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Perspective

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Evidence for the Likely Origin of Homochirality in Amino Acids, Sugars, and Nucleosides on Prebiotic Earth

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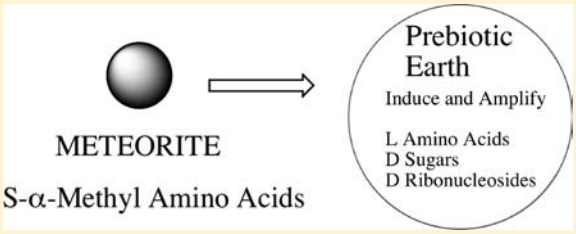

ABSTRACT: Over the past century, the origin of terrestrial prebiotic homochirality has been the subject of much speculation. For life to start on Earth and elsewhere, it is critical that the building blocks of amino acids, sugars, and nucleosides be created in predominant homochiral form. Recent findings of a modest excess L chirality of α-methyl amino acids in some meteorites that landed on Earth have furnished an important piece of evidence. We have shown how these meteoritic components can furnish normal L-amino acids, and therefrom D-sugars and D-nucleosides, in high chiral excess under sensible prebiotic conditions. Some important remaining goals are also described.

INTRODUCTION

Currently we are not surprised that L-amino acids and D-sugars are produced in biological systems, since the enzymes that produce them are themselves homochiral (not a mixture with their mirror images). On prebiotic Earth, no such chirally selective catalysts were there to make the first amino acids or sugars or nucleosides, so many scientists have speculated on how such selectivity could have arisen in a previously achiral world. Some have invoked chiral faces of quartz, and some have suggested an accident that was then promulgated, but the question has had no important new impetus until recently. In 1969, a carbonaceous chondritic meteorite landed in Murchison, Australia, carrying many organic compounds. (See an extensive recent review by Pizzarello and Groy,[1] including the earliest work by Kvenholden et al.[2] and by Cronin and Pizzarello[3] cited in the review.) These compounds were apparently able to survive the frictional heating as the meteorite passed through our atmosphere since they were initially at ca. 10 K, and chondritic meteorites are pieces of rock, with low thermal conductivity, from the asteroid belts that surround the sun. When the meteorite was split open, the interior was still cold enough to freeze water.

Among the compounds identified were the amino acids alanine, valine, aspartic acid, glutamic acid, proline, and leucine, which were racemic, with equal mixtures of the L and D forms, along with achiral glycine. However, five amino acids were found that had methyl groups instead of hydrogens on their α positions (Figure 1), and these had a range of small excesses of

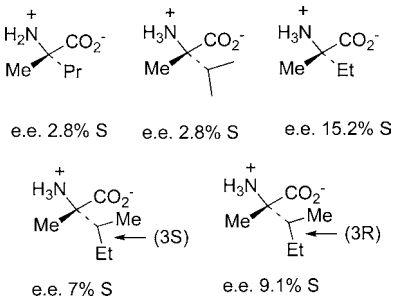

Figure 1. Some α-methyl amino acids discovered in the Murchison and other meteorites, all of which have a small excess of the *S* configuration that was described as L. The enantiomeric excesses showed a range of values in this and later work.

the enantiomers originally described as the L-amino acids (in modern terminology they are the *S* enantiomers). Since that time, these and other α-methyl amino acids with small excesses of the *S* enantiomer have been found in the Murchison, Murray, and Orgueil meteorites.[1]

How do we know that these α-methyl amino acids were not simply contaminants from Earth, added after the meteorites landed? There are three arguments against this. First, the actual α-methyl amino acids isolated from the Murchison meteorite are not found in our biology today, but the meteorite landed here only 41 years ago. Against this, there are some α-methyl amino acids produced by microorganisms[4−6] but not all the ones in the meteorites. Second, enzymes do not produce compounds with only partial chiral selectivities; such partial chiralities are really symptomatic of species that were originally racemic but have since been partially deracemized. If microorganisms had invaded the meteorites after they landed, the microorganisms could perhaps selectively cause destruction of the D enantiomers of the amino acids if they had originally been racemic, but there is no evidence for such an unlikely process. An alternative scenario for such partial deracemization will be described below. Finally, the α-methyl amino acids have levels of ^{13}C and non-exchangeable deuterium much higher than those seen in molecules formed on Earth. These high levels of heavy isotopes are generally seen in atoms delivered from space, where isotopic fractionation is performed at very low temperatures. They are generally accepted to be definitive proof that the species examined are not of terrestrial origin.

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Microwave spectroscopy has detected hundreds of molecules in the interstellar gas clouds in space, and they include ammonia, hydrogen cyanide, hydronium ion, and various ketones and aldehydes and the acetylenes from which they can be derived.[7] Thus, the meteoritic unmethylated and methylated amino acids were probably formed by Strecker reactions[8] from such species. The reactants are aldehydes for normal unmethylated amino acids and methyl ketones for the α-methyl amino acids, along with HCN, NH_3, and H_3O^+. Methyl ketones are the products from reaction of terminal acetylenes with hydronium ion. The multimolecular reactions would occur on solid particles whose larger versions are asteroids, and they would be initially formed as racemates. They could develop some excess of the L-forms if the racemates absorbed circularly polarized light that selectively destroyed one enantiomer, perhaps also using another process to amplify them.[9]

William Bonner had shown that right circularly polarized light at ultraviolet (UV) wavelengths would selectively destroy the D component of racemic leucine, leaving a small excess of the L-amino acid.[10] Astronomers have detected a small excess of circularly polarized infrared (IR) light in space, the energy of which is too low to deracemize amino acids.[11−13] However, one author indicated that the same processes that produce the identified circularly polarized light in the IR might also produce it in the UV.[12] Very high energy light cannot penetrate our atmosphere for observation as IR can, and could not penetrate it when our early atmosphere consisted of nitrogen and CO_2. As one possibility, favored by many astronomers, circularly polarized light could be formed in the universe by cyclotron processes in neutron stars, just as experimental cyclotrons produce circularly polarized light with opposite chirality above and below the circulation plane. Some other astronomers prefer that circularly polarized light could be produced by magnetic dwarf stars. One of the important challenges for astronomy is to observe outside our atmosphere and detect circularly polarized short-wavelength light, if it is there. For instance, observations could be made from orbiting satellites, from the Hubble telescope, or from the new Web Space Telescope. I am trying to get such observations made.

If there was also (yet undetected) right circularly polarized light with energy in the UV or higher irradiating the asteroid belt when the amino acids were present on a particle that later came to Earth, this could account for the small excesses of the L enantiomers seen in the α-methyl amino acids. If this also happened with the unmethylated amino acids that are found in our proteins, they could racemize by reversible loss of their α protons over time, explaining why they are found in racemic form, but no such racemization is possible with the α-methyl amino acids. (Isoleucine has two chiral centers, and it is not completely racemic. The α-center would be equilibrated by reversible loss of its somewhat acidic proton, but the β-center could not be equilibrated, so isoleucine could not be racemized by half conversion to its mirror image.)

Thus, an attractive idea is that the L-amino acids and the D-sugars that are now the basis of life were first "seeded" by the arrival on Earth of α-methyl amino acids in meteorites, formed on asteroid fragments as racemates and then partially deracemized by circularly polarized light of short wavelength.[14] Light of the needed wavelength could not penetrate Earth's atmosphere—now or in the past—so the deracemization occurred in space, and the result was then delivered to Earth. Such homochirality was probably important since mixtures of enantiomers would not form well-defined structures on random incorporation into polypeptides, polysaccharides, or polynucleotides. In fact, it seems likely that homochirality is generally necessary for the origin of life anywhere, so without the kind of processes that started it on Earth, other planets would not produce life. On Earth the amino acid chirality was what we call L, but on other planets the mirror image systems could occur by the processes we describe.

We have recently shown how such α-methyl amino acids can generate normal unmethylated biological amino acids with some chirality transfer, and how that excess chirality can be amplified under credible prebiotic conditions, producing aqueous solutions with very high enantiomeric excesses (ee's). We have also shown how the D-sugars and D-ribonucleosides could have arisen on prebiotic Earth.

RESULTS AND DISCUSSION

We address two questions. (1) What credible prebiotic chemistry could use the small excess *S* (L) chirality of the α-methyl amino acids in a meteorite to seed the formation of L-amino acids without such methyl groups? (2) How could credible prebiotic processes amplify small ee's to available high enantiopurity in solution? The ideal is of course 100%, but ee's of 90% or better could probably be enough for primitive biology to select the dominant enantiomer.

Formation of Unmethylated Amino Acids with Some L Excess. We devised a process of decarboxylative transamination: α-methyl amino acids reacted with α-keto acids to form unmethylated amino acids on simple heating in the presence of Cu(II) (Figure 2).[15] This was based on earlier work

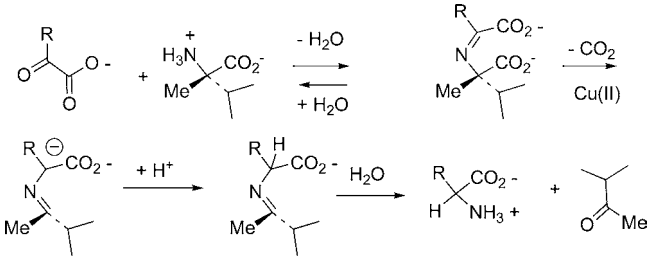

Figure 2. Transaminative decarboxylation of the imine from *S*-α-methylvaline and an α-keto acid. In the presence of Cu(II), which catalyzes the reaction, the product amino acid has an excess of the L enantiomer, but not without the Cu(II). This is expected if a square planar complex is formed between two imines and the Cu(II), so after decarboxylation of one ligand it is protonated selectively, guided by the stereochemistry of the other ligand.

we had done showing that α-methyl amino acids could perform such decarboxylative transaminations with pyridoxal.[16]

We observed some chiral transfer, in which the reaction of 100% ee *S*-α-methylvaline with sodium phenylpyruvate led to a 37% ee of L-phenylalanine, and the same process with sodium pyruvate led to a 20% ee of L-alanine. The reaction of sodium dimethylpyruvate with *S*-α-methylisoleucine afforded L-valine with 17% transfer of chirality. All these processes were successful only in the presence of catalytic Cu(II), a component of some meteorites and surely present on prebiotic Earth. Without it, or with Zn(II) instead, the reactions were much less successful, and the correct chiral transfer was not observed.

The process was credible under prebiotic conditions, involving only heating of the components in the presence of some catalytic Cu(II) ion. As we described,[15] DFT calculations

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indicated that a square planar Cu(II) complex of two imines that were formed from the amino acid and the keto acid would decarboxylate one of them, which would then protonate to form the L-amino acid steered by the chirality of the second ligand, as we observed. However, the few percent of *S* excess in the meteoritic amino acids would produce only a 1% or so ee in the product amino acids. Amplification of the resulting chiral excess would be critical to achieve a dominance of the L-amino acids large enough—of the order of a 90/10 ratio or better of L to D—that new organisms or pre-organisms would select them for evolutionary success.

Amplification of the L-Amino Acid Excesses in Solution. In 1969, Morowitz had proposed a process by which a small ee of an amino acid could be amplified to form solutions with large ee's under simple prebiotic conditions.[17] This was an amplification of the concentration of the excess component in solution by concentrating it and removing the racemate, not by making more of it. We conceived the same idea in 2006,[18] not aware of Morowitz's work, and Blackmond also published a version of the concept in 2006, slightly before our publication.[19−21] All our ideas were based on the general fact that most amino acids form racemic compound crystals that are less soluble, and higher melting, than the crystals of entirely the L or the D enantiomer. In such racemic crystals, neighboring L and D molecules interact to lower the free energy—either by better crystal packing or by direct stabilizing interactions in the crystals—compared with crystals where an L molecule has only other L neighbors.

The idea is that a mixture of D- and L-amino acids with some excess of the L component (or elsewhere in the universe perhaps the D component) would dissolve in water, and as the water evaporates, the less soluble racemate would precipitate, leaving a solution with increased richness in the L component. Because the precipitation of the racemate depends on the solubility product SP(DL) = [D][L], while that of the homochiral L compound depends only on the solubility S[L], there would be feedback to increase the precipitation of the racemate as the concentration of L increases. Thus, starting with a small excess of the L-amino acid, the final L/D ratio would become very large with even a modest difference in solubilities. The Morowitz treatment[17] is shown below:

$$S(L) = [L]$$

$$SP(DL) = [D][L]$$

$$[D] = SP(DL)/[L]$$

$$[L]/[D] = S(L)^2/SP(DL)$$

The solubility product SP(DL) is equal to the square of half the solubility of the racemate. By this equation, if the homochiral crystals were only twice as soluble as were the racemates, the final ratio [L]/[D] would be 16/1, a solution with 94% of the L and 6% of the D. If the homochiral crystals were 3-fold as soluble as the racemate, the final L/D ratio would be 36/1. As we will describe later, this treatment is not quite correct and can overestimate the selectivity for reasons we have demonstrated.

The previous theories and experiments involved solutions at equilibria, but kinetics can often afford different results. With equilibrium solubilities, we saw L-tryptophan amplified to 94.5% L and 5.5% D, starting with any arbitrarily small excess (the treatment is true for any initial ratio, limited only by the practical need to achieve saturation in both the racemate and homochiral compounds, so smaller amounts of water would be needed with smaller initial L excess).[15] However, we found that this ratio was increased to 99/1 in solution when we poured a small amount of water through the final dry mixture, imitating the effect of rainwater.[15] Homochiral and racemic crystals differ in their activation energies for subtracting (or adding) units, a form of dissociation (or binding), and in our case the homochiral crystals dissolve faster beyond the requirements of the equilibrium constants.

Forming D-Sugars under Prebiotic Conditions. We have investigated the formation of the simplest sugar belonging to the D series, D-glyceraldehyde. All other sugars in the D family—including D-ribose, D-glucose, D-fructose, D-erythrose, etc.—are named for the geometry of the chiral center farthest from the carbonyl group in the sugar, and this is the unique chiral center in D-glyceraldehyde. Sugars were probably synthesized on prebiotic Earth by a process called the formose reaction.[22] D-Ribose ($C_5H_{10}O_5$) is a formal pentamer of formaldehyde (CH_2O), whose dimer is glycolaldehyde and whose trimer is glyceraldehyde. In the formose reaction, formaldehyde is treated with a mild base such as calcium hydroxide. There is a period when nothing happens until the sudden conversion of the formaldehyde to glycolaldehyde, glyceraldehyde, and even larger sugars. We proposed and demonstrated the mechanism of the formose reaction (Figure 3) by an autocatalytic cycle many years ago.[23]

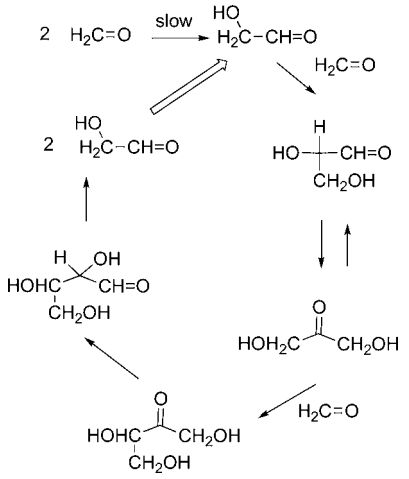

Figure 3. The formose reaction, producing sugars from formaldehyde.

A first molecule of glycolaldehyde is formed from formaldehyde by a slow unknown process, possibly involving ionization by cosmic rays, and this glycolaldehyde then reacts with an additional formaldehyde to form glyceraldehyde. This glyceraldehyde is then in equilibrium with dihydroxyacetone by enolization and ketonization, and it then reacts with another formaldehyde to form a four-carbon ketosugar. By enolization and aldehyde formation, a four-carbon aldehyde is formed that can undergo a reverse aldol reaction to form two molecules of glycolaldehyde. After this, four glycolaldehydes result from another turn of the cycle, etc.

We examined the formation of glyceraldehyde, a three-carbon sugar that is the simplest one with a chiral center.[24] Glyceraldehyde is formed in the formose cycle by the reaction of formaldehyde with glycolaldehyde. Without a chiral catalyst, this reaction would form both D-glyceraldehyde and its enantiomer L-glyceraldehyde in equal amounts, but we studied

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what would happen if the reaction were catalyzed by a chiral amino acid. We can trace the formation of L-amino acids back to the small excesses of *S*-α-methyl amino acids in the Murchison meteorite, so the question was simple. Would L-amino acids catalyze the formation of D-glyceraldehyde preferentially, at least to a small extent, and if so could the preference be amplified to a sufficient extent that the dominant D-glyceraldehyde would be selected by incipient life? If so, then all of the D-sugars—built on the D-glyceraldehyde by adding pieces to its aldehyde group that do not change the geometry of the D center in the glyceraldehyde original unit—are part of the general origin of homochirality tracing back to the meteorites. If not, a new source of homochirality will need to be found for the sugars. As Table 1 shows, we examined various L-amino acids from different classes.

Table 1. Ratio of D- to L-Glyceraldehyde from Glycolaldehyde and Formaldehyde Catalyzed by Various L-Amino Acids[a]

serine	50.3/49.7	alanine	50.8/49.2
phenylalanine	52.2/47.8	valine	52.2/47.8
glutamic acid	60.7/39.3	proline	28.9/71.1

[a]The reaction conditions and analytical method are described in ref 24.

The reaction of formaldehyde with glycolaldehyde is an aldol reaction, and many such reactions are known to be catalyzed by amines. The amines would react with the glycolaldehyde to form an enamine, which would then add to the other carbonyl component. Thus, we carried out the reaction of glycolaldehyde with formaldehyde in water in the presence of a variety of L-amino acids. We found (Table 1) that all the L-amino acids caused the formation of glycolaldehyde with a small excess of the D enantiomer, with one exception: L-proline catalyzed the formation of an excess of L-glyceraldehyde. (Some recent work by Blackmond[25] indicates that in basic solution this proline preference is reversed when the carboxyl group is a carboxylate ion, so proline may not be an exception after all.)

The preferences were modest. There was a 60/40 ratio of D/L-glyceraldehyde catalyzed by L-glutamic acid, for instance, and smaller ratios with the other L-amino acids. Proline was probably not present in large amounts among the early amino acids, since it is formed in two secondary reactions from glutamic acid, so it would not dominate the chiral selectivity. The results with the other amino acids did support the idea that the preference for D-glyceraldehyde—and then the other D-sugars derived from it—was simply the result of the formation of the other L-amino acids on prebiotic Earth.

We then asked whether there was a likely process for amplifying the small excess of D-glyceraldehyde formed in this way, preferably by using the selective solubilities that had worked with the amino acids. This turned out to be possible. D-Glyceraldehyde is a syrup with essentially complete water solubility, but racemic DL-glyceraldehde is a solid with a melting point of 145 °C and a limited water solubility. The striking difference has an explanation. A previously published X-ray structure determination showed that DL-glyceraldehyde exists as a chair-form six-membered-ring dioxane dimer of one D and one L molecule, with all the substituents equatorial as in chair cyclohexane, so this flat dimer molecule packs well into a crystal.[26] With the same structure based on a dimer with D-glyceraldehyde alone, one large group in the six-membered DD ring would be axial, making the dimer less stable and also making crystal packing less favorable. The result was that we could take the 60/40 ratio of D/L-glyceraldehyde formed by catalysis with glutamic acid and turn it into a 92/8 D/L ratio in water solution by slow evaporation of water, causing the racemic crystals to precipitate.

Formation and Amplification of D-Ribonucleosides. An aldol condensation of D-glyceraldehyde wth glycolaldehyde would lead to D-ribose. We are studying the selective catalysis of this reaction, in which two new chiral centers are produced. In the meantime, we examined the possibility that any excess of D over L in ribose could be amplified by selective solubilities, as in the amino acid and glyceraldehyde cases. In contrast to the situation with amino acids, we saw that D-ribose and DL-ribose had the same melting point.[27] Ribose apparently forms a racemate that is a solid solution, with essentially identical properties, solubilities, and melting points at all D/L ratios. In the solids a D-ribose molecule can equally well have either a D or an L as its neighbor. We did not examine their solubility, since in all cases that we know of a lower solubility correlated with a higher melting point—both melting and dissolving break up the crystals. For this reason, D-ribose cannot be amplified by the selective solubility method. Thus, we examined the ribonucleosides (Figure 4).[27]

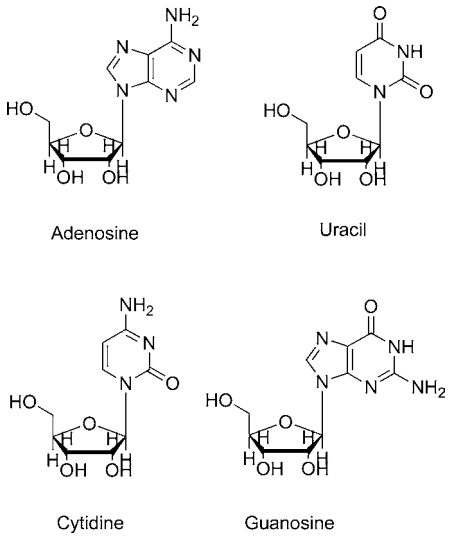

Figure 4. The nucleosides that were examined.

It had been shown previously that ribose reacts with purines under prebiotic conditions to form ribonucleosides.[28] In the first work, pyrophosphate was present to activate the ribose, but in later work it was shown that the pyrophosphate could be replaced by the residue from dried seawater. We are working on extending these results to pyrimidine nucleosides (see another proposal[29] on how pyrimidine nucleosides could have been formed), and in the meantime we examined whether ribonucleosides with small excesses of the D form could be amplified by the solubility method.

We synthesized L-uridine by a literature method and made a 1:1 mixture with D-uridine. We then crystallized the racemate to purity and examined its properties. The crystals of uridine racemate had a melting point of 176 °C, higher by 21 °C than the 155 °C melting point for D-uridine. D-Uridine had a water solubility at 22 °C of 454 mg/mL, while the racemic uridine had a solubility of only 87 mg/mL, 5.2 times smaller. By the

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Morowitz calculation this should afford a D/L ratio of 108/1 at saturation with both crystals. We then dissolved both the D-uridine and the DL-uridine crystals to saturation together in water at 22 °C, filtered away the excess, and saw 96% D and 4% L in solution, a ratio of 24/1. The large ratio makes the D-uridine dominant, but it is lower than predicted by the Morowitz theoretical treatment.

We then examined the situation with adenosine, synthesizing L-adenosine and mixing it with D-adenosine, and then recrystallizing the racemic crystals to purity. In this case the melting point of the racemate was 243 ± 1 °C, while for D-adenosine the melting point was 230 ± 1 °C. The solubility of D-adenosine in water at 22 °C was 5.2 mg/mL, 6.3 times as large as the 0.8 mg/mL for the DL crystal. There should have been a 160/1 D/L ratio at saturation equilibrium from the Morowitz treatment, but we observed a 99/1 ratio of D/L-adenosine—again very large, but again lower than predicted by the Morowitz treatment. With cytidine we saw decomposition on melting of both the D and the DL crystals, so no melting points could be determined, but the solubilities predicted an even larger amplification than for the other two nucleosides. D-Cytidine had a solubility of 192 mg/mL in 22 °C water, while DL-cytidine had a solubility of 24.3 mg/mL. The Morowitz equation predicts a D/L ratio of 250/1 at saturation, while we observed 199/1.

All three of these nucleosides can be amplified to very high D/L ratios by selective solubilities, but the Morowitz treatment overestimated the ratios. We concluded that this could reflect the fact that the solubilities being measured were in pure water, but the solubilities relevant to the amplification experiments are in water along with a second component. In the experiment, the solubility of the racemate that is relevant is that in the presence of the homochiral component that is also in solution. We concluded that the homochiral dissolved material was acting as a cosolvent, increasing the solubility of the racemate over that in pure water.[14] The dissolved homochiral component has two roles. It helps drive the racemate out of solution by its role in the solubility product of the racemate, but in the other role it increases the solubility of the racemate by acting as an antihydrophobic cosolvent like ethanol, in which relatively hydrophobic substrates such as nucleosides have greater solubility than in pure water. If this is true, the solubility of the homochiral crystals would also be increased by the presence of the racemate in solution, but at final saturation—with little dissolved racemate—this effect would be smaller.

To test this idea, we examined the solubility of racemic uridine in water with D-cytidine added to saturation.[14] This can mimic the cosolvent effect of D-uridine but does not play a role in the solubility product of DL-uridine. We found that the D-cytidine increased the solubility of DL-uridine by 40% over that in pure water. Thus, the Morowitz treatment overestimates the amplifications a bit, because it does not include the cosolvent effect. The experimental values are still so high that they could lead to the dominance of the D-nucleosides on prebiotic Earth, even starting from a very small initial excess.

Guanosine behaved differently.[27] D-Guanosine and the DL-guanosine crystals melted with decomposition, but we could still examine their solubilities in 22 °C water. DL-Guanosine had a solubility of 0.84 mg/mL, while D-guanosine had a solubility of 0.46 mg/mL, essentially half that of the racemate. This indicated that the racemate belongs to a third class of racemic crystals. It is not a solid solution as we saw with ribose, nor a racemic compound crystal like those of uridine, adenosine, and cytidine. It is a racemic conglomerate of D and L crystals, each with its own solubility. Such a conglomerate is like that with racemic sodium ammonium tartrate, which allowed Pasteur to separate the D and L crystals by hand.

This inversion in solubilities, with the racemate more soluble than the homochiral compound, makes it impossible to amplify D-guanosine by selective solubilities, but of course the D-ribose from hydrolysis of the other three nucleosides could have been used to synthesize D-guanosine on prebiotic Earth. The D-ribose resulting from hydrolysis of the other three nucleosides could also play additional important biochemical roles, including conversion to D-ribulose whose diphosphate is the key sugar in photosynthesis.

CONCLUSION

This work[30,31] answers some of the questions in the general idea that the unusual amino acids delivered to Earth by the Murchison meteorite and related ones could have led to the dominance of L-amino acids and D-sugars on early Earth that would permit life to start. Of course, showing that it *could have* happened this way is not the same as showing that it *did*. Proper theories need the possibility of falsification. This account would be in trouble if significant examples were found in which meteorites that landed on Earth contained *R*-α-methyl amino acids instead of the *S* examples in the Murchison meteorite and others examined so far. An alternative scenario to ours would use the Murchison α-methyl amino acids to catalyze the formation of some D-sugars, as Pizzarello and Weber have shown[32] (cf. refs 33 and 34 for related work), and then use those sugars to catalyze the formation of the normal proteinogenic L-amino acids. Good credibly prebiotic examples of the latter process have not yet been produced.

Further work is needed to show prebiotic versions of the conversion of D-glyceraldehyde to D-ribose, D-glucose, D-fructose, and D-2-deoxyribose—such efforts are underway in our laboratory. We also need a credible way in which nucleosides and nucleotides could be formed from these sugars and pyrimidines, not just purines. Finally, of course, we all need ways in which these and other sensible building blocks could assemble into structures with the exciting properties of life.

An implication from this work is that elsewhere in the universe there could be life forms based on D-amino acids and L-sugars, depending on the chirality of circular polarized light in that sector of the universe or whatever other process operated to favor the L-α-methyl amino acids in the meteorites that have landed on Earth. Such life forms could well be advanced versions of dinosaurs, if mammals did not have the good fortune to have the dinosaurs wiped out by an asteroidal collision, as on Earth. We would be better off not meeting them.

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Notes

The authors declare no competing financial interest.

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