

# Optical activity and dissymmetry in living systems

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This brief review describes a characteristic property of living systems—dissymmetry. The progression of phenomena beginning with dissymmetry in the simple chiral molecules that make up living organisms and leading to the manifestation of dissymmetry in psychology is examined. The advantages contributed by dissymmetry in simple molecules to the more complex formations, which originate from and are composed of these molecules and which bring about organization in living systems, are indicated. The theory of chirodiastaltic interactions, as an agent of this organization, is examined. The possibility of initiating and maintaining dissymmetry in the form of chiral purity of matter with the participation of autocatalytic and nonequilibrium thermodynamic processes is analyzed. The current hypotheses that explain the emergence of dissymmetry during the evolution of life are reviewed. The fluctuation hypotheses and assumptions concerning the influence of weak constant factors are examined and the corresponding schemes for evolution are presented.

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## CONTENTS

1. Introduction .....	277
2. Manifestation of dissymmetry in living systems .....	277
3. Physical mechanism for optical activity .....	280
4. Interactions between chiral molecules .....	281
5. Advantages gained by living systems as a result of the chirality of their components .....	283
6. Possible paths for establishing optical purity .....	285
7. One-sidedness of metabolic processes in living systems .....	286
8. Possible reasons and mechanisms for the emergence of dissymmetry in living systems .....	287
References .....	291

*Asymmetry, rather than symmetry, can serve as a symbol of diversity and greatness of nature.*

*Ya. Kavabata*

*Who could imagine that God would turn out to be a weak left-hander?*  
*W. Pauli*

## 1. INTRODUCTION

If a physicist is asked what is the most general, purely physical, distinguishing feature of the diverse substances that make up living matter he, however strange it may seem, will only be able to give one answer, namely, optical activity, the property of matter to rotate the plane of polarization of transmitted light.

A mathematician, in answer to the same question, would say dissymmetry.<sup>1,2</sup> He would explain that those objects are said to be dissymmetrical which do not have a center or a plane of symmetry and can exist in two forms, right-handed and left-handed that can be superposed by the operation of mirror reflection.

A biologist will answer the question in greater detail: all the most important substances out of which living organisms are formed consist of dissymmetrical, or, as it is customarily said, chiral, molecules that can exist in two mirror-image forms. Furthermore, the substances that constitute the structural basis of living matter and that carry the basic vital functions are encountered in organisms in the biosphere only in one of these two forms and the maintenance of "optical purity," i. e., prohibition or elimination of the other form, is an important aspect of life processes.<sup>3-9</sup>

A consequence of the unequal number of molecules of the two indicated forms in a substance is the rotation of the plane of polarization of light by this substance. Thus, optical activity, which the physicist discovers in living matter, is an indicator of a particular dissymmetry. This dissymmetry, apparently, is related to

some fundamental properties of life processes and is an inherent property of living matter. In living systems, not only the simplest building blocks (molecules), but also all the more complicated structures including protein polymers have chiral symmetry. Furthermore, morphological dissymmetry is also characteristic of living organisms themselves and of their functions.

Such a clearly expressed inequality between left and right in living systems, not observed in the inorganic world (which was pointed out a long time ago by Pasteur and Curie), is to this day somewhat puzzling or, in any case, difficult to explain.

Thus, the very narrow and specific problem of the rotation of the plane of polarization of light by living matter is unexpectedly developing into an important and fundamental problem in biology, physics, and chemistry. Some experimental information from biology and its physical interpretation are presented below and an attempt is made to discover where does the advantage of chiral molecules as building blocks of living systems lie and to determine the mechanisms by which dissymmetry is established and maintained. As will be seen, analysis of these problems unavoidably leads to consideration of the fundamental problems of the origin of life. The problem of dissymmetry is now, apparently, transformed from a special chemical-biological problem into a general physical problem.<sup>10-16</sup>

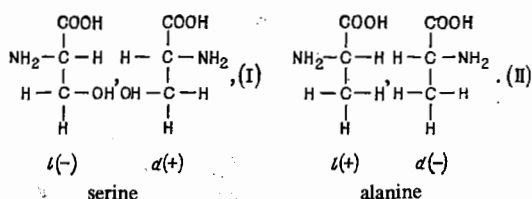
## 2. MANIFESTATION OF DISSYMMETRY IN LIVING SYSTEMS

Let us examine briefly some experimental information from biology that illustrates the overall situation

described above.

The basic elements out of which living matter is built up (constituting approximately 95 to 97% of living matter) are C, H, O, and N. The elements Ca, P, and S are less common and there are 3 to 4 other elements that are still less common, while the content of all the remaining elements is less than 0.01%. It is possible to identify fairly clearly a comparatively small number of classes of substances that comprise the basic, constitutional part of living organisms, including primarily the protoplasts (nuclei, cytoplasm) and consisting, for the most part, of the first four elements mentioned above in various combinations. These substances primarily include proteins, polypeptides, nucleic acids, lipids, and certain polysaccharides.<sup>17-19</sup>

The basic structural elements of proteins and polypeptides are  $\alpha$ -amino acids, more precisely, their acid residues, connected by peptide links. There exists a large number of amino acids,<sup>20-22</sup> of which only 20, in various combinations, enter into the composition of the diverse proteins. These include, for example, serine and alanine.<sup>1)</sup>



All the amino acids are present in all proteins only in the *l*-configuration.

Nucleosides [5 (6) types in all], the basic structural elements of the nucleic acids RNA and DNA, contain only the *d*-configuration of ribose sugar. The other most important sugars that enter into the composition of polysaccharides, glucose and fructose, are encountered only in the *d*-configuration, while the sugar rhamnose occurs only in the *l*-form. This list could be greatly increased.

Thus, there exists a certain set of primary substances that play a basic role in organisms and that have a particular configuration, which is the same for all living systems.

Dissymmetry in the basic substances involves, generally speaking, a definite dissymmetry in the basic products of nutrition,<sup>3,4,23</sup> predetermining their configuration. Thus, yeasts utilize only natural *d*-sugars, leaving the "unnatural" (it is better to say nonbiological or "not found in nature"); they do not grow in a medium consisting only of the latter.<sup>2)</sup> The transport proper-

<sup>1)</sup>The notation *d* and *l* denotes the conformation of the molecule, corresponding to right and left (or right-handed and left-handed isomer). This notation is conventional in stereochemistry. The (+) and (-) signs indicate the direction of rotation of the plane of polarization; this information is less important and less informative.

<sup>2)</sup>Some bacteria can nevertheless live on "nonbiological" nutrition although they grow much more slowly and are less viable. However, at the same time they do not alter the sign of the asymmetry of their substances nor the degree of asymmetry.

ties of the antipodes also differ greatly; biological membranes allow one of them to pass through and block the other.<sup>24</sup>

Substances that play a secondary role in an organism, those that have a metabolic function, metabolites, food supply,<sup>25</sup> and excretions, conform less strictly with the conservation of sign rule and can, depending on conditions, exist in both configurations or in the form of a mixture of the two configurations, a "racemate". For example, terpenes are such substances: in various plants only *d*-limonene is encountered in one group, *l*-limonene is encountered in other groups, and, finally, a mixture is encountered in a third group. Many bacteria, which utilize only one of the glucose antipodes [*d*(+)], separate out as a by-product one type, the left lactic acid; other bacteria separate out the right lactic acid; and, a third group separates out a mixture.<sup>3)</sup> Furthermore, within the organism, these by-products remain optically pure, while outside the organism they rapidly racemize. There are many such examples.

It may be stated that the loss of optical purity on leaving the sphere of influence of the basic life processes is generally characteristic of secondary substances. As will be seen further on, it may be assumed that their optical purity arises or is maintained under the influence of the basic substances or structures.

Here, it is necessary to make some stipulations. In some work, a strict distinction was made between "primary" substances, which have a mandatory asymmetry with particular sign (see, for example, Refs. 3 and 4) and "secondary" substances, for which a definite sign (and, occasionally, dissymmetry in general) is not mandatory. However, at the present time, it is not clear to what extent such a categoric separation is based on some kind of independent considerations.

On the other hand, it is also difficult to make a sharp distinction because during the past decade (see Ref. 26 and 27) it has been discovered that in a number of organisms some substances with the opposite sign are nevertheless encountered (for example, *d*-amino acids and *l*-sugars). The information at this point is still fragmentary and the frequency with which such substances are encountered is not clear, but, in these cases, it has always turned out that the role of *d*-amino acids and *l*-sugars differs from that of the primary substances and they are secondary substances.<sup>27</sup>

Without going further into the details of the biochemical aspects of this problem, the following results, which should not give rise to any doubts and which are basic to our subject, may be stated:

(a) in living systems, chiral molecules are preferred as starting, primary substances;

(b) substances, especially those that relate to the basic constitutional part of an organism, exist in or-

<sup>3)</sup>In many higher organisms, *d*-lactic acid is liberated when muscles are contracted, while the mixture *d*+*l* is liberated when glucose is consumed and processed.

ganisms as optically pure isomeric forms;

(c) for the more important substances, a single configuration with a particular sign, specific for each substance, is clearly preferred.

Dissymmetry in the simple starting molecules also leads to dissymmetry in the conformation<sup>4)</sup> of the following links in the hierarchy of biological structures:

amino acids → polypeptides → proteins,

simple sugars → polysaccharides,

mononucleosides → nucleotides → nucleic acids,

although the sign of the conformation does not have to coincide (see below) with the sign of the configuration of the starting molecules.

It is well-known that right-handed  $\alpha$ -helices are the predominant conformation of proteins. Various types of polysaccharides, such as cellulose in trees, consist of left-handed spiral-shaped formations. Nucleic acid chains are right-handed helices consisting of *l*-nucleotides; the helical structure, as is well-known, is also reflected in the secondary structure of RNA and DNA. Such vitally important pigments as chlorophyll, steroids (derivatives of cholesterol), and many others<sup>18-19,28,29,30</sup> have a definite sign for the secondary conformation. Left-handed polypeptide helices (consisting of *l*-amino acids), if they are formed, are much less durable than the right-handed forms.<sup>18,20,26,31</sup> Apparently, it may be asserted that asymmetrical conformations are, in general, characteristic of biopolymers in living organisms and, in addition, each conformation has a definite sign.

The dissymmetry described is also observed in the upper structural hierarchy, although somewhat less uniquely; there is some scatter.

It is well-known that in nature morphological dissymmetry is widespread, beginning<sup>5)</sup> with the spiral-shaped structure of bacteria colonies, left-handed helical vascula in plants, helically-curved sea shells and so on, and including the dissymmetry of the human body.<sup>2-4,32-35</sup>

However, there is no doubt that the connection with the signs of the basic substances is by no means direct here and, apparently, is not unique.

This can be illustrated with many examples. Thus, the aquatic plant duckweed is encountered in nature in right-handed and left-handed forms. It propagates both sexually (via seeds) and vegetatively (via shoots). In this case, the first method does not lead to an inheritance of the sign, while the second method definitely leads to an inheritance of the sign. In biological objects, the entire spectrum of occurrence of morphological antipodes is represented: from 1:1 (as for duckweed) to an almost complete preponderance of a single sign; the number of "morphologically racemic" forms,

however, is much less than the number of forms with a particular dissymmetry. The manifestation of dissymmetry is itself obscured. Thus, both right-handed and left-handed cones are encountered on a single pine tree, although approximately 70% of the cones are left-handed. The stems of bindweed curl only to the right, while the leaves on the stems are positioned both on the right and on the left sides of the spirals. The inheritance spectrum is also very broad, ranging from a complete absence of inheritance of the sign of the morphological structure to strict inheritance as a family characteristic.

In the latter case, rare specimens of the inverse structure are mutants, have distinguishing biological features (compare, for example, Ref. 36) and, which is important, often are less viable. Thus, the typical (right) form of the snail *Fruticicola lantzi* is more viable than the inverse form<sup>3,34</sup>; the right-handed form of the rhizopoda *Globorotalia truncatulinoides* resists low temperatures, while the left-handed form is thermophilic<sup>9)</sup>; *l*-beets contain more sugar than the *d*-specimens; *l*-potatoes grow better.

However, the work of Kizel<sup>36,37</sup> has shown that the structure of the constitutionally important substances examined above and the system for basal metabolism in all species have the same sign: individuals with right-handed and left-handed morphological structure use food with one sign and so on. In this manner, inversion of the sign of morphological dissymmetry arises not as a result of inversion in the base substances, but as a result of differences in some secondary or tertiary factors, which affect the intermediate stages in the structural hierarchy, i. e., some intermediate links in the long path for transmitting information about the structure of the primary substances into the system that directly controls the morphology. For this reason, it is natural that along this path, the signs can change according to definite rules (as in the transition from *l*-amino acids to the right-handed  $\alpha$ -helices of proteins) and a certain statistical scatter in the signs can occur. As yet, all these mechanisms have not been adequately studied.

Dissymmetry is also observed in the most diverse life functions, including psychology. Thus, sweet *d*-leucine or tyrosine are distinguished from the bitter *l*-isomers and many isomers are distinguished according to smell. Left-handed (-) chloromycetin (levomycetin) is an active antibiotic, in contrast to the inactive *d* (+) form. The compound *l*-phenylalanine causes serious psychic illness, in contrast to the harmless *d*-isomer.<sup>2,3,6,40</sup>

There are differences in the functioning of extremities, as well as differences in the functions of the left and right hemispheres of the human brain.

The effects of dissymmetry even enter into the sphere of psychology. We note, for example, that visual per-

<sup>4)</sup> The term "conformation" here denotes the shape of a polymer chain with a given chemical composition and structure: elongated strand, straight and curved spiral, ball, and so on.

<sup>5)</sup> The tobacco mosaic virus is, as a rule, a right-handed helix.

<sup>6)</sup> This distinction is used by geologists as an argument in favor of the existence of Atlantis,<sup>37</sup> since the geographic territories available to antipodes become sharply limited.

ception of Raphael's Madonna changes significantly on reflection in a mirror.<sup>41,42</sup>

From this cursory review, the profound role dissymmetry plays in biology, undoubtedly originating in some important internal mechanisms, is evident.

### 3. PHYSICAL MECHANISM FOR OPTICAL ACTIVITY

Optical activity is a particular manifestation of the gyrotropic properties of matter, which in their turn are a manifestation of spatial dispersion.<sup>43-46</sup> Spatial dispersion of electromagnetic excitations arises in an atomic-molecular system as a result of interactions between different parts of the system with the characteristic distances for these excitations (for example, the interaction range of particles and the distance over which particles or excitations are transported) being comparable to the wavelength in the medium, while the speed with which the interactions are transmitted is comparable to the speed at which the excitation propagates.

Spatial dispersion is in fact a consequence of the non-local nature of physical coupling in the system.

Thus, for example, the electric polarization in the field of a light wave in the presence of spatial dispersion depends not only on the field at a given point, but also on the field in a certain neighborhood of the point. This can be described by the expression

$$P(r) = \frac{1}{4\pi} \{ (\epsilon - 1) E(r) + \gamma [\nabla, E(r)] + \alpha [\nabla, [\nabla, E(r)]] + \dots \}. \quad (1)$$

The second term on the right side represents first-order spatial (gyrotropic) dispersion. As can be seen, in order for it to appear there must be a definite asymmetry, primarily an absence of a center of symmetry.

In this case, dissymmetry appears, therefore, as a condition under which these interactions are manifested in connection with the excitation. In isotropic media, gyrotropic phenomena are manifested as the rotation of the plane of polarization of light passing through the media. It is this effect that is referred to as optical activity, especially in chemistry and biology. The general theory of optical activity in molecular systems and its relationship to chemical structure are examined, for example, in Ref. 42-55; for optical activity in amino acids, see, for example, Refs. 56 and 57, and in proteins see Refs. 28 and 58.<sup>7)</sup>

Optical activity can be intrinsic to the entire molecule as a whole or localized in a more or less isolated functional group, referred to in this case as the "chromophore of optical activity". Gyrotropy in a substance is determined by the superposition of the contributions of the molecules which make up the substance, as well as by possible collective effects. With a disordered arrangement and orientation of molecules, only the first factor is significant. Analysis shows that in this

case only molecules that lack a center as well as a plane of symmetry,<sup>8)</sup> i. e., chiral molecules, which were mentioned above, contribute to the effect. If the system is ordered, then collective effects that are characteristic of media with spatial dispersion, such as excitons,<sup>43,45,59,60</sup> polaritons,<sup>43,61</sup> and solitons,<sup>62</sup> can arise and contribute to the effect.

Optical activity can arise in systems that consist of particles that are inactive in their free state, if they are situated in a chiral structure. In such systems, gyrotropy arises as a result of the indicated collective processes, special structure of conduction bands,<sup>60</sup> and so on, or it can be induced by the internal chiral field (see below).

Analysis of a great deal of material accumulated in crystal physics shows<sup>45</sup> that spiral-shaped formations (having a screw axis of symmetry) are the most characteristic structural motif of gyrotropic objects. This also relates to objects that consist of chiral molecules. In this case, optical activity is determined by the structure of the molecule as well as by the structure of the formation. It was indicated above that spiral-shaped structures are highly characteristic of biological polymers (for their optical activity, see Ref. 16, 28, 63-66). Many of the liquid crystalline substances that enter into the composition of living systems also have spiral-shaped structures. In large polymer systems, intramolecular or, more precisely, intrapolymer excitons and solitons are also observed.<sup>62,63</sup>

The potential barrier between *d*- and *l*-isomers for free molecules is symmetrical; its height and shape are primarily determined, as for internal rotations in general,<sup>67-69</sup> by the short-range repulsive forces that create spatial barriers. Since this barrier is usually low, the transitions *d*→*l* and *l*→*d* will to some extent occur as a result of thermal motion, especially at high temperatures. This circumstance is very important for what follows.

The transition from the pure isomer to the *d*+*l* mixture (or the association *dl*) is called racemization, and the substance that contains an equal quantity of *d*- and *l*-molecules is called a racemate (naturally, it does not rotate the plane of polarization). Of course, the rate of racemization depends on the external conditions, the temperature, and the state of aggregation. Many substances in the liquid phase racemize spontaneously without external actions. Naturally, the propensity for racemization depends on the details of the chemical structure and varies over a very wide range.

It is stated in the literature that the dissymmetry that gives rise to optical activity arises naturally at a definite stage in the complexity of the molecule. This is incorrect. It follows from the discussion above that optical activity arises in molecules that consist of not less than four atoms because a molecule can be non-planar (and, therefore, lack a plane of symmetry) only if it has more than three atoms. However, for the

<sup>7)</sup> See Ref. 30, page 307 for optical activity in nucleic acids and the same reference, page 352 for optical activity in polypeptides and proteins.

<sup>8)</sup> Strictly speaking, a four-fold rotation-inversion symmetry axis ( $\bar{4}$ ) should also be absent.

simplest chiral molecules (for example,  $H_2O_2$ ) racemization occurs so easily and rapidly that it is impossible to observe optical activity in these substances. In practice, all the molecules that are more or less stable with respect to racemization have 12 to 13 atoms (in particular, the naturally occurring amino acids, serine and alanine have 13 and 14 atoms, i. e., they are some of the simplest relatively stable molecules). There is a large number of substances in nature, for example, pigments and dyes, that are fairly complex but inactive. For this reason, the chirality of a molecule cannot be related to its complexity.

Let us note in passing that the simple separation into *d*- and *l*-forms is directly applicable only to the simple molecules with a single chromophore, for example, amino acids of the type (I) and (II).

For the details of chemical nomenclature see, for example, Refs. 70, 71. For large and complex molecules with several different, spatially separated, and weakly interacting chromophores (for example, proteins such as hemoglobin), it is difficult to make a classification according to *d*- and *l*-forms because the individual chromophores can have different *d*- or *l*-configurations and different absorption bands, and they can impart different signs of rotation in these bands. Nevertheless, in general, it is always possible to isolate out of a large number of possible isomers<sup>9</sup> a pair of mirror-symmetric chromophores. This conformation will play a basic role for protein-type macromolecules. Here, as indicated above, it is very often possible to identify a *d*- or *l*-helix. Below, unless otherwise stated, we will use the labels *d* and *l* and we will refer to the simplest "building blocks", for example, amino acids.

#### 4. INTERACTIONS BETWEEN CHIRAL MOLECULES

In order to understand the role of dissymmetry and the mechanism by which the chirality of the initially simple molecules affects the complicated formations that arise from them, it is necessary to understand the nature of intermolecular interactions.

Already at the time of Pasteur and Van Hoff it was known that the interaction between the chiral molecules *d*-*d* differs from that between the molecules *d*-*l*. It is well-known experimentally that the physical properties of pure *d*- and *l*-substances, in which the forces  $F_{dd}$  and  $F_{ll}$  are involved, are significantly different from from the properties of the racemates (forces  $F_{dl}$ ,  $F_{ld}$ ;  $i, j = d, l$ ).

The components of intermolecular forces of any origin that are different for pairs of chiral molecules with identical and different signs are called chirodiastaltic interactions.<sup>40</sup> It is evident that it is these particular components that are responsible for identifying and distinguishing left- and right-handed molecules. These components must depend especially strongly on the mu-

tual orientation of the molecules, which is what determines their decisive role in creating strictly defined "structures" out of chiral molecules in biological macromolecules and gives them the decisive role in the problem being discussed.

Let us first examine, following Ref. 40, the long-range static interactions between neutral molecules. Their field can be represented in the form of a multiple expansion. Analysis of symmetry properties shows that since each multipole component has, generally speaking, a higher symmetry than the chiral molecule, the chiral components can arise if the molecule contains not less than two asymmetrically placed multipoles. Thus, for example, for a molecule belonging to the symmetry group  $C_1$ , these can be a dipole and a quadrupole; for the symmetry group  $C_2$ , a combination of a quadrupole and an octupole is necessary; and, so on. In the case of complete disorder, when an average with respect to orientation is taken, the electrostatic chirodiastaltic components turn out to be negligibly small. However, in the limiting case of fixed position and orientation, the contribution can be large. A rough estimate for the particular case of antiparallel dipole moments and a distance of 5 Å shows that the combination *ii* must be more stable than the combination *ij* by approximately 80–100 cal/mol. The presence of a constant magnetic field can give a significantly smaller contribution, but again favoring the combination involving like molecules.

For comparatively large molecules, where the corresponding multipoles are usually spatially separated, the chirodiastaltic terms can, with favorable distances and orientations, increase by a factor of 10 to 15, which already exceeds by a factor of two the energy of thermal motion at 20° C.

With an ordered asymmetrical positioning of molecules (for example, in a spiral structure), the effect can also be noticeable when each molecule contains a single multipole, for example, a dipole (strongly polar groups  $NH_2, OH$ ). In this case, interactions will arise between spirals as well as between a spiral and an individual chiral molecule.

The contribution of dispersion interactions for molecules that do not have a constant moment in the ground state turns out to be of the order of 1–2 cal/mol (of the order of 0.1% of the total dispersion energy) favoring unlike pairs. Thus, polar chiral molecules give a significantly larger effect. It may be that it is for this reason that amino acids, which have a large dipole moment (for example, for  $\alpha$ -alanine ~13–19 D), are an appropriate "structural material" for a chiral structure.

For resonance interactions, the magnitude of the term being examined is very small, even in case of ordered orientation in crystals.<sup>72</sup>

For short-range repulsive forces, it is very difficult to make a calculation in general form because they depend especially strongly on the details of the configurations of the partners and their arrangement. From general considerations, it is clear that here the compo-

<sup>9</sup> Thus, cholic acid (11 chromophores) can have about 2000 isomers, of which, however, only one isomer with a definite symmetry is encountered in living organisms.

ment of interest to us will be greater than for long-range forces. In Ref. 40, on the basis of indirect considerations, the upper limit for the energy of chirodiastaltic interactions is estimated, in this case, to be of the order of 700–1000 cal/mol, i. e., this energy is very large. A large quantity of empirical material in modern stereochemistry (compare, for example, Refs. 68, 70, 71) likewise indicates that the short-range steric interactions arising as molecules approach each other and come into contact contain a large asymmetrical component.

With still greater justification it may be said that as yet there is no quantum mechanical theory for exchange forces, for hydrogen bonds,<sup>73,74</sup> and for the forces involved in chemical bonds.

Here, the same stipulation as above should be made:  $d-l$  interactions can only be discussed with respect to simple molecules. For macromolecules such as proteins, interactions with some other molecule will in many cases be determined not by the sign of the conformation of the protein as a whole, but by the "local" sign of the functional group that enter into direct contact.

Let us emphasize for the following that the contribution of chirodiastaltic interactions in various situations can vary over a very wide range, 2 to 3 orders of magnitude, and can become significantly greater or less than the thermal energy depending on the presence of a constant moment, positioning, multipolarity, and so on.

A physically similar phenomenon is the phenomenon of induced optical activity. This phenomenon consists of optical activity arising in a symmetrical achiral molecule  $A$  located near a chiral molecule  $X$  (within the force field of the latter). This effect is observed with purely van der Waals interactions as well as with associations of  $A$  and  $X$ , with the introduction of  $X$  into the substance  $A$ , with the dissolution of  $A$  in the substance  $X$ , and so on. A great deal of experimental material has been accumulated here (see, for example, Ref. 73) that agrees well with theory.<sup>74-80</sup> Induction is also manifested with chiral molecules, for example, protecting them from racemization in a chiral solvent.

It follows from the discussion above that "contamination" of an achiral, and especially a racemic, substance by an admixture of chiral molecules (or an excess of one of the antipodes) can make it optically active, shift the point of equilibrium of the antipodes, and so on. The influence of such impurities can begin at 0.1–0.5%,<sup>78</sup> and of an excess of the antipode at approximately 5% or less.<sup>79,80</sup> Induction phenomena, apparently, play an extremely important role in autocatalytic reactions (see below) and during crystalization.

All the interactions examined above have an electromagnetic character. If we start with the same assumption concerning intramolecular interactions, then from general considerations about the conservation of parity, the wave functions, the energy levels, and the transition probabilities in antipodes must be the same. Then, correspondingly, the force fields of the optical isomers

must have mirror symmetry. From this it follows that binary interactions of free molecules must satisfy the conditions

$$F_{ii} = F_{jj} \neq F_{ij} \quad (i, j = d, l). \quad (2)$$

In addition, in substances that form a racemic mixture or a racemic association, we must have respectively

$$F_{ii} \geq F_{ij} \quad (3)$$

or

$$F_{ii} \leq F_{ij}. \quad (4)$$

In all cases, the potential barrier between the isomers must be symmetrical, and the physico-chemical properties of the isomers must be identical. Indeed, up to the present time no difference has been discovered in these properties of the substances. In ideal, optically pure substances, consisting of a single antipode, we must have

$$F_{ii}^A = F_{jj}^A. \quad (5)$$

However, in real substances, as mentioned above, some quantity of the other antipode is always present. Then, in a concentrated solution or melt, say of the  $d$ -isomer, the forces that act on the observed  $d$ -molecules and on the impurity  $l$ -molecules will be different, especially if the interactions are not binary:

$$F_{dd}^d \neq F_{dl}^d, \quad F_d^d \neq F_l^d, \quad (6)$$

i. e., the barrier between the right- and left-handed forms will be asymmetrical (partially as a result of induction): if, for example  $\mathcal{E}_{dd} > \mathcal{E}_{dl}$ , then the transition  $l \rightarrow d$  will require less energy than the reverse transition. With increasing degree of racemization, the barrier will approach a symmetrical one.

Racemization will proceed more rapidly or more slowly, depending on the balance of the forces being examined; it often continues for minutes, but sometimes for days and years. However, only the racemic state with the greatest disorder and the highest entropy will be in thermodynamic equilibrium; at the same time, the 1:1 ratio of antipodes will be satisfied, of course, only statistically.

The relationships between the forces (2)–(6) and the corresponding energy balance determine all the characteristics of the physico-chemical processes in chiral substances. The chemical combination of optically active substances can form compounds of the type  $A_i B_i$  as well as  $A_i B_j$ , i. e., two pairs of so-called diastereoisomers (the properties of different pairs are different), with the sign of one of the partners not necessarily coinciding with the sign of the other. The most stable and probable conformation will be determined by the balance of chirodiastaltic forces, similar to those examined above. Thus, for example, it is known experimentally that polypeptide chains constructed from amino acids of a single sign are much stronger and longer than chains made of alternating ( $d-l-d-l-\dots$ ) isomers, while chains with an irregular sequence of isomers, in general, do not occur.<sup>18,20,81</sup>

Thus, due to the chirodiastaltic interactions, the



symmetry (sign) of the starting substances, in principle, predetermines the sign of the more complicated compounds of oligomers and polymers that are formed from them, and in addition, this symmetry does not necessarily have to be the same as for the starting substances. Here, the stipulation should be repeated: the degree of uniqueness at different stages of complexity can vary in accordance with the magnitude of the forces at these stages.

## 5. ADVANTAGES GAINED BY LIVING SYSTEMS AS A RESULT OF THE CHIRALITY OF THEIR COMPONENTS

At the present time in biophysics, the basic physical requirements imposed on substances that make up living systems and the conditions necessary for the emergence of these systems have been identified to some extent.<sup>8,18-19,28,82</sup> Let us examine, from the point of view of these requirements and on the basis of the considerations presented above, the physical meaning of the results of Sec. 2 and the potentialities for understanding these results.

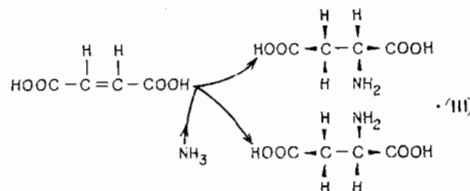
An appreciable manifestation of spatial dispersion implies the presence of closer and stronger interrelationships and of more intense and rapid interactions between the parts of the systems being examined, of intensive collective processes, in particular transport processes, and the development of excitons and soliton effects.<sup>10</sup> In biology, this indicates easier and more rapid intra- and intermolecular communication and transmission of information. It is known that the capability for a cooperative change of state is a biologically valuable property of a system. The advantages imparted to living systems by the presence of spatial dispersion in their components are, undoubtedly, great.<sup>18,28,82</sup> However, these considerations do not explain the reasons for preferring chirality, since it is known that second-order spatial dispersion [the third term on the right in (1)], which occurs in symmetrical systems, also leads to the appearance of the listed effects. And yet, for the particular case of proteins in a helical (i. e., chiral)  $\alpha$ -conformation, the contribution of exciton cooperative effects is much greater than in the achiral  $\beta$ -conformation.<sup>28</sup>

Nevertheless, in general, the special role of chirality must be sought not so much on the energetic and transport level, as on the level of order, coding, information, and self-instruction. It has already been pointed out above that on the atomic level the composition of living systems is very simple and uniform. The diversity is small even on the low-molecular level: 20 amino acids, 5 nucleosides, and so on.<sup>11</sup> The enormous

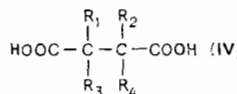
existing diversity of substances in living systems (for example, tens and hundreds of thousands of protein polymers, more than 800 enzymes) appears at a fairly high level in the structural hierarchy as a result of different combinations of the same "building blocks". The number of symbols in the genetic code likewise is small. It has already been noted long ago that from the chemical point of view the uniqueness of living matter consists not in its composition or in some special properties of the reactions, but in the ordered nature of structures and of reactions; the overall plan of the chemical structure of different living organisms has a great unity, as do the chemical reaction mechanisms. At the same time the expenditures of energy on biological ordering are relatively small.<sup>82</sup>

In this situation, an exceptional role in the structure of optimal living systems is played by the minimal nature of the information required, by the ease of identification and discrimination, by the simplification of coding or the "simplicity of the signature" (Quastler<sup>83</sup>), all these considerations simplifying the "instructing actions of information-carrying molecules" (Eigen<sup>84</sup>), by the one-sidedness of the course of chemical reactions, and by the uniqueness of their end results. It is evident that chiral molecules, both as a source and preserver of information as well as an object of identification, satisfy these requirements in the best possible way. Let us illustrate this with a simple example.

When the biologically important asparagine (amino acid) is formed from the symmetrical fumaric acid molecule, the formation of two antipodes of the former (nonplanar) molecule is possible and equally probable:



Here, the reagent can approach and effect a substitution both from the left and the right side of the substrate molecule, so that four equally probable variants in all are possible. At the same time in the completely asymmetrical molecule of the type



it is evident that, in the general case, there will be only one possibility for a substitution.

Since additional chirodiastaltic forces act between chiral molecules, they behave more uniquely than symmetrical molecules when approaching one another and in the presence of exchange interactions, short-range forces,<sup>12</sup> and chemical bonds. In stereochemistry, a large number of rules have been established for determining the path of reactions and the direction of attach-

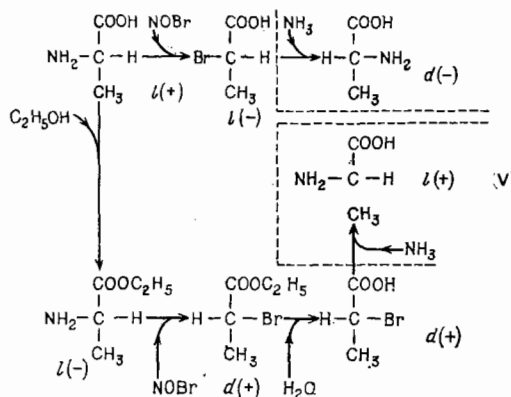
<sup>10</sup>The significant role of soliton effects in biological systems is pointed out in Ref. 62.

<sup>11</sup>At the same time, similar chemical structures are encountered in various components of living organisms. These include, for example, structures that are similar chemical types: ATP ("energy source"), NAD ("hydrogen carrier"), and nucleotides—information carrying components RNA and DNA.

<sup>12</sup>In particular, it is likely that chirodiastaltic forces dictate the arrangement of bases in proteins and nucleic acids.

ment for chiral molecules.<sup>71,86,87</sup> Here, we will present only one example.

Thus, the natural amino acid alanine can be transformed into bromopropionic acid according to two paths:



It is evident that in different links of the reaction the symmetry of the configuration is conserved or changes (the so-called Walden inversion), and in addition, the same reagent will or will not yield an inversion depending on the situation. But, in any case, the alternation of symmetry for the entire chain is uniquely determined by the initial choice of substances and their symmetry, i. e., ambiguity is reduced to a minimum.<sup>13)</sup> The possible continuations of the reaction are shown enclosed in the broken lines. It can be seen that depending on the chosen path a different symmetry is obtained for the end product. The direction of transport is also determined (the diffusion of *d*- and *l*-isomers in chiral media is different<sup>40)</sup>). Since, as was indicated above, the energy necessary for producing order in biological systems is relatively small, the comparatively weak chirodiastaltic forces can create the order or maintain it. On the other hand, since these forces can significantly change their magnitude in the case of a transition from the simpler formations to more complicated ones, at different stages of complication ranging from small molecules to biological structures, the degree of uniqueness can vary. We can speculate that it is this particular circumstance that leads to the scatter in the nature of the morphological dissymmetry and its inheritance that was noted above.<sup>14)</sup>

It is assumed that the considerations presented above explain qualitatively the preference for chiral molecules for the structure of the functioning of living organisms,<sup>90b</sup> then it is evident that the advantages of chirality can be realized only under conditions of optical purity (the presence of molecules with only one type of symmetry), which reduce by a factor of two the required amount of information. A long time ago, Kuhn<sup>91</sup> expressed the idea that the one-sidedness of biochemical reactions is a consequence of this purity. He also made the statement that optical purity in biological systems is based on a few "stereo-independent," basic sub-

stances, i. e., that the substances that make up these systems can be divided, depending on their role in the organism, into "driving" (stereo-independent) and "stereo-dependent" substances, the symmetry of which is dictated by the former and is lost on leaving the sphere of influence of the driving type. Driving substances are the carriers of micromolecular information as well as the macromolecular information that follows from it and that drives and instructs the behavior of the system.

Apart from this, optical purity also provides other advantages:

(a) great strength in the structure of polymers, as mentioned above; in addition, the amount of information for constructing the chain with alternating symmetry would be twice as great;

(b) in a symmetry-alternating chain, cooperative, primarily exciton, phenomena would be practically impossible, especially with an irregular sequence;

(c) a rapid reaction rate; indeed, if the racemic substance *dl* reacts with a racemic substance *DL*, two reactions will occur (say, *d+D* and *l+L*), and, according to the law of mass action, the rate will be four times slower than the rate of reaction of two pure antipodes; in comparison with enzymatic reactions (see below), the rate would be lower by a factor of 10 to 20; this relates both to the rate of growth of polymer chains (the  $\alpha$ -helical polypeptide structures form much more rapidly than the achiral  $\beta$ -forms<sup>26,31)</sup> and to the replication rate of proteins and the rate at which food is utilized (those that are more rapidly assimilated survive more easily<sup>92,93)</sup>;

(d) according to Ref. 94, optical purity of RNA-type formations (more precisely, the fact that they are made up of links with identical symmetry) must provide for their chemical stability relative to such destructive reactions as hydrolysis, which is often encountered under natural conditions.

All the enumerated factors, apparently, lead to a high probability for homeostasis, i. e., stability of internal processes of the medium relative to external actions and their intensification, in particular, for example, by a more rapid response to external action and a more intense exchange with the surrounding medium.

These properties, apparently, impart to chiral molecules and optically pure substances a definite "selective value"<sup>15)</sup> and make them more capable of creating the elements of self-organization, i. e., organisms that consist of such substances have an advantage in natural selection. Here, it is appropriate to mention one of the overall positions of Eigen applicable to this particular problem<sup>94,96</sup>: "No information can be extracted from

<sup>13)</sup> This is especially clearly seen in modern maps of metabolic paths in organisms.<sup>88,89</sup>

<sup>14)</sup> See Ref. 90a for stereospecific details of the genetic code.

<sup>15)</sup> The terms "selective value" and "evolutionary adaptability" applied to individual amino acids or nucleosides and so on are, of course, completely arbitrary: this value, in the full sense of the word, arises at the higher levels of the structural hierarchy. See Ref. 95 for "evolutionary adaptability" of biological macromolecules.



degenerate (in our case racemic—V.K.) carriers of information.”

As already stated, only racemic states, which have the lowest order and highest entropy, can be in thermodynamic equilibrium.<sup>16</sup> It is clear from general considerations that some kind of factors must maintain a highly ordered and cooperative system far from equilibrium. This also pertains to maintaining optical purity.

## 6. POSSIBLE PATHS FOR ESTABLISHING OPTICAL PURITY

Biological systems are intrinsically open thermodynamic systems. The presence of active exchange with the surrounding environment, exchange of energy and matter, and “through-put through the system”, are some of the important properties of such systems or “dissipative structures”,<sup>84,91,96</sup> in which the thermodynamic processes are irreversible and nonlinear.

The thermodynamics of nonequilibrium open structures<sup>97-103</sup> indicates the possibility for the existence of stationary nonequilibrium states, gives criteria for their dynamic stability and leads to the existence of a definite threshold for the occurrence of unstable states. Beyond the threshold for stability of a stationary equilibrium state, fluctuations increase significantly, both with respect to amplitude as well as distribution in time and space. They attain macroscopic dimensions, the system becomes unstable, and, subsequently, evolves toward a new, nonequilibrium, but stationary, state. In the latter state, the entropy of the system is not maximum and the system shows a definite order and cooperative characteristics.<sup>84,96-100</sup> Deferring to the cited references for details, we note the importance, for our purposes, of the fact that in similar types of chemical reaction processes no less than two stationary states, usually symmetric with respect to the composition of components relative to the thermodynamic equilibrium composition, are possible. In this case, there can be spatial separation of the components.

We will examine only a few studies that deal specially with the mathematical analysis of the problem concerning the relationship of antipodes in living systems.

In Ref. 104, using the methods of systems analysis it is shown that a system consisting of chiral molecules has in a closed state only a single stationary state, corresponding to equilibrium with respect to the isomers, i. e., a racemic state. In the presence of exchange with the surrounding environment (“through-put through the system”), two states, favoring one of the isomers, but symmetric with respect to the racemic state, will exist. In this case, the states separate further and further in the direction of optical purity as

the exchange increases. These two states appear instead of a single equilibrium state after the exchange flow reaches a certain threshold value, corresponding to the results obtained by Prigogine. Above this threshold value fluctuations can no longer return the system to the equilibrium racemic state.<sup>105</sup>

In Ref. 105, biological factors were also introduced into the analysis: the probability for capturing definite territories, the possibility for migration of populations, fixed or migratory (for example, on land and in the ocean), and so on. The results agree, in general, with those stated above: either the state with an identical concentration of right and left organisms  $C_1 = C_d$ , or the state with  $C_d = 0$  or  $C_1 = 0$ , is possible. Thus, states with optically pure isomers turn out to be possible and are stable, and in the presence of strong exchange with the surrounding environment, they are the only possible states.

In Ref. 106, the nonlinear kinetic equations, including also possible differences in the diffusion of antipodes and the racemate, are analyzed using the same methods. The same results are obtained: a small, initial inequality in the concentration of antipodes or a large fluctuation can lead to a large increase in the population of the one symmetry type and to suppression or extinction of the other type in large noncommunicating territories. Equality in antipode systems can be maintained only in the case of prolonged existence under the low-probability conditions of complete initial equality of antipodes or absence of fluctuations. In Ref. 107, a similar nonlinear problem with diffusion was analyzed. It was demonstrated that even in the absence of fluctuations the nonlinearity of the kinetic processes can increase the population of either symmetry. Here, it is appropriate to mention a result obtained by Eigen, namely, that selection and evolution cannot occur in equilibrium systems; this result, in particular, relates to racemic systems (in equilibrium with respect to composition).

As an example of macroscopic fluctuations that lead to a separation of antipodes, let us examine the well-studied phenomenon of spontaneous crystallization (the processes of replication of large molecules have a great similarity with crystallization phenomena).

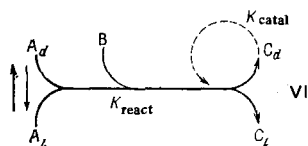
In any racemic melt in which  $F_{ii} > F_{ij}$ , there will be a tendency for growth of  $ii$  groupings, arising as a result of local fluctuations in the concentration of antipodes. Such a fluctuation will become a center which will attract the  $i$ th antipode and which will stimulate the transition  $j \rightarrow i$ , which will be energetically favorable in its vicinity (here, the barrier will be asymmetrical; see above). If the melt is supercooled (i. e., there is an outflow of heat), then the fluctuations in this unstable open state will grow to macroscopic dimensions becoming centers of crystallization and crystals of pure antipodes will precipitate out of the melt. It should be kept in mind that the process of nuclei formation is slow in comparison with the rate of growth of crystals, and for this reason, a relatively small fluctuation during the formation of nuclei can grow into a large fluctuation in crystallization, and sufficiently

<sup>16</sup> An elementary calculation shows<sup>82</sup> that with the transition from a pure antipode to a racemic mixture there is a gain in energy of the order of 1.38 kcal/mol ( $R \ln 2$ ), while the transition from the racemate in an optically pure state requires about 400 cal/mol.

large, so that the system will not return to the equilibrium racemic state. Due to chirodiastaltic forces and induction, the formed crystals will grow,<sup>17</sup> maintaining their purity. In this manner, a unique autocatalytic process occurs here. Such a phenomenon has been repeatedly observed<sup>9,80,109-113</sup> and a large number of organic substances are known that yield optically pure crystals of eutectics.<sup>114</sup> Naturally these phenomena are also observed during crystallization from solutions.

The influence of fluctuations will become stronger as crystallization accelerates, i. e., with departure from equilibrium conditions. This is demonstrated, in particular, in Ref. 111-113.<sup>18</sup> Of course, processes such as this could also have occurred repeatedly with biologically important substances and protobiological molecules in nature: with the drying out of ponds, during the cold seasons, and so on. In the case of crystallization from chiral solvent, due to induction, there can be a very significant overbalance of one of the antipodes, up to tens of percent.

A second example, which is more important from the point of view of biology, are the autocatalytic reactions examined by Calvin.<sup>115</sup> Such reactions can lead to growth in fluctuations up to macroscopic dimensions. Let us consider an example.



Let the substance A (chiral molecules), reacting with the substance B (achiral molecules), yield the substance C, the molecules of which are chiral. Under the usual conditions, as stated above, such reactions lead to the formation of the racemate C.

However, if the molecules C have some catalytic influence, due to chirodiastaltic interactions or chemical properties, the formation of the first molecule, say, accidentally a right-handed molecule  $C_d$ , will subsequently catalyze the formation of the substance  $C_d$ , especially if the rate constants satisfy  $K_{\text{react}} \ll K_{\text{catal}}$ . Calvin and his co-workers gave a number of examples of such reactions; examples of especially active biochemical reactions of this type are given in Refs. 107, 116, and 117. The mechanism for such catalytic action is probably, to a significant degree, also determined by the induction phenomenon described above: the formed molecule C can induce activity in the achiral molecule B, induce activity in A or inhibit its racemization (or the racemization of C) in the case that it is a chiral molecule.

Examples have also been presented of asymmetrical reactions, which proceed in the solid phase and which

are, in essence, autocatalytic: the role of an asymmetrical agent—catalyst (inhibiting racemization) is played by the internal chiral field of a crystal undergoing a transformation.<sup>118</sup>

Apparently an accidental fluctuation can, as a result of autocatalytic processes caused by chirodiastaltic forces, grow into a macroscopic formation in many ways. Naturally, the examples presented are far removed from the processes of self-instruction and self-organization of biological molecules and represent, of course, only a primitive prototype of such processes at a low-molecular level. The discussion above illustrates the general statement: "The presence of catalytic functions together with a feedback mechanism gives the system the capability of autocatalytic growth and represents a prerequisite for self-organization" (Eigen).

## 7. ONE-SIDEDNESS OF METABOLIC PROCESSES IN LIVING SYSTEMS

The exchange flux that maintains the stability of biological systems consists, as already stated, of a flow of energy and matter, occurring as a result of the chemical reactions involved in metabolism.

Chiral molecules can be formed in chemical reactions both from chiral and from symmetrical molecules. In the first case, if the starting molecule is one of the antipodes, then the substance formed will in general be optically active and have a particular sign. If the starting material is a racemate, then two parallel, equally probable, reactions will occur with *d*- and *l*-isomers and the substance formed will be inactive (i. e., a racemate). In the second case, on the strength of and within the framework of the initial considerations, the formation of both antipodes is equally probable and the substance formed will likewise be inactive. The reactions (I) and (III) are examples.

As a result, for synthesis of an active substance from an inactive starting product (with symmetrical molecules) or from a starting racemate, the action of some asymmetrical agent is necessary.<sup>19</sup> This action can be two-fold: (1) synthesis in the presence of an asymmetrical agent ("asymmetrical synthesis")<sup>71,119,120</sup> which could consist of chiral catalyzer, an optically active solvent, circularly polarized light, an impurity compound in an optically active substance,<sup>123</sup> and so on; and, (2) synthesis of a racemate with its subsequent decomposition ("asymmetrical decomposition") again by some asymmetrical action, chiral reagent, and so on. Analysis of the chemical kinetics of such processes shows that the first path always yields a higher rate and a greater optical purity than the second path.

At the present time, as a rule, reactions that proceed under the influence of a chiral catalyzer, an enzyme<sup>20</sup> that is present in the organism, play a role in

<sup>17</sup>The details of the process are analyzed in Ref. 108.

<sup>18</sup>However, the magnitudes of the fluctuations are nevertheless finite. For example, in natural quartz deposits, a statistically equal quantity of right and left antipodes is always found, even though individual crystals can attain tens of kilograms (only optically pure crystals occur).

<sup>19</sup>It is even practically impossible to distinguish separately existing antipodes using chemical methods without any indicator of dissymmetry. In biological systems, chiral molecules have the function of recognition, as mentioned above.

<sup>20</sup>See Refs. 16, 28, 121, and 122 for the physical properties of enzymes.

the processes occurring in living system. In this case, each enzyme "controls" its own reaction and acts only on a substance with a particular symmetry; such enzyme action is the result of precise steric organization of the "chiral" structure of the enzyme applicable to the "instructing" reaction in virtue of the chirodiastaltic interactions and inductive influence. For example, we point out the fact that the reaction (III) in the presence of the enzyme aspartase yields almost pure *l*-aspartic acid.

If, under laboratory conditions, the use of an asymmetrical agent such as circularly-polarized light, a gyrotropic mineral, or an active solvent, yields an optically purity of the order of several percent, then enzymes in living systems yield an optical purity approximately 100%. We emphasize here as well that, for racemic substances, it would be necessary to have twice as many enzymes.

However, enzymatic synthesis reactions, even under the best conditions, cannot by themselves provide a purity of 100%. As is well-known, a catalyzer does not displace the equilibrium point of a reaction; it only changes the ratio of the reaction rates for forming one or the other antipode (in addition, this ratio can attain values of 100:1 and 1000:1). For this reason, in catalytic reactions, the ratio of the quantity of antipodes will increase, reach a maximum, and then will asymptotically drop to 1, although very slowly, if the system is closed and reaches thermodynamic equilibrium. In open biological systems, if the reaction terminates near the maximum, for example as a result of the removal of some component from its sphere of influence, then it can yield a greater purity (we note that the time to establish diffusive equilibrium in a cell is usually comparable to the time for attaining a maximum ratio). However, no catalyst can yield a purity of 100%.

Thus, in addition to asymmetric synthesis, mechanisms are required for removing antipodes that are not needed and products of unavoidable (although perhaps insignificant) racemization. Such mechanisms are actually known in biochemistry.<sup>3,4,26,27,91</sup> From the foregoing it is clear that we have in mind not only (and, perhaps, even not largely) the preference for optical purity, but also the presence in living systems of a whole system of substances and processes that maintain optical purity in the organism, specifically by continuous metabolism, elimination, and acquisition of new substances from the outside. The development of such a system in itself indicates the importance of optical purity to living organisms.

## 8. POSSIBLE REASONS AND MECHANISMS FOR THE EMERGENCE OF DISSYMMETRY IN LIVING SYSTEMS

Let us summarize the results. We point out from a purely physical point of view the advantages gained by living systems as a result of chirality and optical purity. Chirality of primary molecules (amino acids, sugars, nucleosides) of definite symmetry leads to chirality in biopolymers of a definite symmetry. The

mechanism for such a relationship, as well as the advantage of chiral polymers can, in principle, be understood in terms of the considerations presented above. Dissymmetry in biopolymers, apparently, also leads to dissymmetry in living systems. The mechanisms involved in this relationship at the present level of understanding cannot be completely traced, but the importance of their existence, at least in principle, can be understood. However, two of the most important questions concerning the "starting" structures have yet to be answered.

At the present time, it has been demonstrated sufficiently convincingly that such substances, as, for example, amino acids, could have been synthesized under natural conditions from the simplest molecules: HCHO, HCN, NH<sub>4</sub>, CHO<sub>2</sub>, and so on. Apparently, the bases for RNA and DNA, for example adenine and guanine, can also be synthesized from the same molecules (NH<sub>4</sub>CN and so on).<sup>8,9,15,83,87,115,124-132</sup> However, all of the simplest molecules indicated are achiral, and for this reason, under ordinary conditions the formations of both antipodes is equally probable; rademization of an optically pure substance, even if it appears in excess, is very likely. For this reason, obtaining (and maintaining) optical purity requires an asymmetrical agent. The first question follows from the foregoing: what kind of agent led to dissymmetry in the formation of the first biologically important chiral molecules, i. e., what agent created a sufficiently great starting imbalance of such molecules with one type of symmetry?

Further, all the considerations presented above, based on quantum mechanics, thermodynamics, and the theory of electromagnetic interactions, assume that both symmetry types are equally probable. What caused the preference for one particular symmetry in the entire biosphere? This second question can also be stated as follows: at what stage in evolution did the presence of a definite symmetry type become an advantage for living systems?

Evidently, these two questions are one of the most important aspects of the problem of finding a physical mechanism for the origin of life.

Prebiological evolution has been examined in many studies (see, for example, Ref. 8, 15, 126-128, 133). We will introduce only those assumptions that are relevant for the questions stated here.

The first group of assumptions relates the appearance of dissymmetry to accidental processes: an accidental "choice" of symmetry type during the emergence of living systems.

The scheme of evolution is usually presented in the following form<sup>115-133</sup>:

1. molecular evolution: formation of the simplest molecules (NH<sub>3</sub>, H<sub>2</sub>O, CH<sub>4</sub>, CH<sub>2</sub>O, CO<sub>2</sub>, and so on) approximately 5 · 10<sup>9</sup> years ago;
2. chemical evolution: formation of complex molecules (amino acids, carbohydrates, simple polymers);
3. protobiological evolution: protobiological mole-

cules (proteinoids,<sup>134</sup> proteins, enzymes, and so on);<sup>21)</sup>

4. beginning of life: substances with weak signs of life (probiotics), the first, simplest living systems (archeobionts,<sup>22)</sup> blue-green algae) approximately 4–3.2 · 10<sup>9</sup> years ago;

5. biological evolution: differentiation of living systems including man.

Here, two types of hypotheses are stated. According to the first, the symmetry was chosen during the second and third stages as a result of the growth of fluctuations, by the mechanisms examined above, to macroscopic dimensions. The life that subsequently arose was chirally and optically pure from the very beginning. Following some conclusions reached by Kuhn<sup>136</sup> the following mechanisms can be considered, but only as a primitive illustration.

Let a segment of the RNA molecule consisting of 20 bases appear. Polymer formations of this size are realistic; they are even encountered in nonliving matter and are justified by energy estimates.<sup>137,138</sup> If all the possible, purely accidental, variations are considered for the inclusion of *d*- and *l*-ribose molecules into the nucleosides, then one out of 10<sup>8</sup> such segments may be expected to have all ribose molecules of the same symmetry, say, the *d*-symmetry. This formation will have the greatest strength (as a structure made up of elements of a single symmetry type; see above). For this reason, cooperative effects will be more strongly developed in such a structure. This will make the structure most stable with respect to external conditions (for example, destruction due to hydrolysis), i. e., most able to survive in the conventional sense of this term. Having survived, it can become a "coding matrix" (again, conventionally) for subsequent more complicated formations (the mechanism for this is examined in Ref. 136 and, in the final analysis, reduces to chirodiastaltic interactions). In other words, the "*d*-link" would have a "selective value" in Eigen's sense. It should be kept in mind that, for example, for  $F_{dd} > F_{dl}$  (which may be expected for ribose), the probability for the formation of groupings such as *dd* and *ddd*, can be expected to be greater than for groupings such as *ld* and *dld*, while the probability for attachment of, say, *dld* to the initial link of another *d* or *l* molecule would be different, i. e., the polymer nucleus that arises will stimulate a particular symmetry for the "continuation." For this reason, the expectation of a "*d*-segment" or an "*l*-segment" will be greater than that stated above.

However, the transition to contemporary biological systems requires additional, qualitatively new factors. The quantity of information contained in the link being examined is 20 bits, while the formation of an RNA molecule requires 150–200 bits; the formation of a gene or protein requires 2,500 bits; a virus requires

10<sup>5</sup> bits.<sup>90b,139</sup>

For this reason, there must be an intermediate link, "prebiological" or "proto-Darwinian", between the primitive chemical evolution under consideration and the protobiological evolution.<sup>139</sup> Here, different assumptions have been made, for example, concerning the fact that the initial genetic code was more primitive.<sup>140</sup> For other assumptions see Refs. 136 and 139. Leaving details aside, we emphasize that the choice of symmetry in any given versions must be made at the very beginning of chemical evolution. We present here the scheme for evolution as put forward by the proponents of the fluctuation versions based on the ideas of Oparin<sup>108</sup> (Table I).

Other hypotheses assume the initial formation of both racemic and optically pure forms of life. Racemic life did not survive the competition for the reasons indicated above, while of the two biological antipodes, again as a result of fluctuations, but now of a biological character, one gained the advantage between stages 4 and 5 (see the analysis in Ref. 141), and subsequently reproduced forms similar to itself. These hypotheses are losing supporters.

The weak point of both hypotheses is the necessity for assuming that life arose in one particular area, even though the area may be large, and within a particular time interval. Current concepts of the possible paths for natural synthesis make this assumption unlikely; definite opinions have been stated concerning the multiple origins of life (Oparin in Refs. 129–132, Ponnampereuma in Refs. 8 and 128). The emergence of life in multiple acts, in different areas and during different periods of time implies, within the framework of these hypotheses, that chirally pure populations of either symmetry survive with equal probability in nonadjoining territories. Competition between these populations can arise after their (expanding) territories come into contact, but, again, a different outcome can result for different pairs of territories.

Here, we need only note that the spreading of the "seed" of a particular symmetry with dust could rapidly spread this symmetry over enormous areas (under laboratory conditions that cannot be controlled, dust often leads to asymmetrical crystallization<sup>13,112,142</sup>).

An extreme point of view is the proposition, first stated, apparently, by Jordan, that asymmetrical life forms arose as a result of a special event on a global or even cosmic scale. It is difficult to construct a model of such an event.

Along these lines, as in fiction, visitors from other planets have been suggested; this merely transfers the problem to other planets. Organic substances have not been discovered in the samples of lunar soil provided by the Apollo flights<sup>143-145</sup>; traces of amino acids, resembling, in general, those that have been established in problonts and archeobionts, have been discovered on some meteorites. This probably indicates the similarity of the events leading to their creation and, indirectly, points to the multiplicity of such events. Although the results are somewhat contradictory, in no

<sup>21)</sup> The first primitive "enzymes" could have been the amino acids themselves and their chiral oligomers.<sup>135</sup>

<sup>22)</sup> *Fobacterium isolatum* in Swaziland and related organisms (dating  $\approx 3.2 \times 10^9$  years).

TABLE I.

Small molecules	Elements of weak symmetry breaking in isolated reaction volumes
Macromolecules	Selection of antipodal monomers during the formation of polymer structures
Nuclei of living matter; coacervation and development of phase-separated systems	Morphogenesis of dissymmetry
Evolution towards self-replicating metabolic systems and establishment of the biochemical unity of life	Final breaking of symmetry in the biosphere
Further evolution of living matter	Perfection of the chiral purity of biomolecular systems

case has a significant departure from the racemic state been discovered.<sup>144,146-149</sup> Analysis of the data from Mars leads to the same conclusion.<sup>150,151</sup> Traces of a departure from the racemic state in living organisms have been found in old rocks.<sup>8,152,153</sup>

A second group of assumptions relates dissymmetry to the possibility of contact with gyrotropic minerals. Thus, for example, natural quartz is widely dispersed in the form of optically pure, enantiomorphic crystals. On the other hand, it is known that chemical reactions occurring in the presence of quartz as a catalyst lead to the formation primarily of one of the antipodes.<sup>13,119,120</sup> The possibility of a catalytic influence on the formation of life has been noted for many minerals.<sup>154</sup> This possibility cannot be doubted. However, the same difficulty occurs here: within a single deposit the number of right-handed and left-handed crystals is statistically identical. It has also been suggested<sup>155,156</sup> that contact with natural magnetic rocks (for example, ferrimagnetic magnetite) could play a possible role. However, a magnetic field by itself is not enough. As shown by P. Curie long ago, in order to obtain a gyrotropic effect, two asymmetrically situated fields must be present. The possibility of obtaining a single symmetry type is also not clear.

The next group of theories explains the appearance of dissymmetry by geophysical factors. Even the influence of the spiral motion of the earth relative to the galaxy (!) has been suggested.<sup>158,157</sup> The possible role of the earth's magnetic field has also been examined. However, no definite results have been obtained.<sup>158,159</sup> We repeat that two fields are necessary and the gravitational field, apparently, is not to be considered.

A very important factor could be circularly polarized sunlight reaching the surface of the earth. Since chiral molecules exhibit circular dichroism, such light, on absorption by these molecules, can cause photochemical asymmetrical synthesis or asymmetrical decomposition, even in a racemate.<sup>160,161</sup> Many such reactions are known<sup>119,120,161-163</sup> with a maximum yield of the order of 20% (Ref. 164). Short wavelength radiation with  $\lambda < 3000 \text{ \AA}$  is photochemically most active. The fraction of this radiation in sunlight reaching the

earth's surface is of the order of 1.5% (Refs. 115 and 146), i. e., it is not small, and in the initial oxygenless atmosphere it was much greater. There is information in the literature concerning the fact that light scattered by the atmospheres of all planets is partially circularly polarized.<sup>165</sup> Statements have also been made in the literature concerning the excess of right-handed circularly polarized components in daylight at the earth's surface.<sup>10,51</sup> However, the scarce experimental information from geophysics does not provide reliable support for this notion. In Ref. 166(a), the fraction of elliptical polarization in daylight turned out to be very small, and in addition, an excess of a particular symmetry type was not established.

Circular polarization can arise when light is reflected from an absorbing surface (ore bodies, ionosphere), especially under oblique incidence, with total internal reflection<sup>166b</sup> in sea water and in inlets, and so on. However, there are few experimental observations of this type and the presence of a single, definite sign of polarization under different conditions is very doubtful.

Significant elliptical polarization has been noted for scattering of light from aerosols<sup>167</sup> with an asymmetry in signs appearing under real scattering conditions. In this connection, it should be noted that the assumed primary nuclei of life ("coacervates" according to Oparin<sup>129-132</sup> and "microspheres" according to Fox<sup>134,168,169</sup>) were shaped like spherical drops suspended in sea water. In Ref. 170, it is proposed that photosynthesis played an important role on the surfaces of spherical droplets in fog in the initial atmosphere. The scattering of light by such drops can result in significant circular polarization.<sup>171</sup>

Circular polarization can, in principle, arise as a result of the Faraday effect, caused by the earth's magnetic field. The sign of the effect does not change as a result of a back and forth passage, i. e., an accumulation effect is possible. But, the earth's magnetic field is weak and the effect in gases is small (however, the effect is greater in water).

Another important factor has not been adequately analyzed. Synthesis of amino acids and pyrimidine and

TABLE II.

Stages of evolution	Largest formations	Typical structural elements and examples	Degree of dissymmetry	Reason for dissymmetry
I	Nuclei	Protons, neutrons, neutrinos	100%	Weak interactions
II	Atoms	H, C, O	Of order 0	Loss of dissymmetry due to stronger interactions
III	Small molecules	H <sub>2</sub> , CO, H <sub>2</sub> O, CO <sub>2</sub> , NH <sub>3</sub> , CH <sub>4</sub>	Of order 0	
IV	Medium-size molecules	Amino acids, sugars, pyrimidines	Close to 0, but greater than in stages I and II	Dissymmetry arises due to autocatalytic processes
V	Macromolecules	Proteins, RNA, DNA	Between 0 and 100%	Dissymmetry arises due to increase in autocatalytic processes; possible coexistence of right and left geographic territories.
VI	Unicellular organisms	Probiotics, bacteria, viruses	Almost 100%	Dissymmetry amplified by biological reproduction and metabolism. Only one symmetry type, determined by violation of parity conservation in weak interactions
VII	Multi-cellular organisms	Plants, animals	100%	Same

purine bases is possible as a result of lightning discharges. As already mentioned, these chemicals have been synthesized under laboratory conditions with strong electric discharges (see, for example, Refs. 8, 94, 127, 172). Natural lightning discharges yield currents of many thousands of amperes; in past geological epochs, they could have been stronger. These currents simultaneously create powerful electric and magnetic fields. It is known that there exists a preferred direction for these currents: a negative charge most often strikes the earth. These two asymmetric fields, acting on chiral molecules, in which the electric and magnetic moments do not coincide, could under some conditions create<sup>23)</sup> dissymmetry during synthesis. No relevant experiments have been performed.

Finally, a fourth group of theories related the preference of one type of symmetry in molecules in biological systems to the violation of parity conservation in weak interactions. At first, these proposals arose as speculations (compare Ref. 173-177). However, later, they were given a theoretical foundation. Three ideas

<sup>23)</sup> The contribution of discharges to the energy balance of the Earth is small,<sup>115</sup> but the local liberation of energy is enormous.

were proposed along these lines.

1. The effect on molecular structure of bombardment by longitudinally polarized "left-handed" electrons emitted by radioactive elements in the earth's crust, for example <sup>40</sup>K, which emits high energy electrons (1300 keV).<sup>24)</sup> This may involve: (a) asymmetrical decomposition or synthesis of a molecule during radiolysis<sup>178</sup> and (b) asymmetrical polymerization or crystallization as a result of bombardment.<sup>173,174,179,180</sup> The decay of <sup>14</sup>C, which enters into the composition of the molecules themselves, is also indicated as a possible source.<sup>15,181</sup> The energy of the electrons in this case is significantly less (~155 keV), but this atom is one of the basic components of living matter (while the content of <sup>40</sup>K in living matter is negligible and its occurrence in the earth's crust amounts to only ~2.5 at.%<sup>181a,182</sup>) so that the effect of <sup>14</sup>C is significantly more likely (compare also Ref. 181b).

A very large number of experiments have been performed (see the discussion in Ref. 15 and the reviews in Refs. 151 and 183). Stronger sources have also

<sup>24)</sup> The contribution of this decay to the same energy balance is noticeable and was much greater during past epochs.<sup>115,146</sup>



been used:  $^{32}\text{P}$ ,  $^{60}\text{Co}$ ,  $^{90}\text{Sr}$ . The question has been repeatedly discussed and there have been reports of positive effects.<sup>184,185</sup> However, the situation remains unclear and the results of the experiments are contradictory.<sup>186-191</sup>

2. The effect, basically photochemical, of circularly polarized bremsstrahlung, created by the same electrons in matter. Of course, it is not easy to separate this effect from the preceding effect. If the fraction (very small) of the particles that lose their energy by deceleration is computed, the fraction of the radiation that falls into the photochemically active frequency range is taken into account, and the small yield of most asymmetrical photoreactions is also taken into account, then this path turns out to be highly improbable.

Recently, the question concerning the effect of weak interactions on living systems has been analyzed anew in Ref. 192, but the situation remains unclear.

3. Optical activity can arise in molecular systems as a direct result of interactions via neutral weak currents.

The idea that violation of parity conservation could be connected to neutral weak currents (see reviews in Refs. 193-195) was proposed by Ya. B. Zel'dovich<sup>196</sup> and then, as applied by biological systems, in Ref. 197. The mechanism of the phenomenon was analyzed in Refs. 198-200 and in Refs. 201-202; the expected effect was the appearance of an insignificant asymmetry (chirality) in atomic and molecular systems. This should result in the rotation of the plane of polarization by these systems (pairs of heavy atoms were examined), and in addition, the rotation should be very small ( $10^{-7}$ - $10^{-8}$  rad/cm).

Such dissymmetry, if it arises, can, generally speaking, also lead to asymmetric synthesis and asymmetric chemical reactions, although a specific mechanism for this has not been discussed (except for the note of Ref. 197) and appears improbable.

It was noted in Ref. 203 that the effect must be greatest for strongly forbidden transitions and, in that case, can attain an order of magnitude of  $10^{-4}$ . The magnitude  $10^{-8}$  mentioned above lies at the limits of accuracy of modern experiments. The results of experiments so far are contradictory (see Refs. 204-208 and the reviews in Refs. 209 and 210). It was reported in Ref. 211 that in molecular systems it is possible to have an effect that is several orders of magnitude greater; this report has not yet been discussed and has been checked neither theoretically nor experimentally.<sup>212</sup> In Ref. 213, effects involving two-photon excitation were predicted; these also turned out to be small, but, in the opinion of the authors, under special conditions these effects could be greater (two photons with exactly equal energy). This effect could play a role in the presence of a high radiation density.

Recently, it has been proposed that dissymmetry related to weak interactions could also appear as a result of the interaction of neutrons with electron shells in molecules.<sup>214</sup>

All effects connected with weak interactions must be

very small. Supporters of the hypotheses described above point out that small effects can be greatly amplified and accumulate in autocatalytic processes, and processes such as nonequilibrium crystallization or polymerization<sup>11,13,185,187,215,218</sup> connected with the presence of chirodiastaltic forces. Further, it is pointed out that in connection with the presence in cosmic dust<sup>217,218</sup> of comparatively complex molecules (possibly even amino acid type molecules<sup>219</sup>) such molecules could, over long periods of time, be subjected to intense actions (although here the possibility of "accumulation" of the effect for isolated molecules is unclear). We present here, without discussion, the scheme for evolution as it is presented by supporters of these hypotheses (Table II is taken from Ref. 11); they explain the inequality of signs as arising spontaneously.

In this group of hypotheses, the mechanism for the predominance of primary substances with configuration having different symmetry (*l*-amino acids and *d*-sugars, for example) should be explained in greater detail. In light of the remarks made above concerning chirodiastaltic interactions, this does not present any difficulties because depending on the specific conditions both a favored, as well as a reduced, synthesis (or composition) of the given isomer can occur.

As can be seen, the second to fourth groups of assumptions, which relate the appearance of dissymmetry to the effect of a constantly acting factor, remain unproven. Of these, two can be singled out.

The assumption of asymmetric photosynthesis or photocomposition (compare Ref. 220) remains attractive. In this connection, we recall the work described in Ref. 221, in which a noticeable elliptical polarization of light scattered by cosmic dust is demonstrated (using the Crab nebula as an example). However, the indicated shortcoming of geophysical data in general and especially of information concerning a preference for one type of symmetry suggest that for the present this proposition should be treated cautiously.

Recently, a number of reports has appeared concerning success in searching for asymmetrical composition<sup>222,223</sup> or asymmetrical crystallization<sup>224</sup> as a result of the action of longitudinally polarized electrons. Clearly, these studies should continue because this possibility is realistic.

In connection with the whole foregoing discussion it is still difficult to choose between the fluctuation hypotheses and the assumption of a constantly acting factor. We mention here some considerations concerning enantiomorphism on a cosmic scale.<sup>225</sup>

We see that the problem of chirality of molecules in living organisms, which would appear to be strictly biochemical problem, is becoming a big and many-sided problem in physics and biology, which has not yet been solved, and we see that the problem of dissymmetry in living systems, perhaps, is entering within the purview of physics.

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