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Partial transfer of enantioselective chiralities from α-methylated amino acids, known to be of meteoritic origin, into normal amino acids

Ronald Breslow* and Mindy S. Levine

Department of Chemistry, Columbia University, New York, NY 10027, USA

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Abstract—There is overwhelming evidence that meteorites bring α-methylated amino acids to earth with some L(*S*) enantiomeric excess. How does that get transferred into normal biological molecules? In this brief account, we show that an α-methylated amino acid, D(*R*)-α-methylvaline, can react with pyruvate and phenylpyruvate salts in dry mixtures to form alanine and phenylalanine with L enantiomeric excesses, under sensible prebiotic conditions. Thus the meteoritic L(*S*) excesses of this compound would produce excess D-alanine and D-phenylalanine, which are found in some organisms.

One of the most intriguing biological/chemical questions is the origin of homochirality on earth. Various ideas have been discussed including the possibility that there could be some enantiomeric enrichment induced in terrestrial processes by circularly polarized light[1] or chiral minerals, but one of the most interesting recent findings is that enantiomeric preferences have been brought to our planet in organic compounds carried by meteorites. Murray and Murchison carbonaceous chondritic meteorites have been found to contain α-methylated amino acids with L(*S*) enantiomeric excesses (ee) up to 15%.[2–4] It is generally believed that a small excess of this magnitude or lower can be amplified to the point at which the proteins of living organisms could have the known 100% excess of the L amino acids in proteins, for instance, so the enantiomeric excesses seen in the meteorites could be the seed from which our known highly homochiral biological molecules have grown. In fact, such amplification of small ees has been seen in some chemical processes,[5] but not yet in reactions that could play a prebiotic role.[1]

α-Methylated amino acids really cannot racemize, in contrast with normal biological amino acids that have a weakly acidic hydrogen on the stereogenic center and would be expected to racemize on the evolutionary time scale.[6] Previous reports of L-excesses in proteinogenic amino acids[7] found on meteorites have been criticized on the grounds that the sampling procedure permitted terrestrial contamination.[8] By contrast, the observed L-excesses in α-methylated amino acids are generally believed to be indigenous to the meteorites rather than the result of terrestrial contamination. This claim is supported on four grounds:[9] (1) The α-methylated amino acids found are exceedingly rare in nature on earth. (2) There is no correlation between the degree of L-excess and possible terrestrial contaminants. In particular, the finding of an only *partial* ee of a non-racemizable compound is not seen in biologically produced products. (3) The analytical procedures used reduce the likelihood of co-eluting contaminants. (4) Most convincingly, the α-methylated amino acids contain increased abundances of heavy isotopes ^{13}C and (non-exchangeable) D compared with compounds of terrestrial origin. Such isotopic abundances are typical of meteoritic components, reflecting isotopic fractionation in their formation, and distinguish them from materials of terrestrial origin.[10,11]

Carbonaceous chondritic meteorites contain a wide range of other organic compounds, including amino acids, hydrocarbons, α-hydroxy acids, and amines.[12] Thus carbonaceous chondritic meteorites, bombarding early earth, could have delivered enantioenriched

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* Corresponding author. Tel.: +1 2128542170; fax: +1 2128542755; e-mail: rb33@columbia.edu

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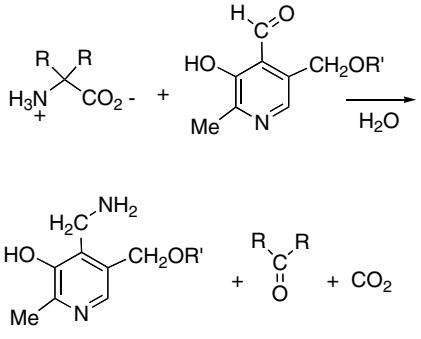
α-methylated amino acids that served as the origin of homochirality on our planet. However, α-methylated amino acids are found only rarely in biological systems. This hypothesis implies that they would have transferred their enantioenrichment to more normal biological molecules, such as sugars or ordinary amino acids.[12]

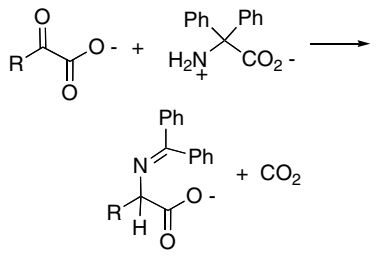
An intriguing chemical challenge is to demonstrate a mechanism by which the enantiomeric excesses in α-methylated amino acids could be transferred into normal biological molecules under prebiotic conditions. As a previous example, Pizzarello has shown that 100% *S* α-ethylalanine can catalyze the dimerization of glycolaldehyde to erythrose and threose with some chiral induction.[13] The erythrose was formed with a 5% ee of the L enantiomer, the non-biological form, while the threose was formed with an 11% ee of D-threose, the biological form. We realized that some work we have recently reported could also provide a mechanism for ee transfer. We had seen that α,α-disubstituted glycines could undergo transaminative decarboxylation with pyridoxal derivatives to form pyridoxamine and a ketone, as part of an overall transamination process with multiple turnovers (Scheme 1).[14] In the course of this work we also saw that α,α-diphenylglycine **1** would react directly with α-ketoacids such as pyruvate to perform a direct decarboxylative transamination without the need for a pyridoxal cofactor (Scheme 2).[15] It occurred to us that this direct process could be a means to transfer enantiomeric excesses from the meteoritic α-methylated amino acids into normal biologically relevant amino acids.

In this letter, we report a mechanism of enantioinduction in the transamination of pyruvates to amino acids, using enantiopure D-α-methylvaline **2** both as the transaminating reagent and as the source of enantioselective protonation. Other mechanistic proposals have been based on octameric clusters,[16] isovaline itself,[17] and incorporation of α-methylated amino acids into peptides with normal amino acids,[12] but none before has demonstrated that enantiomeric α-methylated amino acids can perform the synthesis of normal amino acids, and with some transfer of enantioselectivity.

Our system involves simply heating a mixture of D-α-methylvaline with a pyruvate salt, in which we asked several questions. (1) Does the mixture perform a decarboxylative transamination to convert pyruvate to



Scheme 1.



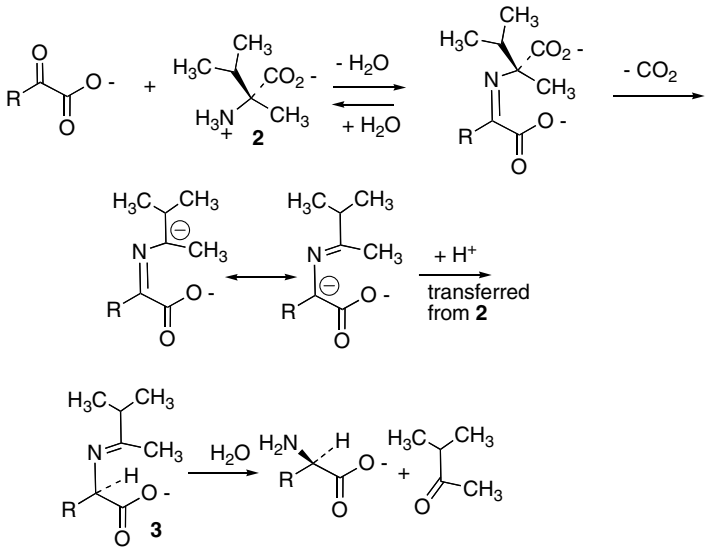
Scheme 2.

alanine, or phenylpyruvate to phenylalanine? Under the right conditions, the answer was Yes. (2) Does the new amino acid have some enantiomeric excess, induced by proton transfer from the homochiral α-methylated amino acid? The answer was again Yes. (3) If so, would the D-α-methylated amino acid lead to a D- or an L-aminoacid as the preferred enantiomer? The answer was L, there was a reverse induction. Thus under our conditions the meteoritic L-α-methylated amino acid would lead to the formation of phenylalanine with the preference for the D, and not the L form. L is of course the normal enantiomer in the proteins of higher organisms, including humans. However, some bacteria contain D-amino acids as well,[18] and D amino acids play an important role in some other lower organisms such as mollusks.[19] Thus the preferential synthesis of D-amino acids by our transamination process is not irrelevant to likely early biology.

By analogy with our previous work using α,α-diphenylglycine to transaminate ketoacids,[14,15] we first used D-α-methylvaline **2** and sodium pyruvate in solution, but no transamination occurred. Thus we went to solvent-free conditions. Reactants were dissolved in a methanol/ethanol mixture or in water, the solvent was then evaporated, and the solid was heated to various temperatures from 100 to 160 °C for a specified period of time, from 1 to 30 min. This mimics the common prebiotic concept of chemistry in a dried lake bed. The mixture was then taken up in water, which hydrolyzed the product imine (Scheme 3), and subjected to reverse-phase hplc analysis. Enantioselectivities were measured to low conversion (<15%) to minimize product racemization.

Our initial substrate, sodium pyruvate, gave at most 3% L ee of product alanine under a variety of times and temperatures (Scheme 3, R = methyl). Higher enantioselectivity was seen with sodium phenylpyruvate, forming phenylalanine (R = Ph–CH_2). With a 2:1 stoichiometric ratio of D-α-methylvaline to sodium phenylpyruvate, up to a 9.5% L ee of phenylalanine was formed (Table 1). Using a 4:1 excess of the D-α-methylvaline afforded L ee's of $7.65 \pm 0.1\%$ at 100 °C after 10 min, and $7.2 \pm 0.3\%$ after 30 min, while at 120 °C the results were $4.5 \pm 0.3\%$ after 10 min, and $3.4 \pm 0.6\%$ after 30 min. Similar data were obtained whether the original solution, before evaporation, was alcohol or water.

In the mechanism of Scheme 3, the D-α-methylvaline plays two roles. First of all, it performs the transaminations that convert a ketoacid to an amino acid, while



Scheme 3.

itself becoming a ketone after hydrolysis. It is also the source of the proton on the alpha carbon of the product amino acid, delivering it stereoselectively. The reaction in a dry mixture minimizes the chance that there will be other non-chiral sources of this proton. When we performed the reactions on montmorillonite clay, for example, we saw no enantioselectivity in the process, probably since clay can supply the proton.

Ketoacids could be formed by air oxidation of the α-hydroxy acids that are components of the meteorites, and the dry hot conditions of our transaminations can certainly be invoked for a prebiotic process. Indeed, our data, such as in Table 1, indicate that racemization accompanies the transamination at higher temperatures, so longer times at lower temperatures could perhaps afford even higher enantiomeric excesses. However, there are still important questions. Perhaps the first one is, why do the meteoritic α-methylated amino acids have a partial enantiomeric excess? The most likely ideas involve high levels of high energy circularly polarized ultraviolet light in space,[20] although there is no agreement on this. Then we still need a credible idea of how partial enantioenrichment in the product amino acids or sugars can be amplified under prebiotic conditions.[4,5] We also need a way in which the more biologically common L-amino acids could be formed from meteoritic components. Thus our enantioselective transaminations by α-methylated amino acids are certainly not the last word on this problem. However, the main point is that there is excellent evidence that enantioselectivity arrived on earth from space, carried by meteorites. The challenge for chemists is to develop other credible prebiotic processes by which the meteoritic components could have induced the extremely high enantiomeric preferences we see in common biological molecules, such as amino acids and sugars. This is a challenge to which W. A. Bonner devoted much of his scientific life.[20]

Table 1. L Enantiomeric excess of the phenylalanine produced from phenylpyruvate and D-α-methylvaline heated as a dry mixture[a]

	1 min	5 min	10 min	30 min
100 °C	[b]	9.5 ± 1.5%	9.4 ± 1.6%	6.87 ± .01%
120 °C	8.3 ± 1.2%	6.0 ± .6%	5.8 ± 1.7%	3.5 ± 0.7%
160 °C	4.0 ± 1.1%		Racemic	

[a] All values are L ee and represent an average of 2 runs.
[b] No reaction occurred.

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