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A Possible Path to the RNA World: Enantioselective and Diastereoselective Purification of Ribose

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Abstract A theoretical mechanism resulting in the prebiotic appearance of enantiopure ribose, which would be needed for the origin of RNA and the "RNA world" is proposed. The mechanism simultaneously explains the emergence of biological homochirality and could answer the question of why nucleic acids are based on ribose rather than another sugar. Cleavage of certain non-chiral mineral crystals is known to lead to formation of chiral surfaces. In a chromatography-like process a mixture of racemic carbohydrates originating from the formose reaction is proposed to have been separated on such a chiral surface. Monosaccharides interact with surfaces through their hydroxyl groups, either by hydrogen bond formation or complex formation with metal ions. α-Ribopyranose, which has all hydroxyl groups on one side of the ring, is known to interact more strongly than other sugars with surfaces, as corroborated by certain chromatographic and electrophoresis data. A similar scenario leading to enantiopure ribose is separation on a flat, but not necessarily chiral surface in the presence of a strong electric field capable of orienting highly polar derivatives of sugars.

Keywords absolute enantioselective separation · origin of homochirality · why ribose

Introduction

One of the most contentious issues in contemporary science is the origin of homochirality (Podlech 2001; MacDermott 2002; Cintas 2002; Weissbuch et al. 2005) which is even

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hijacked by creationists to further their cause (Deem 2004). Other, closely related questions awaiting satisfactory answers include:

(a) why is ribose the monosaccharide of choice as the component of RNA? It was shown that other sugars could also be a viable option (Müller et al. 1990; Bolli et al. 1997; Eschenmoser 1999). On the other hand, it was argued that ribofuranose fits better than other monosaccharides into the ideal nucleic acid structure (Banfalvi 2006),
(b) why did carbohydrates precede amino acids (or, why did the ribozyme RNA world precede the enzyme protein world)?

It is conceivable that simple, non-chiral substances such as formamide, acetic acid, as well as purines and pyrimidines could have been formed abiotically (Podlech 2001; Maurel and Décout 1999). However, the problem is more complex with compounds which may exist as a variety of configurational and positional isomers such as sugars and amino acids. Catalysis under prebiotic conditions, if any, would be very unspecific, thus leading to complex racemic mixtures of isomers and homologues; Butlerov's formose reaction being an example (Mizuno and Weiss 1974). The situation is no different with amino acids. The Miller–Urey process (Urey 1952; Miller 1953; Miller 1955) as well as more recent experiments performed under non-reductive conditions (Plankensteiner et al. 2004) always produce a mixture of amino acids.

We propose here a theoretical mechanism leading to the preferential selection of enantiomerically pure ribose which addresses a number of the issues discussed above.

Enantioselective Separation on a Surface

The energy of adsorption of opposite enantiomers at a surface may be different if conditions of chirality at or near the surface exist. This boils down to the presence of three orthogonal (or close to orthogonal) physical factors exerting influence on interacting molecules. There are basically two ways this can be brought about. In the first, two factors (represented by the vectors, $\boldsymbol{D_1}$ and $\boldsymbol{D_2}$) orthogonal to each other and parallel to the surface are defined by the arrangement of atoms and/or molecules on the surface. The third factor, represented by the vector $\boldsymbol{G}$ normal to the surface, is the presence of the surface itself. Together, $\boldsymbol{D_1}$, $\boldsymbol{D_2}$ and $\boldsymbol{G}$ define the surface and its vicinity as chiral. In the second case, only one factor is defined by the atoms' arrangement on the surface (vector $\boldsymbol{D_1}$). The second factor is an external electric field E, parallel to the surface and perpendicular to $\boldsymbol{D_1}$ which can orient molecules of interest. As shown previously, molecules possessing large but realistic dipole moments can be strongly oriented by E of the order of magnitude of several MV/cm (Bielski and Tencer, 2003). $\boldsymbol{D_1}$ and $\boldsymbol{D_2}$ may exist naturally, e.g., as an effect of cleavage of some achiral crystals (Chrenchaiah et al. 1982; Chrenchaiah et al. 1986; Flack 2003) or by design, e.g., through surface modification. Here, only the former case is of interest, as well as the question of a naturally existing E.

The concept of absolute enantioselective separation on a flat surface is shown in Figure 1 using an example of two enantiomers of a cyclopentene derivative. The X and Y substituents are such that the molecule of either enantiomer is oriented on the surface in the direction of $\boldsymbol{D_2}$ (or E), e.g., through the introduction of a prominent dipole moment. Assume that substituents X, Y and Z are such that (due to specific interaction with a pattern on the surface) they can orient the molecules in the direction of $\boldsymbol{D_1}$ as shown. We can see that the energy of interaction with the surface of enantiomers oriented in this way will be different since in one enantiomer it is R which interacts and in the other, Z.

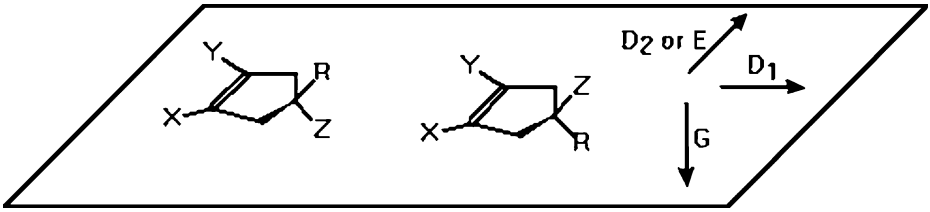

Figure 1 Absolute enantioselective separation (*AES*).

If this surface with adsorbed enantiomers is subjected to the movement of an appropriate carrier, opposite enantiomers will move with different rates. This process has been described as *absolute enantioselective separation* (Bielski and Tencer 2005). The more groups that specifically interact with the surface that are present in the enantiomers, the more pronounced is separation as shown in Figure 2.

Diastereoselective Separation Accompanying Enantioselective Separation

Let us consider the absolute enantioselective separation of a mixture of two racemates, **1A**+**1B** and **2A**+**2B** (Figure 2). Assume that – due to the presence of substituents X,Y and Z, Z – all the compounds are oriented under the influence of $\boldsymbol{D_1}$ and $\boldsymbol{D_2}$ (or $\boldsymbol{D_1}$ and E) as shown in Figure 2. If the surface is capable of forming hydrogen bonds with hydroxyl groups, the molecules of **1B** will exhibit the weakest interactions with the surface of all the discussed compounds. Thus, in the chromatography-like process **1B** will move fastest along the surface. On the other hand, the molecules of **1A**, which have two hydroxyl groups directed towards the surface, are expected to move the slowest. The R_f values of enantiomeric **2A** and **2B** should be comparable and have intermediate values. We can see that the conditions of absolute enantioselective separation will also lead to separation of diastereoisomers. This is particularly important with monosaccharides.

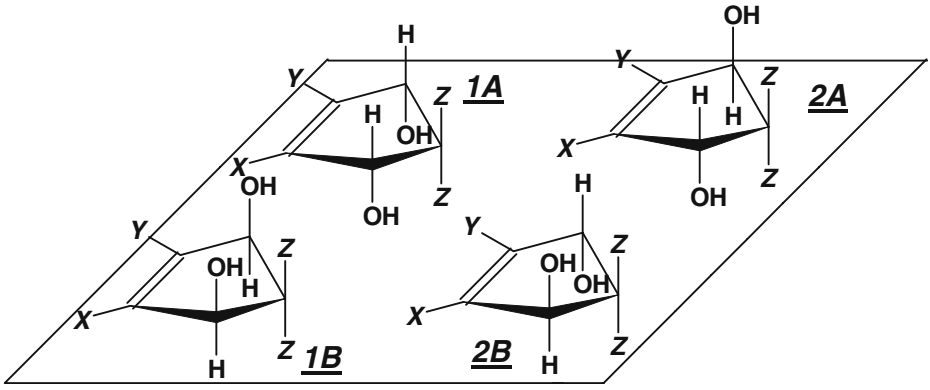

Figure 2 Separation of enantiomers and diastereoisomers on a flat surface in a chiral environment.

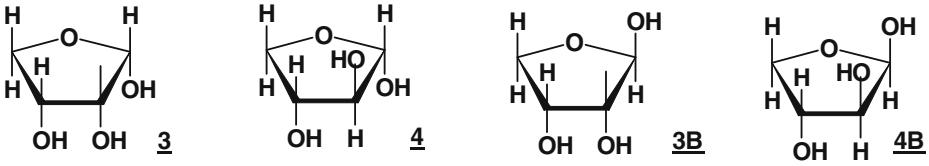

Figure 3 *Aldotetrofuranoses* [**3**=α-*D*-erytrofuranose; **4**=α-*D*-threofuranose; **3B**=β-*D*-erytrofuranose; **4B**=β-*D*-threofuranose].

Separation of Sugars

Consider a separation of a mixture of racemic monosaccharides. Assume that the surface structure and/or external *E* field can impose their orientation as shown on the following figures and let it be that of the Haworth projection. Additionally, for the sake of simplicity we will disregard processes related to mutarotation and the fact that conformationally, pyranoses exist as an equilibrium of two chair forms. For brevity, only *D*-series compounds are shown in the Figures 3, 4, 5. The *L*-series compounds will have all the hydroxyl substituents oriented in the direction opposite to the one shown for *D*-enantiomers as would be visualized in their Haworth projection.

Let us first compare aldotetroses. It is clear that only α-*D*-erythrofuranose (**3**) (see Figure 3) has all three hydroxyl groups capable of interaction with a surface located below the furanose ring and parallel to it. α-*L*-erythrofuranose (**3L**) has no hydroxyl groups directed towards the surface. Thus, enantiomeric α-*D*-erythrofuranose is expected to be the slowest of all the enantiomeric aldotetrofuranoses in the AES process and this racemate (**3**+**3L**) is the easiest to separate into enantiomers.

Aldopentopyranoses are another example of monosaccharides containing all the carbon atoms in the ring. Figure 4 shows α anomers. Only α-*D*-ribopyranose (**7**) has all four hydroxyl groups capable of interaction with a parallel surface below the pyranose ring. Thus, enantiomeric α-*D*-ribopyranose is expected to be the slowest of all the enantiomeric aldopentopyranoses in the AES process. Moreover, the racemate (**7**+**7L**) will separate better than any other racemic α-aldopentopyranose, and also, better than α-*DL*-erythrofuranose.

β-anomers of aldopentopyranoses have hydroxyl groups on both sides of the ring, and therefore, their racemates will not separate as efficiently as (**7**+**7L**). α and β-aldopentofuranoses as well as α and β-aldohexopyranoses contain a hydroxymethyl group at the carbon atom adjacent to the ring oxygen atom (Figure 5) which introduces crowding, thus reducing interaction of the ring hydroxyls with the surface. Similarly, ketoses contain at least one hydroxymethyl group and aldohexofuranoses contain an even bulkier two carbon substituent.

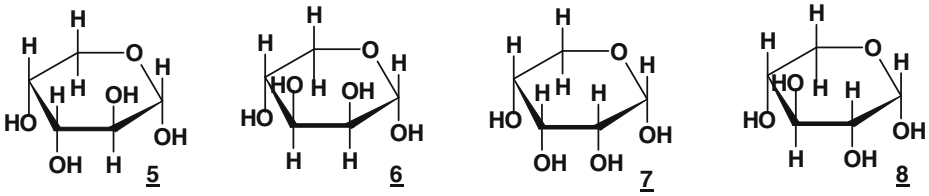

Figure 4 α-*Aldopentopyranoses* [**5**=α-*D*-arabinopyranose; **6**=α-*D*-lyxopyranose; **7**=α-*D*-ribopyranose; **8**=α-*D*-xylopyranose].

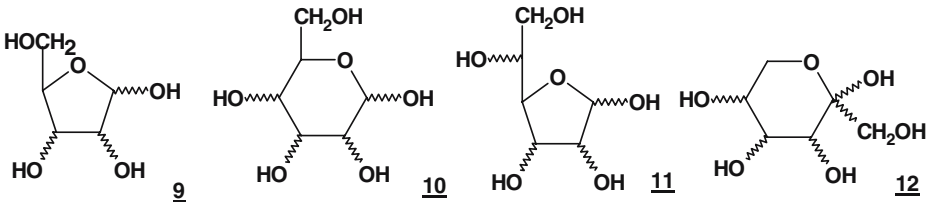

Figure 5 Aldopentofuranoses and hexoses [**9** = aldopentofuranose; **10** = aldohexopyranose; **11** = aldohexofuranose; **12** = ketohexopyranose].

We may thus conclude that the racemic α-*DL*-ribopyranose is the easiest racemic monosaccharide to separate in the AES process.

Purification of Enantiomeric α-ribopyranose

Hydrogen bonding is not the only possible interaction between hydroxyl groups and the surface. For example, monosaccharides form strong complexes with cations (Angyal 1989). Such interactions (at least in solution) are particularly strong if the monosaccharide contains three adjacent hydroxyl groups and when they take axial-equatorial-axial positions. Each chair form of α-D-ribopyranose does contain such an arrangement (Figure 6, hydroxyl groups at positions 1,2,3 in the conformation on the left side and hydroxyl groups at positions 2,3,4 in the conformation on the right side).

Consequently, the stability constant of an α-*D*-ribopyranose with calcium ion is larger than that of other aldopyranoses with the exception of α-*D*-allopyranose (Angyal 1989).

While there are no literature data concerning the absolute enantioselective separation of racemic ribose (or other racemic monosaccharides), it is interesting to compare the chromatographic and electrophoretic properties of ribose to those of other monosaccharides. As expected, the relevant literature data show that ribose exhibits the lowest R_f. For example, ribose was the slowest moving monosaccharide in capillary zone electrophoresis on polyimide-coated fused silica (Hu et al. 2001), in HPLC using an ion-exchange column (Cheng and Kaplan 2003) and in ion-exchange chromatography of comparable carbohydrates on resins containing calcium or lanthanium ions (Angyal and Mills 1985).

In terms of the ease of AES, all the monosaccharides which turned out to act as comparable or better players than ribose in RNA (Eschenmoser 1999) are significantly more difficult to separate to enantiomers. This is further reinforced by Angyal (1989) who states in his review on complexes of metal cations with carbohydrates that "sugars common in Nature, with the exception of *D*-ribose, do not complex readily".

Thus, it is our view that Nature selected ribose because other (in many aspects better) candidates could not appear in the enantiomerically or chemically pure form as readily as ribose.

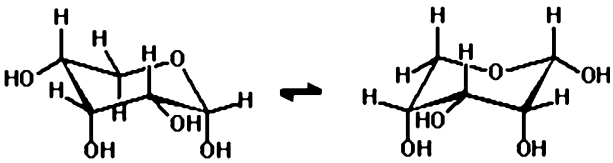

Figure 6 Both chair forms of α-*D*-ribopyranose.

Abiotic Formation of Enantiomerically Pure α-ribopyranose

In the light of the considerations presented above, we propose here a general scenario leading to the formation of homochiral ribose under abiotic conditions. The first stage is the formose type reaction, likely in the variant described by Müller et al. (1990) in which glycolaldehyde monophosphate reacts with formaldehyde under slightly basic conditions to form ribopyranose 2,4-diphosphate (**13**) as one of the major products. It is worth stressing that the formose reaction has been recently challenged as the source of prebiotoc sugars (see, e.g., Arrhenius 2003). The reservations stem from the fact that no convincing separation mechanism has been offered, a situation which we hope is alleviated here. In the second stage, the mixture of monosaccharides may have been modified chemically, for example, by losing one of the phosphate groups or by forming an *N*-glycoside. Next, this mixture may have been adsorbed on the surface of a specific mineral. The mineral has to have a structure which, via interactions with the monosaccharides, enforces the orientation of molecules in two directions. Strong interactions with the metal ions on the surface would require that the phosphate not be present anymore at position 2 leading to the adjacent hydroxyl groups located at carbon atoms 1, 2, and 3 being advantageously axial, equatorial, axial (Figure 6, left hand side), while the large phosphate group at position 4 (not shown) is equatorial.

As far as the other possible scenario (a flat surface enforcing orientation in one direction+ strong electric field) is concerned, one has to consider the dipole moments of the sugar derivatives to be separated, as well as the possible source of the *E* field. The value of the dipole moment of ribopyranose 2,4-diphosphate (**13**) is not available, however, based on measured or calculated dipole moments of related compounds it is expected to be large. For example, the molecular dipole moments for the singly and doubly deprotonated glyceraldehyde phosphate were calculated to be 7.4 and 13.4 D, respectively (Luty et al. 1993). The dipole moment of adenosine triphosphate (ATP) was measured to be as large as 230 D (Lampinen and Noponen 2005). Electric fields have long been implicated in prebiotic chemistry. Recently, Plankensteiner et al. (2004) showed that amino acids can be formed in a neutral atmosphere by electric discharge. A possible source of *E* high enough to achieve AES while maintaining its direction is yet to be identified. However, electric fields as high as 10^{21} V/m have been postulated to be present in the vicinity of neutron stars (Ray et al. 2004.

Of course, for the chromatography-like process, a solvent is also necessary. Besides water, such 'organic' solvents as hydrogen cyanide and its hydrolysis products (formamide and formic acid), acetic acid, acetonitrile and supercritical carbon dioxide are possible candidates (Maurel and Décout 1999). As discussed above, those monosaccharides that have no or only one hydroxyl group directed towards the surface would move fast, including one of the α-ribopyranose enantiomers, (by pure chance the *L*-enantiomer). The slowest moving being its opposite enantiomer. Thus, α-*D*-ribopyranose can be separated from all the other carbohydrate components of the mixture.

The amounts of thus purified ribose must have been limited. However, the surface Nature used could have been very large. While we can only speculate on the nature of the surface(s) active in the described process, it is worth noting that the involvement of surfaces, such as that of TiO_2 (Senanayake and Idriss 2006), montmorrilonite (Kawamura and Ferris 1994; Ferris et al. 1996) and pyrite (Huber and Wächtershäuser 1998), has been invoked in the formation of the first macromolecules essential to life, as well as in the formation of *L*-amino acids from RNA (Bailey 1998). Furthermore, it has been

demonstrated that surfaces of kaolinite (Julg and Ozias 1988) and calcite (Hazen et al. 2001) can exhibit preferential adsorption of specific amino acids or their precursors. Also, it has been shown (Weissbuch et al. 2005) that racemic α-amino acids undergo spontaneous separation with the assistance of glycine crystals grown at the air/water interface.

The proposed scenario does not answer all the questions. Probably the most significant of them is how the furanose form of optically pure ribopyranose became a component of RNA . However, the existence of pyranosyl-RNA (p-RNA) has been postulated previously (Bolli et al. 1997; Schwartz 1997).

At this stage we can only speculate as to the type of flat surface on which AES could have taken place. For instance, since monosaccharides form the strongest complexes with La^{3+} and Ca^{2+} (Angyal 1989) it is possible that separation took place on a surface containing calcium cations. Another aspect of interest is the relatively low stability of the ribose formed under formose reaction conditions. Springsteen and Joyce (2004) have shown that this stability can be significantly enhanced by reaction with cyanamide. Incidentally, Sacerdote and Szostak (2005) have demonstrated recently that semipermeable lipid bilayers favor ribose as compared with other diastereoisomers. Furthermore, borate complexes stabilize ribose derivatives (Ricardo et al. 2004; Scorei and Cimpoiaşu 2006). There are more than two dozen minerals containing calcium and borate. They include ulexite (crystal system – triclinic) and colemanite (crystal system – monoclinic). The cleavage of both of these minerals is {010} perfect.

Conclusion

The scenario proposed here offers possible answers to a number of questions: the origin of homochirality (absolute enantioselective separation – AES), why monosaccharides and not amino acids (amino acids contain only one or two chiral centers which may be insufficient for the successful AES), why ribose (α-*DL*-ribopyranose or its derivative is the easiest racemic monosaccharide to separate into enantiomers under the conditions of AES), and how ribose was separated from other formose reaction products (in the chromatography-like AES process, the separation of racemates was accompanied by the separation of diastereomers). Moreover, the AES process, under proper conditions, could have led not only to a certain enantiomeric excess but even to optically pure ribose. If these speculations are correct, chiral amplification (Frank 1953; Plasson et al. 2004; Soai et al. 2001; Klussman et al. 2006) might not have been necessary.

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