

## SOLID-STATE PHYSICS

### BIOPHYSICAL ASPECTS OF THE BIOSPHERE'S CHIRAL SAFETY

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Most biological molecules are composed with the participation of asymmetric (chiral) carbon that governs the optical activity and stereospecific properties of these compounds, namely, the enzymatic activity of proteins, the specificity of cellular receptors, the replication of nucleic acids, and so on. This most important property of all living systems has been fixed during the course of evolution. Nowadays living organisms are meeting with numerous toxic chiral compounds produced by chemical, pharmaceutical, and food industries that poses the new problem of chiral environmental safety for mankind.

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#### INTRODUCTION

The chiral asymmetry of biomolecules is one of the fundamental physical properties of the biosphere. The stereospecificity of the living matter, fixed during the course of biological evolution, is realized at the genetic level and in biosynthesis. The environmental safety of people and their natural ecosystem in conditions of anthropogenic catastrophes and anthropogenic effect on the environmental quality is an extremely urgent problem. A new hazard to public health has emerged because of the disturbance of the natural asymmetry as a result of intense use of enantiomers of organic substances having an adverse effect on living systems. The problem of the chiral purity of the biosphere is gaining in importance. The development of a theoretical and methodical basis for monitoring chiral compounds is the most important task of physics and biophysics.

#### 1. THE NECESSITY OF THE BIOSPHERE'S CHIRAL ASYMMETRY

Chiral compounds contain one or more asymmetric carbon atoms. These compounds are optical enantiomers that rotate the plane of light polarization in opposite directions and cannot be matched with their mirror image [1].

The ionic and chiral asymmetries had formed the basis for the thermodynamic nonequilibrium of the primary three-dimensional pre-biological formations. The chiral purity of monomers, *L*-amino acids and *D*-sugars is the necessary condition for the use of proteins and amino acids as molecules of informational significance. The necessity of the chiral and ionic asymmetry is also dictated by the requirement for the thermodynamic nonequilibrium of the system, because it is only in a nonequilibrium system that the formation of regular, ordered structures, such as living cells, is possible.

Such dynamic structures as thermodynamically nonequilibrium ice–water, water–air interfaces and surfaces of nanometer-sized water clusters possess the property of partial fractionation of *L*- and *D*-isomers and are capable of concentrating them in water–air aerosols. The ocean–atmosphere boundary is a thermodynamically nonequilibrium structure, for the evaporation of water and infrared emission cool down

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a thin surface layer and facilitate the formation of a temperature gradient. Within such a nonequilibrium surface layer, known as the "cold film", oscillatory and wave-like regular dynamic structures can form and the thermodiffusion processes of separation of ions and organic substances can occur [2].

Numerous chirally asymmetric organic compounds had chemically been formed during the period of abiogenous evolution. It is believed that chirally pure compounds cannot be obtained by way of simple chemical synthesis, but the group of researchers headed by G. Cooks (Purdue University, Lafayette, Indiana) have found that it is only the *L*-form of serine that is capable of forming peptide clusters which in turn can form compounds only with the *L*-isomers of amino acids. What is more, serine can probably change its chirality under the effect of chiral physical factors (polarized light for one), which could have led to the abiogenous formation of predominantly levorotatory amino acids in the primary broth.

In this chiral primary broth, there had taken place the isolation of the protocells. A protocell must have a store of free energy to create its reaction and metabolism regulation systems. The criterion for the production of this store should be the osmotic equality between the protocell and its environment in the absence of thermodynamic equilibrium in conditions of enrichment with potassium and calcium ions that are few in sea water instead of the sodium and magnesium ones that are many. Thus, the concentrations of the osmotic active particles within and without will be approximately the same, but owing to the ion asymmetry, a free energy store will arise in the thermodynamically nonequilibrium system.

The formation of the protocells had most likely occurred by the following scheme. When on the surface there is a rarefied monolayer of phospholipides, the "film" microdroplets formed upon rupture of cavitation air bubbles and enriched with potassium, calcium, and enantiomers concentrated in the surface layer can form lipide vesicles. Such formations are considered as prototypes of cells that can serve as objects of selection in the process of biological evolution.

## 2. EFFECTS OF CHIRAL COMPOUNDS ON LIVING SYSTEMS

The principle of the action of biologically active substances on the organism consists in the susceptibility of its certain receptors to them. The shape of a biologically active molecule must ideally fit that of its responsive receptor molecule (like a "key and slot"), otherwise there will be no interaction, or the interaction will be weakened. The interrelation between a spatial structure and biological activity is referred to as the action stereospecificity, i. e., the structure of the sensitive area of the cellular membrane must be replicated in a complementary manner in the structure of the biologically active substances. The "friend-and-foe" isomer identification system can be realized upon combination of enzymes with substrates, passage of isomers through membrane channels, and distribution of substances among tissues or in intracellular processes [1, 3, 4].

The degree of interaction between an asymmetric molecule of a biologically active substance and the active center of the receptor depends on their contact at several points, and in the substance and the receptor structures there can be both points of coupling and points of mutual repulsion. If the forces of interaction between the asymmetrically structured biologically active molecule and the active area of the receptor or enzyme are concentrated at three points, then the two stereoisomers of the molecule can similarly orient relative to the given surface only two out of the three groups taking part in the process of interaction. The different orientation of the third group can explain the difference in biological activity between optical isomers. For example, three groups of the *D*(-)-adrenaline molecule can combine with the corresponding groups of the receptor. In the *L*(+)-adrenaline molecule, the alcohol hydroxyl group is so oriented with respect to the surface of the receptor that the molecule can interact with the receptor only at two points, and it is exactly for this reason that *D*(-)-adrenaline is tens of times as pharmaceutically active as its synthetic *L*(+)-isomer [1].

The effect of medicinal agents, insecticides, and also organoleptic compounds is fundamentally associated with their chiral purity. Because of their action stereospecificity, chiral isomers differ in immunomodulating, cytostatic, teratogenic, and mutagenic properties. A number of pharmaceutic preparations used to treat diseases of the enzyme and immune systems are a mixture of two and more optical isomers differing in biological action [3].

As a rule, drugs have a positive effect in their levorotatory form, which is due to the evolutionary stereospecificity of the organization of the cellular receptors and transport systems and the complementary

character of interaction of proteins and nucleic acids with ligands. Let us cite as an example the history of application of Thalidamide. Its *L*-isomer had a positive effect, whereas its dextroisomer, a manifest teratogenic effect. Such examples are numerous: the antitumorigenic drug sarcosine is active only in its levorotatory form, the anticoagulant varfavein and a number of antiinflammatory agents slow down metabolic processes only in their *L*-form, insulin, dopamine, and many other synthetic hormones should also be chirally pure *L*-isomers. By virtue of its specificity, the enzyme *L*-asparaginase is used to treat lympho- and reticulosarcomas only in its natural *L*-configuration [5, 6]. At the same time, the susceptibility to the *L*-form is not an absolutely positive property, because the *L*-isomers can also cause undesirable effects.

Many biologically active substances, such as antitumorigenic, antimetastatic, radioprotective, and neurotropic drugs, growth inhibitors and stimulators, hormones, immunomodulating agents, and antioxidants that effectively act on biological objects in the region of "ordinary" concentrations lower their effect in the region of relatively low concentrations and again enhance it in the region of "ultralow" doses ( $10^{-12}$ – $10^{-15}$  M) [4, 7, 8]. The biological effect of ultralow doses of biologically active substances is caused by the bonding of their individual ligands with the receptors and can be explained on the basis of the notions of the existence of highly effective receptor signal transmission and amplification systems with positive and negative feedback. There are examples of the synergetic amplification of the action of drugs one of which is present in an ultralow concentration. The resultant activity of several herbicides is thus increased if one of them is used in an ultralow dose [4].

Such actions are characterized by a nonlinear dose–effect relationship. Activity maxima are observed to occur in certain dose intervals and are separated by a range of concentrations (from  $10^{-11}$  to  $10^{-15}$  M) wherein the system is practically insensitive to the actions. The ultralow dose effect is manifest in such substances as hormones, morphines, and vitamins.

The isomeric forms of various substances in ultralow doses can also exhibit different effects than in the ordinary doses. Therefore, it seems important to take into consideration the effective action of ultralow doses of chiral compounds on biological systems.

### 3. THE USE OF CHIRAL COMPOUNDS

At the present time, out of tens of thousands of organic compounds synthesized throughout the world, it is only those used in the pharmaceutical industry (30%) and agrochemical industry (25%) that can be considered to be homochiral. The novel methods of protection of agricultural plants also use chiral neuropeptides, stereoisomers of the traditional pesticide. It is only 15% of synthetic drugs that are manufactured in Europe in the form of individual isomers, the remaining 85% are mixtures. The demand for chiral reagents and intermediate compounds necessary for the production of medicinal agents in Europe is growing at a high pace. Included in the first group are numerous compounds for the production of medicinal agents for treating cardiovascular diseases and also herbicides. Classed with the second group are the stereoisomers of phenylglycine and hydroxyphenylglycine used to obtain antibiotics and amino acids.

Around 30% of the total emission of man-made pollutants in the world is accounted for by agricultural wastes [9], and some plant protection methods are based on the use of chiral neuropeptides.

Having placed emphasis on the development of biotechnologies in the field of manufacturing pharmaceuticals, bioactive agents, and products for agriculture, the ICI company have developed a process for the production of *L*-chlorpropionic acid used in the manufacture of one of their herbicides.

The Avecia company is also manufacturing around 150 complex chiral compounds and semiproducts. Bayer AG is the manufacturer of fine chiral compounds, aromatic and fragrance compounds, cardiacs based on calcium antagonists, herbicides, and systemic insecticides. A vast amount of chiral products are manufactured by ICN [10]. Fluca and Riedel-de Haën companies are manufacturing some 22 000 chiral chemical compounds [11, 12].

Up to 30% of the pollutants contaminating Great Lakes (USA) are products of the pharmaceutical industry or cosmetic industry wastes, another 30% being accounted for by agricultural wastes. There has been recently revealed the so-called Great Lakes self-cleaning effect resulting from the evaporation and wind carry-over of toxic products, which means the spread of chiral pollutants as part of water–air aerosols to the adjacent territories, thus aggravating the problem of transfrontier pollution.

Terpenoids are included in the composition of many food additives and cosmetics. Methods have been found to synthesize a vast amount of terpenoid compounds that are promising semiproducts for fine organic synthesis and the manufacture of chiral complexes of transition metals. It should be noted that the world industries associated with the production of food additives that make wide use of chemical synthesis fail to control the enantiomer composition of the compounds used by them [3].

Chiral compounds are used by electron optics in multiple-component fibers, including polylactic acid polymers differing in the proportion of *L*- and *D*-isomers. Such fibers can be used to manufacture nonwoven structures, for example, disposable absorbing products. Methods have been developed to synthesize chiral liquid-crystal polymers and a wide range of chiral polymer compounds containing binaphthol derivatives with substituents changeable in a purpose-oriented manner.

The problem of the chiral purity of the metabolites of chiral compounds seems important. There are few biological species in nature that are capable of utilizing the enantiomers of biologically active substances, changing their chirality, or making them achiral. Some bacteria that use sugars of different chirality as a means of natural protection can be classed with these species. But organisms utilize and synthesize chiral compounds, such as vitamins, hormones, antibiotics, eicosanoids, terpenoids, metabolites of coniferous species, and photosynthesis pigments, of one and the same chiral configuration.

It should be noted that practically no satisfactory standards exist today for the maximum permissible concentration of many chemical compounds in natural environments, the existing ones giving rise to unfavorable criticism by the conservancy bodies. But what is most important is that neither the sanitary standards in force for the maximum permissible concentrations of chemicals [13], nor the normative documents in the field of international legislation give any consideration to the problem of the maximum permissible concentrations of isomeric forms, especially in ultralow doses. The isomeric forms are thus not included among the main components of ecodiagnosics. For example, the hygienic standards for xylydine isomeric mixture (six isomers in all) contain no information as to the individual isomers. Xylydines enter into the composition of the Grade TG-02 fuel, or samin, used as a fuel component for liquid-propellant rocket engines. Samin is a mixture of isomeric xylydines and commercial triethylamine (excerpt from the USSR State Standard GOST 171147-80). It is pertinent to note in this connection that some 40 tons of samin were burned near the Pechora River in 1997.

## CONCLUSION

Despite the fact that the chiral pollution hazard becomes quite real today, there is as yet no biospheric monitoring system, and chiral compounds are posing an environmental problem not only in industrial regions polluted by accumulations of chemical and fuel industrial wastes. Domestic wastes containing isomeric forms of quite harmful compounds are accumulated in residential areas and can aggravate the epidemic situation. At present there is no integral system in the world for monitoring the atmosphere, hydrosphere, and soil ecosystems. This problem is associated not only with zones where petroleum refining and chemical industries develop actively, but also with those where aerosols are formed and atmospheric precipitations take place. For example, around 30% of all the pollutants in the vicinity of the Great Lakes in the USA is accounted for by medicinal and hormonal agents. Besides, there are also areas where the secondary emission of pollutants occurs. The "cold film" where air masses and clouds saturated with chiral biologically active substances are formed as a result of the rise of microdroplets [3] can be classed with such zones. These substances are carried away from the surface of the ocean for intercontinental distances by barogradient water and wind currents, and the consequences of the fractionation of racemates from industrial wastes are absolutely unknown. To separate a mixture of enantiomers, it is sufficient for it to be exposed to such physical factors as circularly polarized light, a combination of convection (due to evaporation) and a constant magnetic field plus constant electric and gravitational fields that always exist at the water-air and ice-water interfaces [2]. Thus, the necessary set of factors differentiating chiral molecules is always present at the water-atmosphere interface. Worthy of note is also the fact that when they get into sea water, chiral bioactive compounds can augment their toxic properties owing to the ultralow dose effect.

The attempt made by the chemical industry to synthesize chirally safe enantiomers is a positive but costly and so far inadequate enterprise. Of importance to the biosphere is not only its contamination with chiral industrial pollutants, but also the rate of the biochemical utilization of various enantiomers in

natural conditions. There are as yet no specialized methods to utilize isomeric forms of biologically active substances.

It is necessary to compile the relevant data base, to work out standards for the maximum permissible concentrations of chemicals, and to develop a complex of biosensors for the determination of the chiral configuration of biologically active substances, based on the Langmuir–Blodgett film technology using *L*- and *D*-specific enzymes, to create industrial control and ecological monitoring systems.

Along with the radiation and bacterial pollution and the greenhouse effect, the hazard posed by the spread of synthetic chiral compounds and the rise of the concentration of the natural isomeric forms of various organic compounds can become a limiting factor in the evolution of mankind. Enantiomer-containing pharmaceuticals and technical products become more and more widespread, and the scale of oil pollution is constantly growing. All these factors can bring about irreversible changes in ecosystems of various hierarchy levels.

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