication.

The assumption that the concentrations of corresponding intermediates, and their activation parameters, in the two enantiomeric reaction branches are equal became untenable after the evaluation of the electroweak enantiomeric inequivalencies. A recent quantitative analysis of the autocatalysed competitive reaction sequences in the Frank mechanism shows that, at the critical point where racemic production becomes metastable, the choice of the particular homochiral reaction branch adopted becomes determinate if corresponding enantiomeric intermediates in the two branches differ in relative concentration by the excess, $[(\text{L} - \text{D})/(\text{L} + \text{D})] \geqslant 10^{-17}$, or, equivalently, differ in activation energy by ΔE, such that $(\Delta E/\text{kT}) \geqslant 10^{-17}$ [43]. The lower limit of the condition is satisfied by the enantiomeric excess due to the electroweak interaction at 300 K evaluated for the D-sugars studied [39, 40], the L-α-amino acids and the L-peptide moiety in the α-helix or the β-sheet conformation [37, 38]. A computer simulation of the open flow-reactor system, with typical rate constants for the elementary kinetic stages of the Frank mechanism, indicates that, at the lower limit of the selection condition, the energetically favoured enantiomeric series is selected with 98% probability if the passage through the critical metastable stage occupies some 10^4 years, during which the input concentration of the substrate increases by 10^{-3} to 10^{-2} moles in a reservoir of some 4×10^9 litre capacity, corresponding to a lake one kilometre in diameter and four metres deep [43].

Cumulative mechanisms for chiral amplification are more complementary than opposed to the catastrophic mechanisms. Preceded by a cumulative enhancement of the electroweak enantiomeric excess, the bifurcation catastrophe of the Frank mechanism, from racemic production to one of the two enantiomeric branches, is expected to require less restrictive conditions, a shorter time interval for the critical transition, a smaller flow-reactor volume, and more latitude in other variable factors.

An early and typical cumulative mechanism envisaged an enhancement of the enantiomeric excess or the differential stabilisation energy of a chiral monomer on condensation, the amplification being proportional to the degree of polymerisation [44]. The proportionality holds only if the polymer is chirally homogeneous. The polymerisation of the *N*-carboxy anhydride derivative of a near-racemic α-amino acid does not afford a chirally homogeneous product but, if the polymerisation is partial (~50%), the initial enantiomeric excess is enhanced by some 3–14% in the polymer formed, dependent upon the conditions and the particular amino acid. If the polymer produced is partly hydrolysed (~50%), an additional and comparable optical enrichment is found in the residual polymer, while the monomer from the hydrolysis, like the monomer remaining from the partial polymerisation, becomes optically depleted and closer to the racemic composition [45].

The condition of chiral homogeneity over the units of the aggregate as a whole is satisfied by an enantiomorphous crystal built up from a chiral unit cell, as in the case of quartz. The terrestrial distribution of quartz crystals, documented for a total of 17,738 crystals collected from a variety of locations, suggests a global bias with an enantiomeric excess of 1.4% of the morphologically left-handed (−)-quartz form, significant at the 1.9 standard deviation level [46]. For a unit cell of quartz with an electroweak advantage ratio, $(\Delta E_{ew}/\text{kT}) \sim 10^{-17}$, typical of chiral atomic assemblies of the lighter elements, the 1.4% enantiomeric excess of the (−)-enantiomorph corresponds, according to the cumulative chiral amplification mechanism, to an aggregate of some 10^{15} units cells, which are contained in a macroscopic single crystal with dimensions of ~0.1 mm along each main edge [37, 47].

The terrestrial enantiomeric excess of (−)-quartz has implications for the natural optical enrichment of organic biomolecules. Finely powdered (−)-quartz preferentially absorbs L-alanine from solutions of racemic alanine hydrochloride with a fractional enantiomeric excess of 1–20%, dependent upon the particular conditions [48]. The enantioselective adsorption, taken in conjunction with the 1.4% global mean fractional dominance of (−)-quartz crystals, gives L-alanine an enantiomeric excess, or an equivalent energy advantage at ambient temperature $(\Delta E/\text{kT})$ over its D-enantiomer, of $>10^{-4}$

for subsequent physical or chemical processes mediated by the crystal surface [47].

An enantiomeric excess of $\sim 10^{-4}$ provides a conceivable starting point for subsequent optical enrichment by sequences of partial polymerisation and incomplete polymer-hydrolysis. Equally an enantiomeric advantage ratio of $\sim 10^{-4}$ at ambient temperature allows a brief passage through the critical bifurcation transition from racemate to enantiomer production by the Frank mechanism, in a flow-reactor of modest capacity, and thus plausibly uniform and homogeneous in reactant composition and reaction rate throughout its volume. Given prebiotic seasonal variations comparable to those today, uniform reaction conditions, slowly changing over 10^4 years in a flow-reactor of 4×10^9 litre capacity, appear to be unrealistically restrictive, but such conditions are required at the 10^{-17} level for the enantiomeric excess derived directly from the electroweak interaction. Some preliminary enhancement of the electroweak enantiomeric excess appears to be quantitatively essential. However, the qualitative result that the excess evaluated favours both the D-sugar and the L-amino acid series, including the regular conformations of the L-polypeptides, has fundamental significance.

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