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High Temperature Sublimation of α-Amino Acids: A Realistic Prebiotic Process Leading to Large Enantiomeric Excess.

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The reiterative high temperature co-sublimation of an enantiopure or an enantioenriched α-amino acid mixed with racemic α-amino acids leads to deracemization of the latters. A synergistic effect is observed for complex mixtures, and the sense of the handedness is, for all compounds, identical to the one of the enantioenriched starting material.

The enantioselective formation of chiral building blocks of life on the Primitive Earth is one of the cornerstones in the theory of the origin of life. In spite of the diversity of the proposed plausible pathways discussed in the literature,[1-3] the subsequent transfer and amplification of the slight imbalance between the enantiomers still provokes lively scientific debates.[4-6] Among proposed scenarios can be mentioned the transfer of asymmetry from extraterrestrial matter, chiral symmetry breaking and segregation of enantioenriched fractions as a result of phase transitions. Based on the distinctive feature of enantiomers and racemates in the majority of cases to be physically non-identical, a lot of attention has been recently paid to changes of enantiomeric excess in solid-solution and solid-gas transition phases.[4] For example, Lahav et al. described chiral resolution of amino acids on enantiotopic facets of achiral α-glycine and subsequent complete enantioenrichment at the air-solution interface.[7] In the group of Kojo it was found a stochastic enantioselective crystallization of racemic complex mixtures of amino acids in the presence of racemic asparagine.[8]
Paradoxically the processes of the loss of asymmetry (e.g. racemization) in one of the phases of heterogeneous systems can sometimes lead to the emergence of homochirality and total symmetry breaking. For optically inactive mixtures of chiral crystals which are in contact with their saturated solutions, Viedma et al. demonstrated application of mechanical attrition for the homo-chiral Ostwald ripening.[9] Based on the works of Arai,[10-12] several researchers[13-16] reported the mechanism of spontaneous evolution of solid phase single chirality via multiple racemization-recrystal-lization cycles applying the Viedma methodology of ripening.[9] On the other hand, the group of Soai in first,[17,18] then Tsogoeva et al.[19-21] and later Gehring et al.[22] found striking examples of asymmetric

autocatalysis providing either enantiopure product without any chiral auxiliaries or external asymmetrical inductors.
In the particular case of α-amino acids, dissolution, saturation of solutions and recrystallization have been recently re-examined revealing a general tendency of the non-racemic mixtures to change the enantiomeric excess of each phase based on simple physical processes.[3] Another series of experiments has been focused on sublimation of a non-racemic proteinogenic amino acid, showing enantiodepletion, enantioenrichment and deracemization as a result of the solid gas fractionating.[23-29] The clearly marked aptitude of some amino acids to form ionic oligomeric clusters in the gas pha-se[30] has been taken into account while interpreting the segregation of enantiomers from racemates. On the other hand, Soloshonok et al. published a series of works on fluorinated hydroxyacids considering the energies of the crystal lattice of racemates and the corresponding enantiomers as well as their different rates of sublimation as the main cause of the enantioenrichment.[31-33] More recently, in a very original experimental approach, Viedma et al. showed that very high temperature sublimation of some aliphatic amino acids induces asymmetric amplification.[34,35] We report here reiterative high temperature sublimations of mixtures of α-amino acids in the aim to find a way of deracemization of these compounds.

For the first experiments, we introduced two α-amino acids in an Erlenmeyer flask with the bottom heated to 490°C by a hot plate and we quickly closed. White particles began to turn in the flask before to be deposited on the wall and move slowly upwards. In such experiments, *all the starting material is sublimed and the analysis reflects the composition of the whole mixture*. Such Reiterative High Temperature Sublimations (RHTS) of mixtures containing an enantiopure (Leu or Val) and a racemic amino acid (resp. Val or Ala and Val) led to a significant enantiomeric excess (ee) of the primordially racemic compound with a handedness identical to the one of the enantiopure: for example, one equiv. of racemic valine and 4 equiv. of enantiopure leucine gave an ee of 26% for valine with a 77±5% % yield in weight † (Table 1, entry 1). With alanine instead of valine, an ee of 35% was obtained (Table 1, entry 4). Results were much better with an enantiopure:racemate ratio of 1:0.25 (Table 1, entries 1-4) than for a 1:1.5 ratio (entry 5).

Thus, the sense of the handedness of the enantiopure determines the sense of the other one. This effect was more clearly evidenced using samples of enantiopure valine with leucine at various ee's, and even with a sense of handedness opposite to the one of the enantiopure (Val) (Fig. 1 and Table S1). In all cases, the percentage of the enantiomer corresponding to the handedness of the enantiopure has been increased. As a typical example, starting from L-Val and 23 % ee D-Leu in a 4:1 ratio, a 9 % ee of L-Leu was obtained after

Table 1: RHTS of mixtures containing one enantiopure and one racemic amino acid.[a]

Entry	Starting mixture (equiv.)	Sublimed mixture (ee %)
1	D-Leu (1) + DL-Val (0.25)	D-Leu (100), D-Val (26.7)
2	L-Leu (1) + DL-Val (0.25)	L-Leu(100), L-Val (26.6)
3	L-Val (1) + DL-Leu (0.25)	L-Val (100), L-Leu (26.0)
4	L-Val (1) + DL-Ala (0.25)	L-Val (100), L-Ala (34.9)
5	L-Val (1) + DL-Leu (1.5)	L-Val (100), L-Leu (~1)

[a] Mechanical mixtures, prepared by careful grinding of components. Each reaction was performed on 1-2 mmol (1 equiv. corresponds to 0.854 mmol). T = 490°C, time 15 min. Yields range around 77±5% for each experiment.

sublimation, showing that the most abundant amino acid imposes the sense of its handedness. Better results were found by using a higher temperature of sublimation (530 °C, Fig. 1, black dots): a leap from 30% ee (D) to 16% ee (L) was observed for leucine sublimed with L-valine.
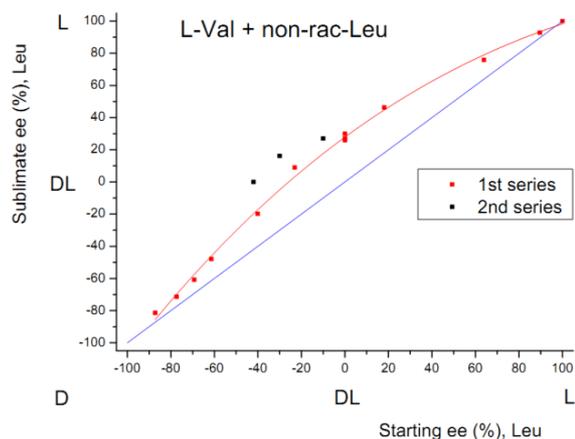
Figure 1. RHTS of L-Val and Leu with various ee. Temperature of sublimation: 490°C (red dots), 530°C (black dots). Yields range around 77±5% and 60±5% for experiment at 490°C and 530°C resp.

Furthermore, better results were obtained using several racemic amino acids with one enantiopure: the ee's of the previously racemic amino acids were higher when the enantiopure and two racemates in a 4:1:1 ratio were sublimed than using a 4:1 ratio of enantiopure and racemate (Fig. 2, Tables 1 and 2). High enantioenrichments were found using any amino acid among Val, Leu, Ala, iso-Leu, 2-Aba (2-Aminobutyric acid), nor-Val, nor-Leu and tert-Leu as enantiopure but Ala led to more modest results.

The synergistic effect was still observed when increasing the complexity of the mixtures. Thus, with a mixture containing a

4:1:1:1:1:1:1 ratio with Val as enantiopure and Ala, Leu, iso-Leu, nor-Leu, 2-ABA and nor-Val as racemates, each previously racemic amino acid possesses a ee ranging from 20.4 up to 55.3 % after sublimation (Fig. 2 and Table 2, entry 19). The set represents 1.5 equiv. of racemic amino acids with 1 equiv. of the enantiopure. For comparison, an increase of less than 1% of the ee was observed in a two-component mixture of 1 equiv. of Val and 1.5 equiv. of Leu, although that corresponds to the same ratio between enantiopure and racemate(s) (Table 1, entry 5 and Fig. 2, A). A greater number of racemic amino acids in the starting mixture gives a greater enantioenrichment of each of them after sublimation.

A fast heating of the solid mixture from room temperature to 490° led to the almost same ee's than those observed using Viedma conditions (Table 2, entry 3a and 3 resp.). However, it should be noted that ee's and yields are strongly dependent on the temperature. In spite of the similar formation of the "snowflakes-like" sublimate on the first stage of the process, we found very weak enantioenrichments at 390°C (Table 2, entry 8) and small ones at 420°C (Table 2, entry 7), while the sublimate layer was not significantly moving after the initial deposition on the wall. On the other hand, a considerable enantioenrichment associated with the moving of the sublimate on the wall was observed at elevated temperatures such as 490 – 515°. Thereby the multiple sublimation-deposition cycles seem to be responsible for the emergence and evolution of enantiomeric excess; this is in accordance with the data reported by Viedma et al. having revealed no enantioenrichment immediately after the initial stage of deposition (see ESI). [34]

The role played by the gas phase during the sublimation is also crucial: with pure dinitrogen or carbon dioxide, the apparent behavior is similar to that using air but the ee's are lower; with pure nitric oxide, results are comparable to those obtained with air, while the "snowflakes-like" behavior is not observed for experiments performed under vacuum resulting in very low ee's (Table 2, entries 9-15). Thus, the deracemizations are effective in the presence of an atmosphere. On the other hand, ee's of sublimates in RHTS conditions do not depend on the nature of the starting mixture and solubilized, dried and then ground samples have given similar results than those only ground (Table 2, entries 20-21).
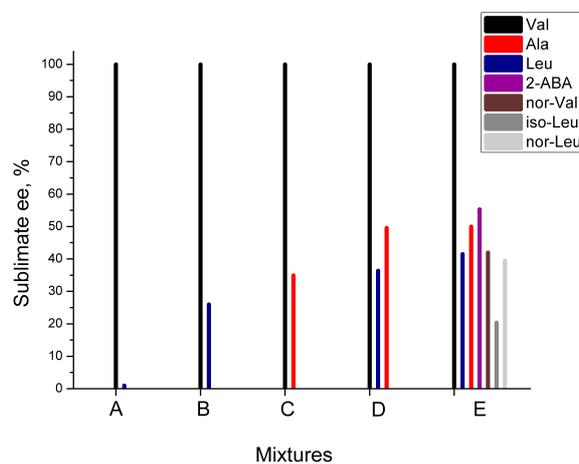
Figure 2. Synergistic effects in RHTS. A: Val (1 equiv.), Leu (1.5 equiv.); B: Val (1 equiv.), Leu (0.25 equiv.); C: Val (1 equiv.), Ala (0.25 equiv.); D: Val (1 equiv.), Leu,Ala (0.25 equiv. for each); E: Val (1 equiv.), Leu,Ala,2-Aba,nor-Val,iso-Leu,nor-Leu (0.25 equiv. for each). T = 490°C, time 15 min. Yields range around 77±5% for each experiment Each reaction was performed on 1-3 mmol (1 equiv. corresponds to 0.854 mmol).

Table 2. RHTS of mixtures with one enantiopure and several racemic amino acids [a].

Entry	Starting mixture (equiv.)	Sublimed mixture (ee %)
1	L-Ala + DL-Val + DL-Leu 1:0.25:0.25	L-Ala: 86.2; L-Val: 8.5; L-Leu: 20.7
2	L-Leu + DL-Ala + DL-Val 1:0.25:0.25	L-Leu: 99.5; L-Val: 52; L-Ala: 53.1
3	L-Val + DL-Ala + DL-Leu 1:0.25:0.25	L-Val: 100; L-Ala: 49.6; L-Leu: 36.4
3a	L-Val + DL-Ala + DL-Leu 1:0.25:0.25	L-Val: 100; L-Ala: 44.1; L-Leu: 33.3
4	L-Val + DL-Ala + DL-Leu 0.5:0.25:0.25	L-Val: 99.3; L-Ala: 31.6; L-Leu: 29.1
5	L-Val + DL-Ala + DL-Leu 0.25:0.25x2	L-Val: 96.9; L-Ala: 18.5; L-Leu: 14.8
6	L-Val + DL-Ala + DL-Leu 0.5:1:1	L-Val: 98.1; L-Ala: 4.7; L-Leu: 3.7
7[b]	L-Val + DL-Ala + DL-Leu 1:0.25:0.25	L-Val: 100; L-Ala: 13.8; L-Leu: 12.5
8[c]	L-Val + DL-Ala + DL-Leu 1:0.25:0.25	L-Val: 100; L-Ala: 2.5; L-Leu: 1.5
9[d]	L-Val + DL-Ala + DL-Leu 1:0.25:0.25	L-Val: 96.0; L-Ala: 11.6; L-Leu: 17.7
10[e]	L-Val + DL-Ala + DL-Leu 1:0.25:0.25	L-Val: 98.5; L-Ala: 9.1; L-Leu: 11.4
11[f]	L-Val + DL-Ala + DL-Leu 1:0.25:0.25	L-Val: 99.5; L-Ala: 16.3; L-Leu: 16.6
12[g]	L-Val + DL-Ala + DL-Leu 1:0.25:0.25	L-Val: 99.8; L-Ala: 22.8; L-Leu: 21.8
13[h]	L-Val + DL-Ala + DL-Leu 1:0.25:0.25	L-Val: 99.8; L-Ala: 55.4; L-Leu: 53.4
14[i]	L-Val + DL-Ala + DL-Leu 1:0.25:0.25	L-Val: 99.5; L-Ala: 22.2; L-Leu: 24.6
15[j]	L-Val + DL-Ala + DL-Leu 1:0.25:0.25	L-Val: 100; L-Ala: 3.0; L-Leu: 7.1
16	L-2-ABA + DL-(Ala, Leu, Val) 1:0.25:0.25:0.25	L-2-ABA: 98.9; L-Ala: 54.3; L-Leu: 49.4; L-Val: 63.9
17	L-norVal + DL-(Ala, Leu, Val) 1:0.25:0.25:0.25	L-norVal: 98.9; L-Val: 49; L-Ala: 37.9; L-Leu: 52.6
18	L-isoIleu + DL-(Ala, Leu, Val) 1:0.25:0.25:0.25	L-isoIleu: 97.7; L-Ala: 49.2; L-Leu: 40.2; L-Val: 45.5
19	L-Val + DL-(Ala, Leu, 2-ABA, norVal, isoIleu, norLeu) 1:6x0.25	L-Val: 100; L-Ala: 50.0; L-Leu: 41.5; L-2-ABA: 55.3; L-norVal: 42.0; L-isoIleu: 20.4; L-norLeu: 39.4
20[k]	L-Leu + DL-Ala + DL-Val 1:0.25:0.25	L-Leu 99.0; L-Ala: 58.5; L-Val: 58.8
21[k]		L-Leu: 98.7; L-Ala: 62.6; L-Val: 61.6

[a] Mechanical mixtures, prepared by careful grinding of the components. Each reaction was performed on 1-5 mmol (0.854 mmol of enantiopure was used). T = 490°C (entries 1-6, 9-19), time 15 min. The solid mixture in the experiment 3a was placed on the cold bottom of the flask followed by a gradual heating up to 490°C in several minutes. [b] 420°C. [c] 390°C. [d] in N₂. [e] in water vapor with N₂. [f] in 10% NO with N₂. [g] in 50% NO with N₂. [h] in pure NO. [i] in CO₂. [j] under vacuum. [k] example of sublimation with one sample cut in two parts; one was directly sublimed (entry 20), and the second one was solubilized in water before drying and sublimation (entry 21), 515 °C.

Thus, we have showed that α-monoalkylated, α-amino acids sublimed by RHTS can be deracemized in the presence of an enantiopure amino acid. The necessity to have a gaseous phase (atmosphere), the "contagious behavior" of the enantiopure and the synergistic effect observed for the most complex mixtures make these studies relevant for prebiotic chemistry and, more specifically, for the enhancement of ee's of amino acids on the Primitive Earth.

Since a scenario with a pure enantiomer of an amino acid in the starting mixture cannot be easily proposed to simulate prebiotic conditions, we sublimed mixtures containing racemate(s) and a slightly enantioenriched amino acid: with a modest ee ranging from 20 to 6 % for L-Val and one or two racemates, the RHTS gave ee's higher for all amino acids than those of the starting mixture (Table 3), and these results illustrate the potentialities of this approach.

Table 3. RHTS of enantioenriched L-Val and racemic amino acid(s).[a]

Entry	Starting mixture (equiv., ee %)	Sublimed mixture (ee %)
1	L-Val (1, 20) + DL-Leu (0.25, 0)	L-Val (32), L-Leu (5.6)
2	L-Val (1, 11) + DL-Leu (0.25, 0)	L-Val (14.6), L-Leu (2.7)
3	L-Val (1, 6) + DL-Leu (0.25, 0)	L-Val (7.6), L-Leu (1.3)
4	L-Val (1, 20) + DL-Leu (0.25, 0) + DL-Ala (0.25, 0)	L-Val (30.1), L-Leu (10.4), L-Ala (14)

[a] Mechanical mixtures, prepared by careful grinding of the components. 0.854 mmol of the enantioenriched compound was used. T = 490°C, time 15 min.

Several mechanisms have been proposed to explain the enantioenrichment of building blocks of life on the prebiotic Earth since the work of Biot and Pasteur[¶].[3] Our approach, even if it is efficient only with α-monoalkylated α-amino acids, has the huge advantage to be very simple, dependent on few parameters and is effective for many simple or complex mixtures of amino acids where any of them may act as an inductor. High temperature sublimations are compatible with the drastic conditions of syntheses occurring four billions years ago on the warm surface of the Young Earth subjected to frequent meteorite bombardments and to lava flows. Since its effectiveness is enhanced for complex mixtures, multiple RHTS in a large range of temperatures could be the key of huge enantioenrichments of several α-monoalkylated, α-amino acids on the Primitive Earth at the early stage of the chemical evolution and just after the formation of amino acids by hydrolysis of products coming from electric discharges (Miller experiments),[44] photolysis or Strecker reactions. Subsequently, in the liquid aqueous phase, these L-amino acids may have guided many enantioselective syntheses of other chiral building blocks of life.[3,36-38,45]

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Notes and references

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† At the opposite of Viedma et al. [34] where yields of 100% by weight were reported, we observed a decomposition around 23% of the starting material in all our experiments with monosubstituted amino acids and for a temperature of 490°C. More details are given in ESI.

¶ Enantiomeric excesses have been measured for several α-amino acids in meteorites[39-43] and that constitutes to date the sole experimentally detected sources of an initial enantiomeric imbalance for organic compounds on the Primitive Earth. The L-enantiomer is the major component for almost all of them.

Electronic Supplementary Information (ESI) available: Sublimation and preparation of samples for GC, Yield of Sublimation and reaction pathway, Chiral GC analysis, Table S1. Sublimation of mixtures of L-Val and non-racemic Leu See DOI: 10.1039/c000000x/

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