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Review

Origin of Homochirality of Amino Acids in the Biosphere

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Abstract: Discussions are made concerning realistic mechanisms for the origin of L-amino acids in the biosphere. As the most plausible mechanism, it is proposed that a mixture of racemic amino acids in the prebiotic sea caused spontaneous and effective optical resolution through self crystallization, even if asymmetric synthesis of a single amino acid has never occurred without the aid of an optically active molecule. This hypothesis is based on recrystallization of a mixture of D,L-amino acids in the presence of excess of D,L-asparagine (Asn). The enantiomeric excess (ee) of each amino acid in the resulting crystals indicates that crystallization of co-existing amino acids with the configuration same as that of Asn took place, although it was incidental whether the enrichment occurred in L- or D-amino acids. In addition, the resulting ee was sufficiently high (up to 100%) to account for the predominance of L-amino acids on the earth.

Keywords: homochirality; L-amino acid; crystallization; chemical evolution; optical resolution; asymmetric synthesis; enantiomeric excess

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1. Introduction

Explanation of the homochirality of amino acids in the biosphere is one of the most important mysteries in the origin of life [1,2]. According to the long history of asymmetric synthesis, it is considered that absolute asymmetric synthesis, namely asymmetric synthesis without the aid of an asymmetric molecule as a reactant or catalyst, is impossible. Circularly polarized light [3-5] and light in a magnetic field [6] are types of asymmetric reactants or fields. It is reasonable to suppose that L-amino acids cause asymmetric synthesis and optical resolution [7,8]; however, the formation of a single L-amino acid from the racemic products, which are formed by prebiotic chemical evolution, has

never been shown. Breslow and Levine [9] reported that solutions with as little as 1% enantiomeric excess (ee) of D- or L-phenylalanine were amplified to 90% ee (a 95/5 ratio) by two successive evaporations to precipitate the racemate. This study elegantly highlights the enigma concerning how the tiny 1% ee required for chiral amplification was initially created from the racemate. Sublimation of L-serine (Ser) with 3% ee yielded a sublimate with 69% ee [10]. In addition solubility-based chiral amplification of nucleoside [11] and attrition-enhanced evolution of solid-phase ee of nearly racemic phenylglycinamide derivative [12] were reported. However, the generation of an ee must be strictly distinguished from the chiral amplification by a chiral molecule even if the ee of the involved chiral molecule is very small.

Since the discovery of ribozyme [13], an "RNA world" is postulated as an initial stage in the origin of life [14]. However, from the stereochemical viewpoint, it is much more difficult to explain the origin of four ribonucleic acids, each of which contains as many as four chiral carbons, than that of L-amino acids, which contain only one chiral carbon, except for threonine and isoleucine.

Concerning the crosstalk between amino acids and sugars, the strong but incomplete chiral preference for the L-Ser/D-glucose and D-Ser/L-glucose combinations on the Ser octamer homoclusters has previously been reported [15]. Sixteen optical isomers are components of hexose, which has four chiral carbons. It would be interesting to know which hexose has the strongest affinity for the L-Ser octamer. In addition, chemical aminoacylation of D-poly(adenylic acid) with imidazolide of N-protected D,L-alanine (Ala) gave rise to adducts with ee of 58% [16], while D-amino acids were preferred in the esterification of 5'-AMP [17].

Spontaneous optical resolution by crystallization of an enantiomeric mixture has been proposed as a possible mechanism for the formation of homochirality [18–20]. Homochiral preference of Ser in thermal cluster formation [21] and chiral amplification of oligopeptides in two-dimensional crystalline self-assemblies on water [22] were reported. The fact that glycine (Gly) crystals float in the solution such that only one face is available for growth caused optical resolution of added amino acids such as leucine (Leu), histidine (His), valine (Val), phenylalanine (Phe), glutamic acid (Glu), and methionine (Met) [23]. Unlike amino acid monomers, homochiral peptides were generated from racemic mixtures by random polymerization [24].

At the same time, another problem is to elucidate the selection of 19 L-amino acids with apparently different structures, except for the configuration of the α-carbon. The nomenclature of L-amino acids was introduced by Fischer on the basis of his nomenclature of sugars, implying that L-amino acids do not have any other chemical properties in common. For example, if L-alanine (Ala) is generated by a specific mechanism, this mechanism is not always applicable to the origin of L-Phe. Therefore, in theory, 19 mechanisms are expected to exist for the selection of 19 L-amino acids, while it is unclear how many L-amino acids were necessary to form the most primitive proteins. Ikehara [25] proposed the "GADV-protein world" hypothesis, which states that Gly, Ala, aspartic acid (Asp), and Val formed protein in primitive life on the basis of studies on microbial genes, origin of genes, genetic code, and catalytic reaction of peptides prepared using these four amino acids.

In the present review, we will focus our discussion on the possible and realistic mechanisms of the origin of L-amino acids on the earth, although the formation of L-amino acids in the extra-terrestrial space is suggested on the basis of analysis of amino acids in meteorites [26].

Discussions on frequently reported asymmetric synthesis and optical resolution using a chiral molecule are also deliberately eliminated.

2. Specific Nature of D,L-asparagine among Amino Acids

2.1. Generation of ee by a simple recrystallization of asparagine

Since the famous experiment performed by Pasteur [27], asymmetric resolution has been attempted through recrystallization [18,19,28], despite the fact that Pasteur achieved optical resolution and did not find any evidence of the generation of an ee. Racemic amino acids would have been generated by chemical evolution in the high temperature of the prebiotic sea. As the prebiotic sea cooled down, crystallization took place and homochirality was probably attained at this stage, when the rate of thermal racemization and the solubility of amino acids became low. Then how did homochirality arise?

Among amino acids, D,L-asparagine (Asn) spontaneously forms crystals of either isomer during recrystallization [29]. Supposing that two crystals, composed of L-Asn and D-Asn, respectively, are growing during recrystallization of racemic D,L-Asn, it is highly probable that the rate of crystallization of these crystals is not identical. Under these conditions, the ee of Asn crystals arises from the kinetic difference in the crystal growth. We define the ee of an amino acid as shown in Equation (1). A positive ee value indicates that the L-isomer is more abundant than the D-isomer, a zero value denotes a racemic mixture, and negative ee value indicates a D-rich mixture. Usually a negative ee value is not used, but we define it here to plot it in a graph for this review.

$$\mathbf{ee\ (\%) = 100 \times (L - D)/(L + D)} \quad (1)$$

In our previous experiments, a simple recrystallization of D,L-Asn was undertaken. D,L-Asn monohydrate (2 g) was dissolved in water (10 ml) heated in a boiling water bath. After filtration, the solution was stored in a glass vial with a screw cap and left at room temperature until a measurable quantity of crystals was formed. Crystals were collected by filtration, dissolved in an appropriate amount of water, and the ee was determined by high performance liquid chromatography (HPLC) performed with a chiral column {Crownpak CR (+), Daicel Chem. Ind. Ltd., Tokyo, Japan}. The ee values of L-Asn were 4.8, 11.2, 11.5, 11.7, 15.5, 26.7, 26.8, 27.1, 64.7, 88.9, and −59.7%, indicating that L-rich crystals were obtained 10 times and D-rich crystals were formed once in 11 recrystallizations [30].

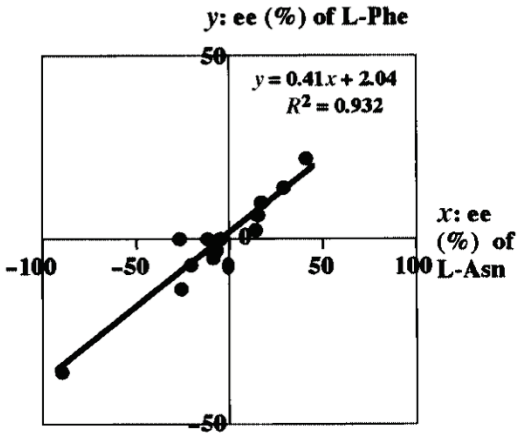
These results do not necessarily imply that L-Asn is formed preferentially. If recrystallizations were performed many times, the formation of L-rich Asn might be as common as that of D-rich Asn. Anyway it is clear that the crystals formed by recrystallization of D,L-Asn show an ee as a whole. To elucidate the mechanism of this enantiomeric enrichment, the ee of each crystal taken randomly from the recrystallization experiments was measured. Among 35 crystals, three crystals gave an ee of either isomer of about 70%, and 32 crystals gave an ee of more than 90% [30], indicating that each crystal consists of an almost pure enantiomer and that the ee of the total crystals is determined by the weight percent of crystals of the enriched isomer. This also implies that the interaction energy between L-Asn and L-Asn (and between its mirror images D-Asn and D-Asn) is larger than that between L-Asn and D-Asn. This finding apparently contradicts Wallach's 1895 rule [31,32], stating that racemic

crystals tend to be denser than their chiral counterparts. Wallach's rule is applicable to Ala [33] but not to Ser [34].

2.2. Optical resolution of D,L- amino acids by D,L-Asn

The next problem was whether D,L-Asn could cause enantiomeric enrichment of other coexisting D,L-amino acids. D,L-Phe (300 mg) and D,L-Asn monohydrate (2.1 g) were dissolved in 10 ml of water at 100 ˚C. By a similar recrystallization process, crystals were obtained, dissolved in water, and analyzed by HPLC. Thirteen independent experiments were carried out. The ee values of L-Asn (x-axis) and L-Phe (y-axis) for each sample solution were plotted as shown in Figure 1 [30]. The maximal ee values of the L-isomer were 22.3% and 41.1% for Phe and Asn, respectively. The maximal ee values of the D-isomer were 35.6% and 89.8% for Phe and Asn, respectively (Figure 1). Namely D,L-Asn causes asymmetric selection of Phe to a significant extent. Furthermore, the ee of Phe almost linearly correlates with that of Asn (Figure 1) [30]. The ee of each crystal indicates that the ee of Asn of either isomer is nearly 100% and that of Phe of the corresponding isomer is 60%–93% [30]; L-Asn crystallizes preferentially involving L-Phe, and D-Asn crystallizes involving D-Phe, and asymmetric selection results from the relative content of crystals enriched with either Asn isomer. This finding also indicates that the interaction between L-Asn and L-Phe (and between its mirror images D-Asn and D-Phe) is greater than that between L-Asn and D-Phe or D-Asn and L-Phe. Of course, recrystallization of D,L-Phe always gives racemic mixtures [30].

Figure 1. Plot of ee values of L-phenylalanine (L-Phe) and L-asparagine (L-Asn) of crystals obtained from recrystallization of D,L-Phe (300 mg) in the presence of D,L-Asn (2.1 g). The ee values of Asn (x-axis) and Phe (y-axis) for each sample were plotted as (λ) [30].

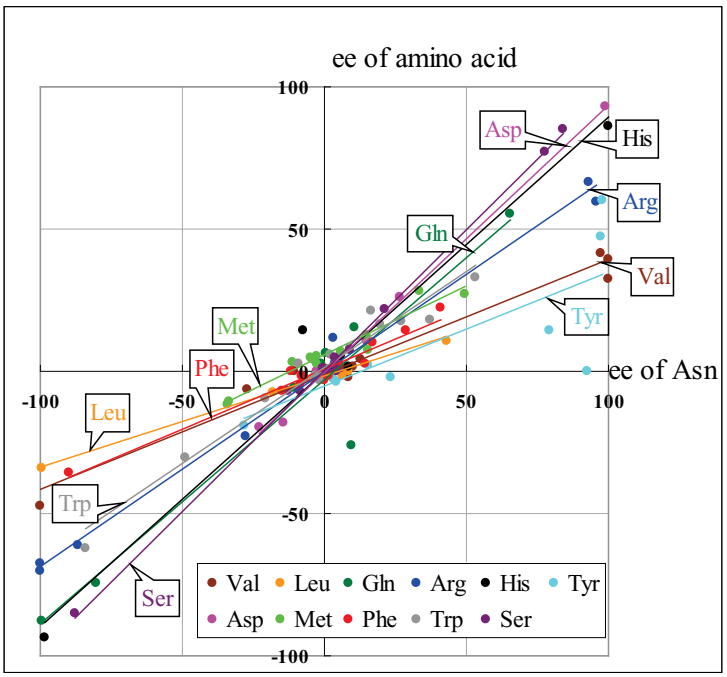


The ability of D,L-Asn to cause enantiomeric enrichment of D,L-Phe is specific, because other D,L-amino acids such as glutamine (Gln), Glu, His, Ser, Asp, Met or Val, do not induce ee in D,L-Phe by similar procedures [35]. Other amino acids were not appropriate for this experiment because of their inappropriate solubility in water, (solubility either too high or extremely low). The ability of D,L-Asn to induce enantiomeric enrichment of other D,L-amino acids may be ascribed to its solubility, solubility change with temperature, and the appropriate position of its three polar functional

groups, which interact with other amino acids (including Asn). Therefore, a molecule that induces homochirality in other amino acids must satisfy stereochemical conditions, and a molecule that merely exhibits a definite ee is not sufficient to fulfil this role. It would be very interesting if such a molecule were found in a meteorite, even of a non-terrestrial type such as isovaline, norvaline, and 2-amino-2,3-dimethylpentanoic acid [36,37].

D,L-Asn can be shown to induce enantiomeric enrichment of coexisting D,L-amino acids such as arginine (Arg), Asp, Gln, His, Leu, Met, Ser, tryptophan (Trp), tyrosine (Tyr), and Val, by similar recrystallization experiments as shown in Figure 2 [38], demonstrating that D,L-Asn causes an enantio-selective crystallization of coexisting racemic amino acids and that interaction between L-Asn and other L-amino acids or between D-Asn and other D-amino acids is also greater than that between L-Asn and other D-amino acid or their mirror images. ***It is a moot point whether the enrichment took place in L- or D-Asn; however, once the selection was made, the coexisting amino acid with the same configuration at the α-carbon was preferentially involved.*** On the other hand, D,L-Ala and D,L-Glu did not afford a significant ee by similar treatment with D,L-Asn [38].

Figure 2. Plot of the ee values of Asn and other amino acids contained in crystals obtained by cocrystallization of excess D,L-Asn and individual D,L-amino acids. Excess D,L-Asn was recrystallized in the presence of each D,L-amino acid. The resulting crystals were dissolved in water, and the ee value of each amino acid was analyzed and plotted, as described in the text. The ee values of Asn (x-axis) and the other amino acid (y-axis) for each sample are shown [38].



2.3. Optical resolution of a mixture of D,L-amino acids by a large excess of D,L-Asn

A mixture of 2.0 g of D,L-Asn monohydrate, 50 mg of racemic Ala, Asp, Arg, Glu, Gln, His, Leu, Met, Ser, and Val, and 25 mg of D,L-Phe and D,L-Tyr was dissolved in 10 ml of hot water, and recrystallized. After collecting and dissolving all crystals in an appropriate volume of water, the ee of

all amino acids was determined by chemical derivatization and HPLC [39–41]. The results are shown in Table 1 [38]. In trial 1, a nearly racemic mixture was obtained. In trials 2–5, L-rich mixtures were obtained, and in trial 6, a D-rich mixture was obtained.

Table 1. ee values (%) of amino acids contained in crystals obtained by recrystallization from a mixture of excess D,L-Asn with 12 D,L-amino acids [38].

Trial	Asn	Ala	Arg	Asp	Gln	Glu	His	Leu	Met	Phe	Ser	Tyr	Val
1	0.23	−6.6	−2.4	1.2	2.3	−3.9	0.2	0.4	−9.8	−2.5	8.0	−5.5	−8.2
2	37.9	30.8	20.4	40.1	37.5	26.5	18.9	3.6	26.0	14.6	48.4	6.7	−0.4
3	33.1	43.0	35.2	48.5	52.2	41.8	18.8	8.0	40.0	22.5	56.6	14.5	5.0
4	79.4	91.0	82.6	100	94.9	92.0	70.0	42.4	40.6	71.2	100	ND	41.8
5	62.9	52.8	39.2	59.7	50.6	61.3	26.1	11.2	54.9	41.4	67.4	36.1	22.8
6	−94.6	−87.1	−43.0	−100	−72.4	−77.4	−66.9	−13.3	−62.0	−39.9	−90.1	−30.1	−6.3

ND: not detected

These results demonstrate that the coexisting amino acids with the same configuration as Asn were also preferentially cocrystallized in this experiment. This highlights a very important point; all these amino acids give the same enantiomer-rich crystals by the recrystallization. In other words, ***recrystallization is a mechanism that gives rise to a set of L-amino acids or D-amino acids.*** Therefore, the 19 independent mechanisms for each amino acid, as postulated in the Introduction, are not necessary to cause optical resolution of amino acids. This may be explained on the grounds that an amino acid has two polar groups to interact with each other by strong Coulomb forces during crystallization and their configuration predominantly determines the structure and ee of the crystal.

Interestingly, the ee of Ala and Glu, which did not give an ee by recrystallization with D,L-Asn alone, was induced from a mixture of these 13 racemic amino acids. It is surprising that the maximal ee was 100%, and that these ee values are much higher than those observed in the recrystallization of each amino acid with D,L-Asn alone. One can conclude that ***a racemic mixture of amino acids causes spontaneous and effective enantiomeric enrichment by itself***, even if asymmetric synthesis of a single amino acid does not occur without the aid of an optically active molecule.

A selection in the very early stage of the crystallization process may also determine the ee of entire crystals. It is easily understood that a strong chiral field is generated when the crystal surface of L-Asn or D-Asn appears in a racemic solution. Based on these results, we propose that enantio-selective crystallization of racemic amino acids induced by spontaneous resolution of a coexisting racemic molecule such as D,L-Asn, is a simple and realistic mechanism for the selection of L-amino acids in the biosphere [38]. Furthermore, the resulting ee was sufficiently high to account for the predominance of L-amino acids on the earth, if the L-selection occurred by crystallization comparing with the small ee of amino acids contaminated in meteorites [26].

D,L-Asn, the unique amino acid, is formed using contact glow discharge electrolysis against an aqueous solution containing alanine and formamide [42]. However, it is unknown whether D,L-Asn was produced in sufficient quantities by chemical evolution to allow crystallization. It is incidental

whether D,L-Asn gave either L-rich or D-rich crystals as described above; thus, it may be speculated that random crystallizations at many points may not have induced an L-rich world, but have lead to a racemic world. It is very interesting to consider whether an L-amino acid world was formed accidentally or necessarily generated by the interaction of D,L-amino acids, especially D,L-Asn with D-sugars or RNAs.

3. Other Hypotheses Explaining Homochirality of Amino Acids

Absolute asymmetric synthesis and optical resolution have been examined under physical fields [2,43,44]. Irradiation of Cr(III)tris-oxalato complex with unpolarized light in a magnetic field at 7.5 T parallel to the irradiation direction yielded an ee of -1×10^{-4} [6]. This was an epoch-making study, but based on this small value, it may be debated whether magnetochiral reaction has a realistic meaning in the formation of homochirality. A confined vortex motion induced an ee in the oxidation of isophorone and hydrogen peroxide [45], although a relationship of this study with the amino acid was unknown.

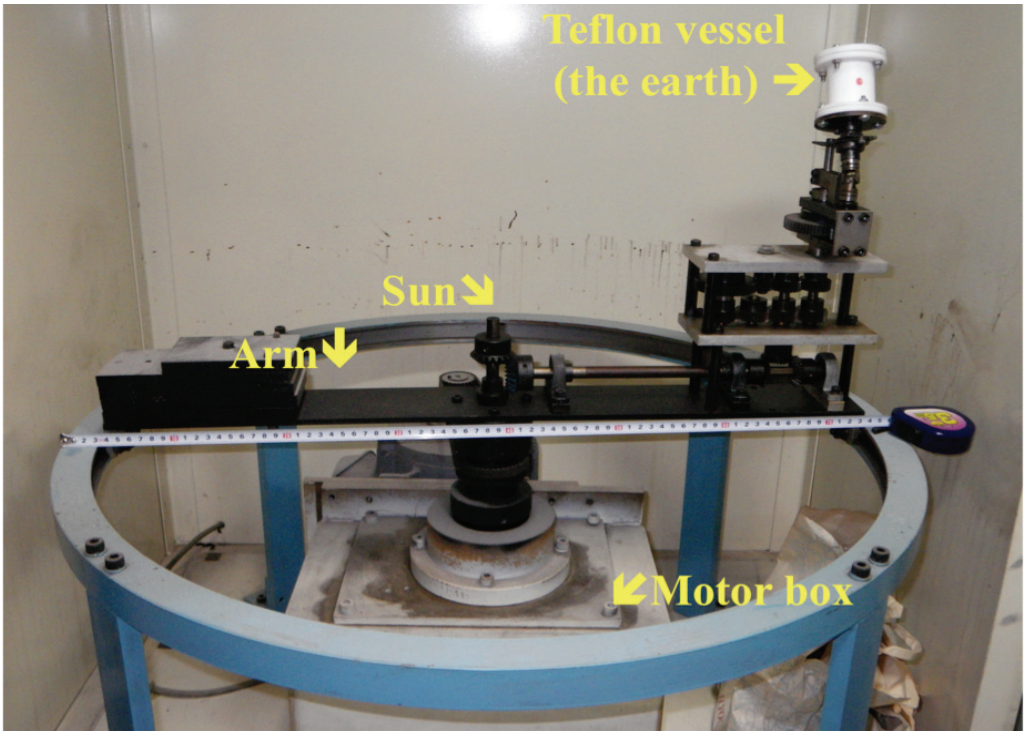
Two orientations of a molecule must be regulated to generate an ee. If the molecule orients by a flow of the solution, e.g., the smallest substituent moves forward, and the largest substituent locates at the outside position by the centrifugal force, the movement of the earth (revolving both around the sun and on its axis) possibly induces an ee. As the tilt of the earth's axis to its orbital plane is 23.5°, the movement of the earth itself is asymmetric. If chemical evolution occurred in the solution (including the gas phase) that synchronized with the movement of the earth, generation of an ee may be expected.

We constructed a model of the earth about 20 years ago (Figure 3). The radius of the arm was 30 cm. The inner diameter of a Teflon vessel was 4 cm, and the height of its inner cavity was also 4 cm. This vessel revolves three times around its axis per one rotation around the sun (center) using a motor and gears (Video 1). The maximum rotation speed was 150 rpm. Unfortunately, we have not succeeded in inducing appreciable ee in oxidation of methyl p-tolyl sulfide with sodium periodate, epoxidation of stilbene with m-chloroperbenzoic acid, or solvolysis of 1-chloro-1-phenyl-ethane with this model. To avoid the effects of side products, we determined the ee by HPLC, in which the standard deviation is usually ~1%–2%. Therefore, an ee smaller than 1% could not have been detected even if it had arisen. Recrystallization of D,L-Asn with this model gave crystals with either plus or minus ee and did not give only L- or D-rich crystals, showing that the results were similar to those obtained by recrystallization made in a stationary vessel. At present, no experimental evidence is available indicating that the asymmetric movement of the earth causes homochirality of amino acids.

Even simple stirring of the solution gave optically active crystals of sodium chlorate ($NaClO_3$), although this molecule is not chiral [19]. Since this process regulates only one direction, the yield of optically active crystals of $NaClO_3$ may be a very specific case, and this may not be applicable to amino acids. However, it is possible that optically active crystal surfaces provide an asymmetric field with amino acids. Selective adsorption of amino acids to crystals of nonchiral inorganic molecules is a possible mechanism for the condensation of either enantiomer. Quartz [46] underwent asymmetric preferential adsorption of Ala in anhydrous dimethylformamide solution. However, Bonner [47] casted doubt on any significant role of quartz in chiral selectivity on the basis of equal abundance of (+)- and (−)-quartz on the earth and the strictly anhydrous conditions required for optical resolution. Calcite

($CaCO_3$) displayed significant adsorption and chiral selectivity of Asp [48,49] and Ala [49] on pairs of mirror-related crystal growth surfaces, although it was not determined whether the ee of Asp or Ala was induced as a whole on the total crystal surfaces. If either crystal field preferentially oriented to the aqueous phase in the prebiotic sea, selection of an amino acid such as Asn, which causes optical resolution of other amino acids [30,38], may have been possible similar to the floating Gly crystal [24].

Figure 3. Earth model. The tilt of the axis of the Teflon vessel to its orbital plane is 23.5°. A red mark appears every 10 cm for measurement. The earth revolves both round the center (the sun) and on its axis.



4. Conclusions

Since the selection of homochirality takes place only once in the history of the earth, it may be almost impossible to prove the mechanism scientifically and to reproduce the situation with confidence. For example, even if a large quantity of D-amino acids remained somewhere after the L-selection, it is impossible to find them, because almost all living organisms equip with metabolic enzymes of D-amino acids like D-amino acid oxidase to consume them as an energy source. Therefore, discussions on this issue will last forever, and new and surprising ideas corresponding to the progress of science and technology will be proposed one after another. These ideas will affect chemistry, especially in fundamental concepts concerning interaction among molecules. Whether this is scientific or romantic, or both, is not for us to say.

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