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ORIGINS OF BIOLOGICAL HOMOCHIRALITY

On the Origin of Sugar Handedness: Facts, Hypotheses and Missing Links-A Review

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Abstract

By paraphrasing one of Kipling's most amazing short stories (*How the Leopard Got His Spots*), this article could be entitled *"How Sugars Became Homochiral"*. Obviously, we have no answer to this still unsolved mystery, and this perspective simply brings recent models, experiments and hypotheses into the homochiral homogeneity of sugars on earth. We shall revisit the past and current understanding of sugar chirality in the context of prebiotic chemistry, with attention to recent developments and insights. Different scenarios and pathways will be discussed, from the widely known formose-type processes to less familiar ones, often viewed as unorthodox chemical routes. In particular, problems associated with the spontaneous generation of enantiomeric imbalances and the transfer of chirality will be tackled. As carbohydrates are essential components of all cellular systems, astrochemical and terrestrial observations suggest that saccharides originated from environmentally available feedstocks. Such substances would have been capable of sustaining autotrophic and heterotrophic mechanisms integrating nutrients, metabolism and the genome after compartmentalization. Recent findings likewise indicate that sugars' enantiomeric bias may have emerged by a transfer of chirality mechanisms, rather than by deracemization of sugar backbones, yet providing an evolutionary advantage that fueled the cellular machinery.

Keywords Prebiotic chemistry · Carbohydrates · Homochirality · Ribonucleosides · Amino acid interactions

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Introduction

If there is one sentence that pervades introductory remarks in the literature dealing with the origin of homochirality, enantioselection, deracemization, and chiral systems in general, it most likely is (or variations thereof) that *homochirality as a feature of life is portrayed by the existence of D-sugars and L-amino acids*. Repeated to tedium, which might be a matter of study in psychological science (if one may say so), the argument is both a truism and an unquestionable mystery.

The abiotic generation of amino acids and short peptides, and their enantioseparation, has been extensively explored and documented, including comprehensive monographs (Barret 1985; Coppola and Schuster 1987; Meierhenrich 2008), which account for the key role of these biomolecules as the dynamic machinery of life, leading to enzyme-like structures of catalytic activity required for metabolic cycles. With most proteinogenic amino acids bearing only a single stereogenic center, they are also suitable platforms for the transfer of chirality through covalent bonding and non-covalent interactions. The other essential ingredients, lipids and carbohydrates, adopt largely structural roles in cells, even if sugar-based genetic polymers would have emerged in early stages of evolution. The role of carbohydrates in prebiotic chemistry is of course indisputable, and different analyses have tried to shed light into their formation and inherent chirality. Most studies concentrate on the paradigmatic formose reaction (vide infra), which should certainly be regarded as a key credible route to sugar synthesis, although the whole transformation is messy indeed and poorly selective. It has been postulated that a carbohydrate polymer would have preceded the RNA world, with phospho-sugar nucleic acid analogs capable of forming stable Watson–Crick pairs, thus serving as preliminary pathways toward RNA and subsequently informational DNA and proteins. Chirality's emergence could be an accidental mechanism derived from template-driven syntheses that facilitated the appearance of glycopolymers. The first successful synthesis of a template for replication would have occurred by chance with one handedness, either D or L, being at slight preponderance, followed by accumulation of that enantiomer. Differences in eutectic temperatures between L- and D-amino acids, and between D- and L-sugars, especially at solid–liquid interfaces, might also have boosted that bias (Stern and Jedrzejas 2008). Moreover, the enantioenriched templates would force the synthesis of stereoregular polymers preserving a given chirality (Joyce et al. 1984). Moreover, it is worth mentioning the importance of carbohydrates as soluble species that favored concentration, cross-linking and phase separation of other biomolecules, aided by metal ions, through hydrophobic, H-bonding, and other electrostatic interactions (Tolstoguzov 2004). This and related arguments reinforce the idea of screening parallel and intertwined channels of molecular interactions, rather than unimodal routes accounting for a certain building block (Eschenmoser 2011; Ruiz-Mirazo et al. 2014; Sutherland 2016). Notably, carbohydrates interact with other biomolecules through weak, yet specific, interactions as they coat cell surfaces and are present on more than 50% of human proteins (Pilobello and Mahal 2007; Dedola et al. 2020; Richards and Gibson 2021). Actually carbohydrate-peptide interactions are the basis of glycobiology and mediate essential functions such as transduction, fertilization and pathogen infection (Lee and Lee 1995). The sugar-peptide interaction is likely rooted in evolutionary mechanisms and one could reasonably speculate regarding its role in the origin and transmission of homochiral sequences. Furthermore, carbohydrate architectures are as diverse as peptide and enzymes tailored for multiple functionality. Sugars exhibit a huge structural diversity arising from the assembly of monosaccharides through different glycosidic linkages, at

different positions and variable stereochemistry that result in the complexity of the glycome (Laine 1994, 1997; Bertozzi and Kiessling 2001). We shall revisit this background, on the sugar-peptide world, regarding the generation of pentoses and sugar oligomers in formose-type reactions. A salient (perhaps overlooked) idea, noted by Ribó and Hochberg (2019) is that symmetry breaking during the chemical connection between amino acids and carbohydrates can only imply simple asymmetric induction or transfer in linear kinetic dependence between enantiomers. It is noteworthy that metabolic cycles, regardless of the stereospecific catalysis supplied by enzymes, involve little or no enantiomeric compounds, i.e. chirality was merely accidental and not linked to the energetic function of the cycle (Fig. 1). *Homochirality in metabolism likely appeared by interconnecting with parallel networks and pathways where symmetry breaking had already occurred.*

It is unclear, and still debated, whether homochirality is both *a necessary and a sufficient condition for life to occur*. The detection of asymmetry in known stars and nebula, and celestial bodies like comets and meteorites, suggests that chirality occurs naturally, even without evidence of life. On our planet at least, enantiomeric excess (unichirality indeed) is interlocked with living systems. Which came first, enantiopure blocks or life, may be of interest, but not crucial to pursue a research line in the prebiotic field, *simply because we cannot move backwards*. Numerous physical and chemical mechanisms break the mirror symmetry of chiral carbon molecules (Atzori et al. 2021; Barron 2021; Blackmond 2020; Buhse et al. 2021; Rosenberg 2019; Sallembien et al. 2022; Tassinari et al. 2019; Viedma and Cintas 2011), so that homochirality apparently predates life. A point often ignored is the fact that chiral structures dominate over achiral ones as the number of carbon atoms increases (Siegel 1999). A recent numerical simulation provides theoretical evidence on that atomic threshold to cause the appearance of homochiral sequences (Laurent et al. 2021). A posteriori homochirality, where life emerged from a racemic molecular world with something breaking the symmetry between left-handed and right-handed forms has received less attention and it is equally plausible (Green and Jain 2010). Nevertheless it is difficult to unravel such mechanisms by retrieving the otherwise extinct enantiomeric

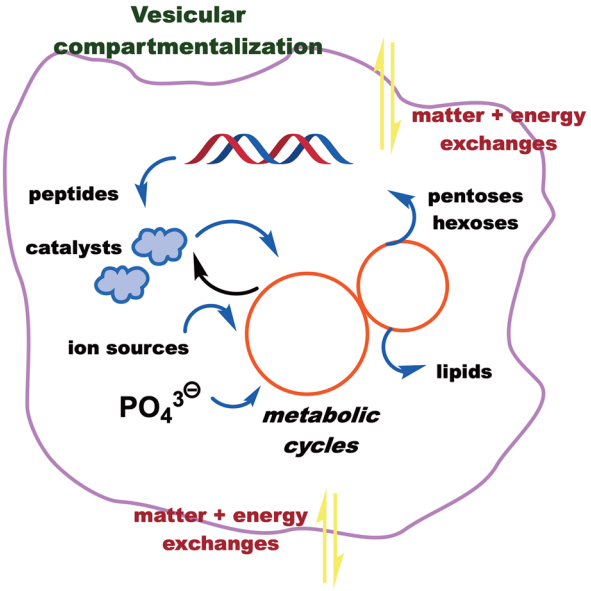

Fig. 1 Schematic cartoon of a working hypothesis: different synthetic routes affording primeval molecular worlds become interconnected after compartmentalization. The latter would ensure the spontaneous symmetry breaking generated at certain points and determine the handedness of tandem and parallel reactions through chirality transfer and (auto)catalytic cycles. Adapted and re-designed from Ribó and Hochberg (2019): open access article under the CC BY license

relic. How primitive forms of life could have emerged by enforcing homochirality upon themselves can be more logical than amplification mechanisms, if one considers the symmetry breaking associated with complexity and affording unique chiral sequences. The point can be illustrated by a collection of small monomers (let us say nucleotides containing *ca* 20 heavy atoms each) that assemble into all possible sequences of L- and D-links (chirality at the sugar backbone). In a level of complexity with chains composed of a small number (*N*) of monomers, the system will be racemic. As *N* increases, the number of possible sequences is so high that it cannot be accommodated in the chemical space available and most possibilities will not exist. Every sequence will be unique and chiral; the probability of encountering its mirror image is statistically negligible (Avetisov and Goldanskii 1996; Bolli et al. 1997; Cintas 2015).

Additional troubles associated with sugar chirality not only derive from the stereogenicity and promiscuous reactivity of polyol structures, thus rendering multiple and similar diastereomeric products, but also to the fact that carbohydrates are difficult to crystallize from reaction mixtures. Oligo- and polysaccharides are often obtained as amorphous materials. Unlike amino acids, for which chiral polymorphs and conglomerates can be isolated, the phenomenon of racemic conglomerate formation, a condition for spontaneous resolution to occur, is virtually nonexistent in monosaccharides of biological interest, thus hampering crystallization as a suitable means of asymmetric sorting and propagation (Avalos et al. 2004; Weissbuch and Lahav 2011). Only a recent study discloses that D- and L-xylose crystallize as a conglomerate mixture (Tyson et al. 2022).

Sugars from above

The Murchison, Murray and Orgueil carbonaceous meteorites, among others, have been invaluable sources of cosmic information. Their extracts have revealed the presence of numerous chemical species and organic compounds in particular, some regarded as potential biosignatures. Amino acids are invariably the long-sought after compounds in terms of chemical evolution and enantiomeric imbalance in order to establish, if any, a constant sign of chiral bias. The subject has been re-examined from time to time, as the enantiomeric excesses (*ees*) reported in the 1970s and 1980s should be viewed with caution due to terrestrial contamination. More recent analyses conducted with improved techniques surely provide more accurate figures (Glavin et al. 2020; Pizzarello 2016; Sephton 2002). Perhaps, the first detailed analysis of sugar derivatives in meteorites was documented in the early 2000s (Cooper et al. 2001) showing the existence of polyhydroxylated structures, namely sugars (aldo- or ketoses), sugar alcohols and sugar acids in the Murchison and Murray meteorites in amounts comparable to amino acids. Analyses of aqueous extracts suggest that extraterrestrial processes involving formaldehyde (HCHO) condensations or photo-irradiations of other small molecules present in interstellar ices could explain the product distribution. Further screening in subsequent decades fine-tuned the results and unveiled their enantiomeric ratios (Cooper and Rios 2016). The most abundant species are 3C-polyols, followed by 4C, 5C and 6C-alditols, aldonic acids, and 2-deoxysugar acids, with variable *ees*, albeit D-configured structures were prevalent (Fig. 2). It is interesting that the identification of rare 2-deoxy sugars and nonbiological branched 4C species such as 2-hydroxymethyl glycerol and 2-hydroxymethyl glyceric acid, the latter being abundant substances in meteoritic samples, give evidence of indigenous abiotic syntheses.

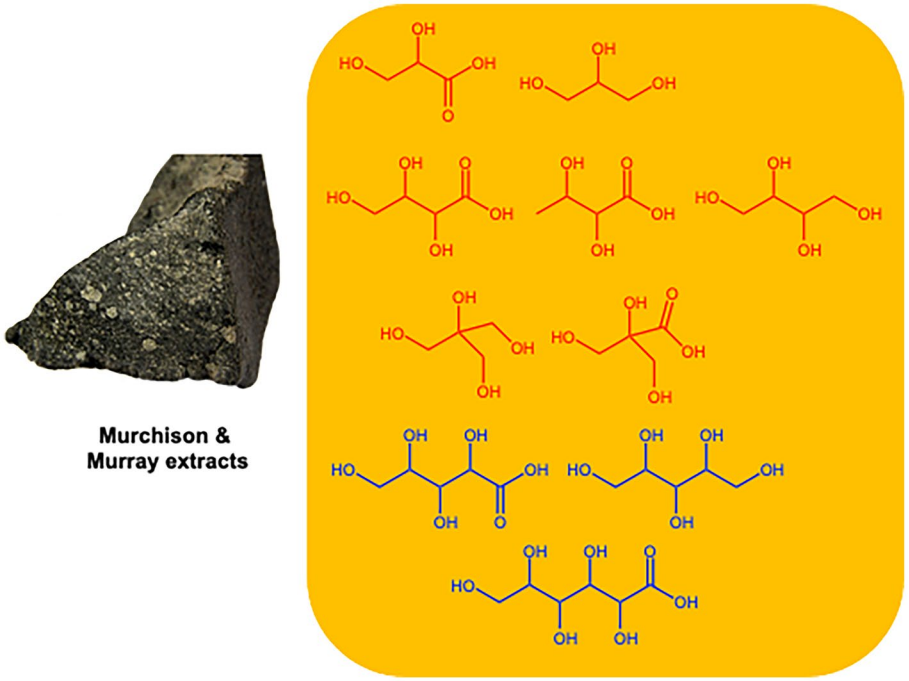

Fig. 2 Representative skeleta of sugar polyols and acids detected in meteorites. Up to 11 tetrose, 7 pentose, and 8 hexose derivatives could be identified. D-configured structures are the most abundant isomers, especially for 5C and 6C diastereomers, while racemic mixtures (50:50 D/L mixtures) are observed for 3C and 4C derivatives

The enantiomeric imbalance increases with increasing carbon number. While the smallest sugar acid, glyceric acid, is essentially racemic, significant D-*ees* could be measured for 4C-6C-alditols and aldonic acids. In multiple samples, threonic acids showed *ees* in the range 33–55%. The 5C acids, like arabinonic and xylonic acids, exhibited much larger D-*ee* (up to 82%) and only D-configurations could be detected for the 6C-aldonic acids (Fig. 3). However, as the authors noted, the 5C and 6C higher sugar acids were present in much lower abundance than their 3C and 4C analogs; in fact, identification of the 6C derivatives could not be achieved in all meteoritic samples. Terrestrial, including microbial, contamination cannot be excluded. The absence of aldoses (e.g. glucose, galactose or mannose) against the presence of their aldonic acids like gluconic acid (D) or mannonic acid (the latter in racemic form) points to abiotic or biological oxidation of the parent sugars, provided they were obtained initially through formose reactions. Isotope ratio ($^{13}C/^{12}C$) measurements on the most abundant species, glyceric acid and glycerol, are indicative of indigenous origin. Lower ratios were observed for D-threonic and D- and L-erythronic acids, yet consistent with extraterrestrial origins, while this conclusion could not be determined with confidence for higher carbon derivatives. The origin of the *ees* should be ascribed to *truly chiral influences* (Barron 2009), especially circularly polarized light or magnetochirality (requiring a static magnetic field parallel or antiparallel to an *unpolarized* light beam), both mechanisms suggested by the authors, although magnetochiral effects are expected to be much weaker than those produced by UV-polarization.

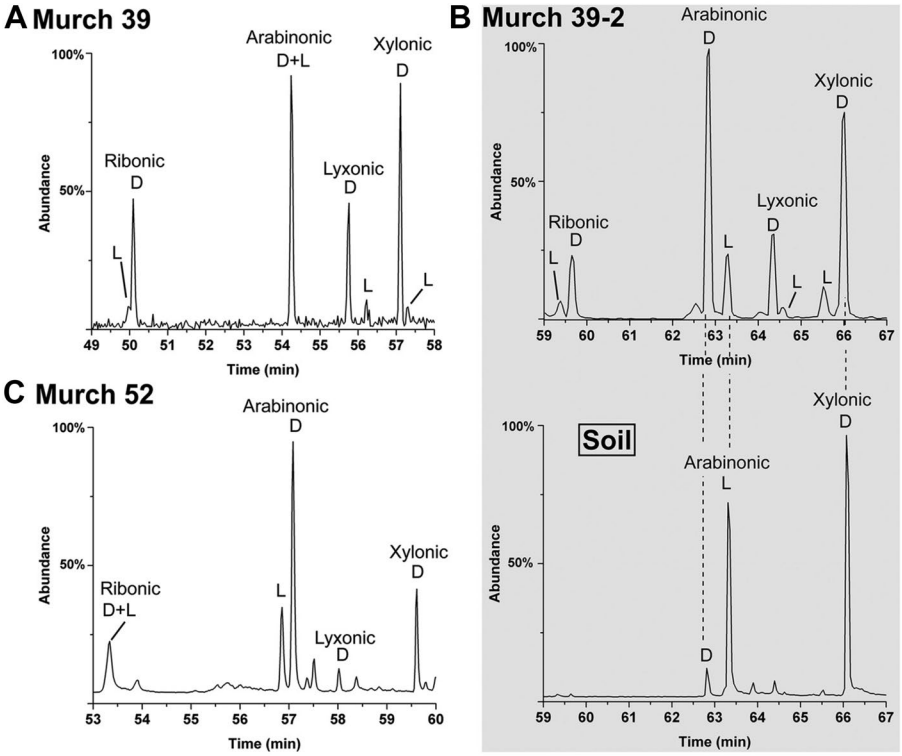

Fig. 3 GC–MS Analyses of the 5C sugar acid enantiomers present in aqueous extracts and soil/dust meteoritic samples. The Murchison meteoritic samples were analyzed after extraction, centrifugation, acid hydrolysis with trifluoroacetic acid (TFA), and further derivatization as esters (isopropyl for Murch 39 samples and Murch 52 compounds as their ethyl esters). Either Chirasil Dex-CB or HP-Chiral-20B columns were employed. Peak detection was achieved by interfacing GC to an ion trap mass spectrometer or a quadrupole mass spectrometer. Reproduced with permission from Cooper and Rios (2016). Copyright National Academy of Sciences

Remarkably, all four aldopentoses (namely ribose, arabinose, xylose and lyxose), together with dihydroxyacetone (the tautomeric form of glyceraldehyde) have been detected (in the ppb range) in three carbonaceous chondrites (Furukawa et al. 2019). The ^{13}C-enriched isotope compositions point to extraterrestrial origin. Unfortunately, pentose's chirality was not investigated in this study. The authors simulated a laboratory experiment (via the formose reaction, after examining the alkaline mineral composition of samples), which led to a similar product distribution of such sugars.

The existence of molecules of astrobiological interest in interstellar media, including the organic inventory leading to sugars (Sandford et al. 2020), provides clues to simulations of such astrochemical conditions attempting to produce the primeval biomolecules. Formaldehyde and other oxygenated molecules can be produced in these sort of artificial ices at cryogenic temperatures (Schutte et al. 1993). In context, the first sugar, glycolaldehyde, yet achiral, could also be detected in interstellar media by mm-wave rotational emissions (Hollis et al. 2000), and aliphatic aldehydes and ketones have been identified in carbonaceous meteorites as well (Aponte et al. 2019). Glycolaldehyde has also been recently detected on the nucleus of comet 67P/Churyumov-Gerasimenko (Zellner et al. 2020).

Notably, a few amino acids in racemic form were obtained by photolysis of interstellar ice analogs (Bernstein et al. 2002; Muñoz Caro et al. 2002). Thus, UV irradiation in a high-vacuum chamber at 12 K of an ice mixture containing H_2O, CH_3OH, NH_3, CO and CO_2 afforded up to 16 amino acids, the chiral ones (Ala, Asp, Ser and Val) showed enantiomeric separation, with the exception of proline (on the basis of chiral GC analysis), although they were racemic within experimental error as photosynthesis was conducted with unpolarized light (Muñoz Caro et al. 2002). In order to detect sugar derivatives, photoprocessing of an interstellar ice analog composed of H_2O, CH_3OH and NH_3 (10:3.5:1 molar ratio) was performed at 78 K and 10^{-7} mbar (Meinert et al. 2016). Potential carbon contamination during manipulation was excluded by using ^{13}C-labeled methanol. A broad range of aldoses and ketoses could be identified, being 3C and 4C sugar alditols and acids as the most abundant species together with another 4C ketose (erythrulose). All aldopentoses, including biologically relevant ribose, and two ketopentoses (ribulose and xylulose) could be identified. The abundance of free pentoses, in the range 260–145 ppm (ribose > xylose > arabinose > lyxose) was significant, nevertheless. The authors suggest that all sugars arise from a formose-type network where HCHO and glycolaldehyde would be the initial precursors. Actually, the identification of branched chain species, such as 2-hydroxymethyl glycerol and 2-hydroxymethyl tetritol evidenced the formation of formose side products. However, the generation of higher carbon derivatives might have occurred above 78 K when warming the mixture to room temperature. This aspect is intriguing and in fact, Kawai (2017) criticized the results by claiming that aldol reactions leading to ribose and other sugars may have occurred during work-up and analysis of the reaction mixture, not in the parent ice, and also questioning some pathways (hydride shift for instance at low temperature). In their reply (Meinert et al. 2017), the authors indicated that aldopentoses and other sugars do not form in a classical formose reaction in aqueous alkaline solutions during work-up. The light brownish residue prior to extraction and derivatization suggests that aldopentoses were already formed in the ices and not after warming. IR monitoring showed the existence of absorptions at 2925 and 2875 cm^{-1}, indicative of CH_2OH groups, and hence polyol structures, in the astrophysical ice. In a related approach (Nuevo et al. 2018), 2-deoxyribose (the sugar present in DNA) and deoxy sugar derivatives were produced by UV irradiation of ice mixtures containing H_2O and CH_3OH (2:1 ratio) at 12 K (Fig. 4). These results might a priori contradict the analysis of astronomical bodies (meteorites for example), where deoxy sugars are generally absent. However, such substances may form in interstellar media, yet lacking sufficient stability between their formation and their incorporation into bodies like asteroids and comets, or undergoing further redox processes leading to the corresponding alcohols and acids, which are detected.

Formose-type variations: chemical and stereochemical puzzles

There is little doubt that the so-called formose reaction should reasonably be invoked as the most plausible source of carbohydrates in prebiotic scenarios on earth and beyond. It was first noted by Butlerow (1861a, b), who reported the formation of sugar-like compounds by simply treating HCHO with a mild base, $Ca(OH)_2$, $Pb(OH)_2$ or other divalent metal hydroxides, resulting in the rapid formation of a brownish mixture, whereas NaOH or KOH afforded poor or negligible results. The process is naively described as the autocatalytic oligomerization of HCHO, but it is obvious that two electrophilic molecules cannot self-assemble and one should have an "umpolung" reactivity. Although the puzzle lasted for nearly one century, the identification of glycolaldehyde in the initial mixture, whose

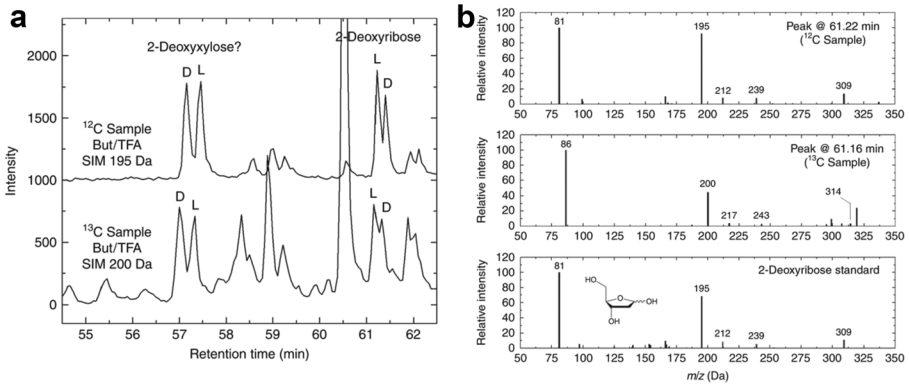

Fig. 4 Identification of 2-deoxyribose in photolysis of icy H_2O-CH_3OH residues. Single-ion monitoring (SIM) chromatograms of residues after derivatization with (+)-2-butanol-TFA (trifluoroacetic acid). The 2-deoxyribose structure is shown without derivatization. Reproduced from Nuevo et al. (2018). Open access article licensed under a Creative Commons attribution 4.0 international license

addition also suppresses the long induction period of the formose reaction, is the key species enabling the aldol reaction with HCHO. This mechanism, postulated by Breslow in the late 1950s (Breslow 1959) is still regarded as the logical landscape. Other substances, acting as glycolaldehyde surrogates, may trigger the transformation as well, and recent studies suggest the existence of paths once thought to be improbable, like hydride shifts (Appayee and Breslow 2014). Even so, the mechanistic conundrum is not completely solved (vide infra), as the origin of glycolaldehyde is uncertain; it seems we need something to be the "CH_2" source. A simplistic view of the formose reaction is shown in Fig. 5, which captures its essence, i.e. the successive condensation of HCHO-glycolaldehyde adducts, through enediol intermediates, with more HCHO or carbonyl groups under basic conditions, fuels an iterative chain elongation that ultimately leads to pentoses, hexoses and higher oligomers.

This linear sequence, however, evolves into a messy and uncontrolled multichannel reaction (Benner et al. 2010), where a variety of aldol reactions at different carbon positions,

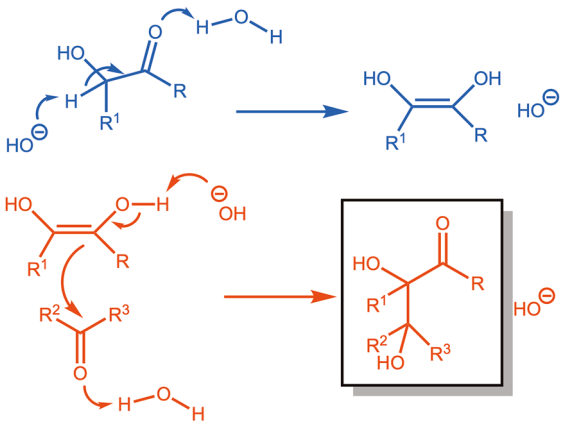

Fig. 5 Simplified depiction of the catalytic formose reaction. HCHO and glycolaldehyde furnish an aldol product in alkaline solution. Divalent cations actually stabilize the enediol intermediates. Subsequent condensations with either HCHO or functionalized carbonyls give rise to higher saccharides

retro-aldol, isomerization, epimerization, and rearrangement reactions emerge as the reaction progresses, owing to the promiscuous reactivity of OH groups and enol intermediates (Fig. 6). There is no prebiotic reaction mimicking the primordial soup like the formose reaction. Even worse, this complex network would have in addition coexisted with parallel chemical routes forming other biomolecules and interacting with one another.

These intractable mixtures, which invariably result in very low yields of individual components, difficult to isolate, cast doubt on our conventional approaches to solve the origin-of-life puzzle (Schwartz 2007, 2013). Regarding the formose reaction, it is currently assumed that minerals, surfaces and/or hydrothermal conditions would have guided more selective condensations by avoiding/bypassing side reactions (Colón-Santos et al. 2019; Haas et al. 2020; Kim et al. 2011; Kopetzki and Antonietti 2011; Nitta et al. 2016; Russell and Martin 2004), and leading eventually to secondary products, like carboxylic acids, which would have been integrated into metabolic cycles (Omran et al. 2020). However, the conjecture of linking complex networks to metabolic or pre-metabolic cycles has been considered to be highly improbable until a simplification of product mixtures can be established (Orgel 2008), probably via self-organization mechanisms and compartmentalization (Butch et al. 2021). On the other hand, alternative precursors and conditions might also have formed polyhydroxylated substances required for evolution and energy reservoirs, thus circumventing the formose reaction ending up in pentoses. Instead of the non-selective base-catalyzed HCHO oligomerization, UV irradiation of HCHO solutions at alkaline pH efficiently produces pentaerythritol (Schwartz and De Graaf 1993), which can be converted into nucleotide analogs. Likewise, glycerol is susceptible of rendering acyclic nucleotides, although template-directed oligomerization of such species is less efficient than those of ribose or 2-deoxyribose (Schwartz 1993). However,

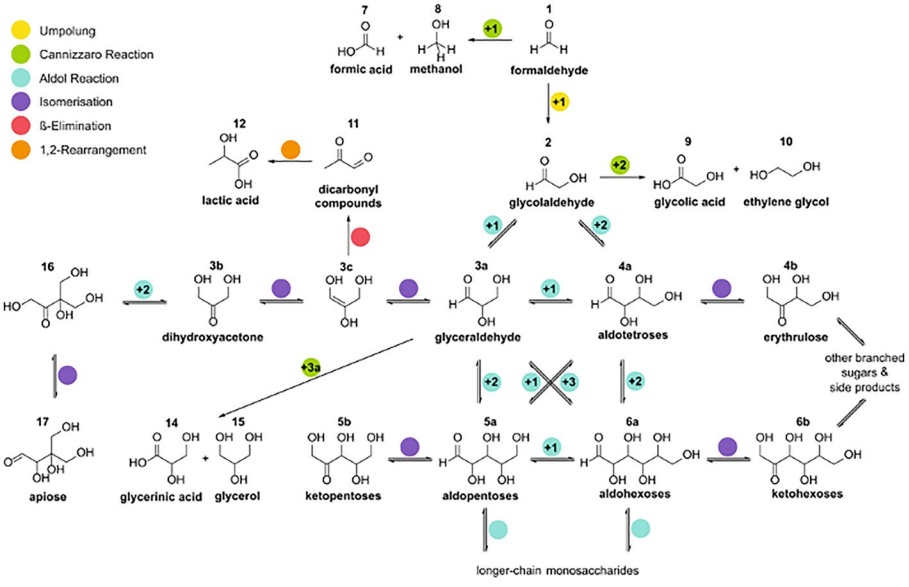

Fig. 6 Complexity is the hallmark of the formose reaction, affording a huge variety of polyhydroxylated compounds through inter-related reactions. Numbers (+1, +2, +3a) within the circles denote the addition of formaldehyde, glycolaldehyde, and glyceraldehyde, respectively. Reproduced from Haas et al. (2020). Open access article licensed under a Creative Commons attribution 4.0 international license

such analogs could have preceded an RNA scenario and contributed to solve the otherwise impossible direct stereoselective nucleosidation of ribose.

In recent decades there have been some reformulations of the formose reaction, in the search for more selective routes. Conceptually neither of them satisfactorily solve the stereoselective formation of the nucleoside repertoire, and the approaches re-start from identical precursors. In any case, they focus on the combination of 2C-3C oxygenated monomers as ancillaries of pathways involving other O/N/S-containing substrates. As a result, the HCHO oligomerization is significantly hampered at the expenses of creating a varied molecular origami depending on the secondary monomers present in the mixture. Within this background, one should credit Weber's variation, initially coined as the *triose model*, involving glyceraldehyde as the pivotal unit, and subsequently expanded to a *sugar model* by incorporating additional catalytic or autocatalytic routes that account for both biomolecules, peptides in particular, and heterocycles (Weber 1987, 1998, 2001, 2007). Obviously, glyceraldehyde stems from HCHO and glycolaldehyde, although its formation occurs at HCHO concentration much lower than those used in the formose reaction (~ 10 mM, even as low as 0.1 mM formaldehyde could be used). Rapid conversion into hemiacetal adducts and/or oxidation to glyceric acid, may also be accompanied by the oligomerization to poly(glyceric acid), with a potential catalytic activity. The actual structure of this polymer is uncertain, albeit it might adopt helical conformations similar to poly(alkanoates) or poly(lactide). It is assumed a rudimentary replicating ability of poly(glyceric acid) by copying the sequence of D- or L-residues (Weber 1987). The replication process could be fully stereoselective (yet globally racemic) through directional H-bonding between the D- or L-residues of the template and either glyceraldehyde, hemiacetals or esters, being used for the synthesis of a new strand (Fig. 7). Each glyceric acid has the ability of generating two H-bonds, one that involves its carbonyl oxygen as a H-bond acceptor and a second with its free OH as a H-bond donor or acceptor. Thus, a homochiral sequence should be establishing favorable non-covalent interactions with monomers of identical configuration adding to a growing chain. As a result, and by analogy with the assembly of β-sheets in peptides, two homochiral strands running in the same direction are held together through complementary H-bonding.

As noted above, the most interesting aspects of this model lie in crossing reactions with ammonia (or amines) and H_2S (or thiols), affording amino acid derivatives among others. Thus, alanine and homoserine can be generated under mild aqueous conditions in the presence of thiol catalysts (Fig. 7). Likewise, glyceraldehyde can undergo dehydration to pyruvaldehyde, along with formation of phosphoanhydrides or phosphate esters, so long as phosphate sources are available. Thermodynamic data suggest that most transformations would be viable exergonic processes, albeit no energy barriers were reported. At this stage, it is pertinent to mention that other reagents could have tempered the random reactivity of formose reactions, such as hydroxymethanesulfonate, generated from volcanic sulfur dioxide (Kawai et al. 2019), or bisulfite (Rimmer et al. 2021), thus serving as masked substrates or reservoirs of formaldehyde and its sugar derivatives.

Within the aforementioned context of carbohydrate-amino acid interactions, it is also noteworthy a recent study exploring amino acid synthesis using aldehydes and ammonia in a formose-like reaction (Koga and Naraoka 2022). Aerobic conditions are required as they increase the amino acid production, which points to the oxidation of aldehydes as a crucial step. A glycine precursor arises from ammonia and glyoxylic acid, the latter generated by oxidation of glycolaldehyde.

Small monomers other than HCHO have been taken into account as ways of producing sugars through less complex routes. A suitable candidate is glyoxylic acid, HCOCOOH,

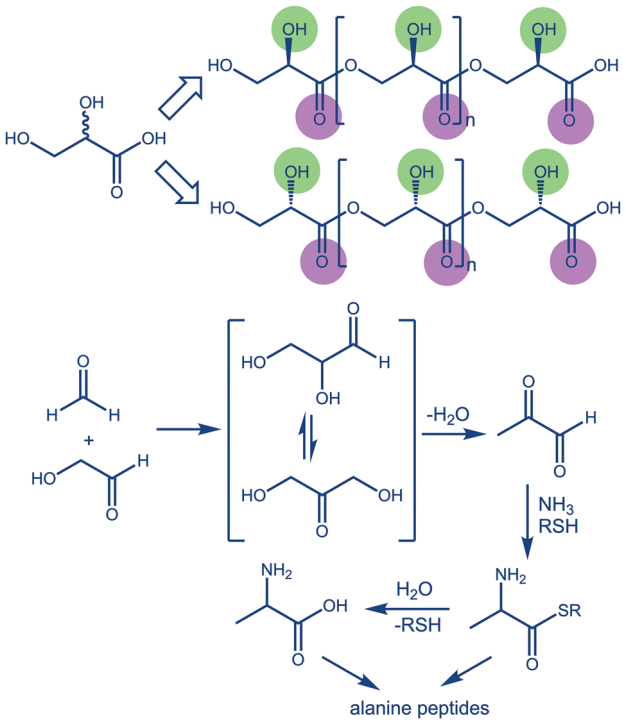

Fig. 7 Sugar models of prebiotic evolution. Top: a primitive polymer of poly(glyceric acid) could have catalytic properties. Stereoregular templating affording either all-D or all-L (R or S) configurations is assumed. Colored circles highlight OH groups as H-bond donor/acceptor (green) and carbonyl oxygens as H-bond acceptors (magenta) within a homochiral strand. Bottom: a simplified version of the triose-ammonia reaction leading to amino acids from glyceraldehyde

which can be regarded as "carboxylated formaldehyde" in Eschenmoser's words (2007). Formation of glyoxylic acid can be accomplished in an interstellar simulation from a CO-H_2O ice at 5 K with ionizing radiation (Eckhardt et al. 2019). The glyoxylate cycle shares some similarities with the formose reaction, but is more selective. Both glyoxylic acid and glyoxylate salts can lead to a variety of primeval molecules and constituents of the citric acid cycle (Eschenmoser 2007). A formal glyoxylate dimer, dihydroxyfumarate (DHF) can undergo self-condensation to a pentulosonic acid with further decarboxylation to erythrulose, a ketose (Sagi et al. 2011, 2012). DHF can also experience thermal bis-decarboxylation to glycolaldehyde in aqueous solution (Hay and Harvie 1965).

Probably, the most appealing route, often viewed as iconoclastic to the widely held RNA world, is Sutherland's aminoxazole-based chemistry achieving the bottom-up construction of pyrimidine ribonucleotides from simple prebiotic precursors, as schematically depicted in Fig. 8 (Borsenberger et al. 2004; Anastasi et al. 2006; Powner et al. 2009, 2010, 2012; Sutherland 2016). It is another formose-type reaction and much more as well, as glycolaldehyde and glyceraldehyde enter new pathways involving cyanamide, cyanoacetylene, inorganic phosphate, and other species, leading to nucleotides or their immediate precursors. Further work devised a protometabolic scenario capable of merging such two- and three-carbon sugars with HCN and its derivatives under photoredox catalysis

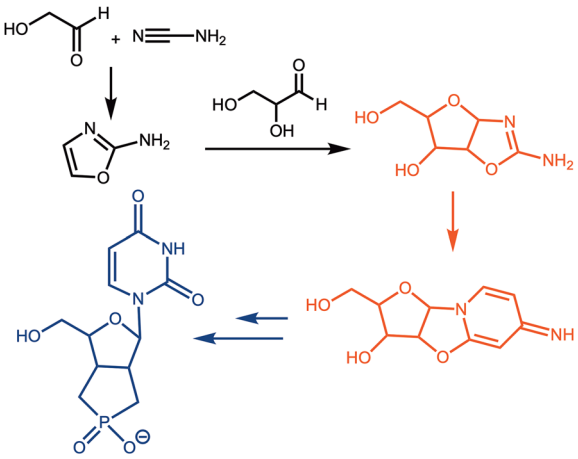

Fig. 8 Building up nucleoside skeleta from aminoxazole and glyceraldehyde. The configuration of chiral centers in this general diagram has been deliberately omitted for clarity

(UV irradiation with copper cyanometallates and H_2S as the ultimate reductant). Focusing this time on dihydroxyacetone, in equilibrium with glyceraldehyde, additional products could be obtained such as phosphorylated glycerols (precursors of lipid membranes), α-aminonitriles as precursors of amino acids, together with nucleosides and nucleotides, thereby broadening the scope of prebiotic syntheses (Ritson and Sutherland 2012; Patel et al. 2015).

Within the aforementioned results, the concept of a *photo-formose reaction* (Schwartz and De Graaf 1993) gains renewed interest, because UV light as energy for prebiotic syntheses on the surface of early earth might have boosted the production of the biomolecular inventory, including ribo- and 2-deoxyribo nucleotides (Ranjan and Sasselov 2016; Rimmer et al. 2021; Green et al. 2021; Ranjan et al. 2022). Photochemical and radiolytic mechanisms for the formose reaction are not new (Irie 1984; Sorrell 2001). These photoreactions in aqueous media would have formed hydroxyl radicals along with other high-energy or excited species. Likewise, such processes would also reconcile the formose reaction with the chemical inventory of interstellar media and gas-phase reactions, where the source of "CH_2" units, as outlined above, is the central piece, supplied by CH_3OH for instance. However, the mechanistic proposals that deviate from the classical formose reaction may involve intermediates other than free radicals. A mechanism based on a carbene pathway for the reaction of hydroxymethylene (CH_2OH) and HCHO yielding glycolaldehyde and glyceraldehyde has been suggested (Eckhardt et al. 2018), which may be operative under gas-phase conditions. Gas-phase formose reactions could also be mediated by ion–molecule reactions, whereby the reaction of HCHO and a hydronium cation would account for the synthesis of glycolaldehyde (Jalbout et al. 2007). Nucleophilic attacks involving carbanion and hydride intermediates could also be plausible (Appayee and Breslow 2014; Weiss and John 1974). All these insights, while describing the generation of sugar oligomers, fail to explain the prevalence of ribose, as a single enantiomer, under abiotic conditions. A recent computational study returns to a credible radical pathway in aqueous alkaline conditions, which proceeds with low energy barriers for the formation of ribose and RNA nucleobases (Jeilani and Nguyen 2020). Working at the DFT level using the

common hybrid functional B3LYP, with the unrestricted UB3LYP for open-shell species, all relative energies for the radical pathway were estimated from (U)B3LYP/6-311G(d,p)+ZPE (zero-point energy) computations. The initial dimerization step is the reaction of HCHO with hydroxymethyl radical ($^{\bullet}CH_2OH$) leading to glycolaldehyde. Interestingly, the formose reaction can proceed either with or without Ca^{2+} or $CaOH^{+}$ cations, although an autocatalytic cycle can be identified for the formation of glycolaldehyde and glyceraldehyde if such calcium species are involved. Apparently, however, Ca^{2+} does not participate in the catalytic formation of ribose from glyceraldehyde, which reacts sequentially with $^{\bullet}CH_2OH$ as the source of carbon atoms. The last step to ribose proceeds with a small activation energy (2.1 kcal/mol) and releases the product with − 1.4 kcal/mol. D-erythrose arises from dihydroxyacetone within this pathway as well (Fig. 9). Although this insightful theoretical assessment speaks of "D-ribose", surprisingly no stereoformulas are given. It is clear that D-ribose comes from D-glyceraldehyde and, accordingly, a similar reasoning could be reached for L-ribose. The study presupposes that the driving force favoring ribose, irrespective of the given enantiomer, lies in metal coordination from scratch leading to stable geometries with glycolaldehyde and glyceraldehyde.

The role of Ca^{2+} as Lewis acid by coordinating neutral and radical intermediates (oxygen atoms act as Lewis bases) seems plausible. The formation of the glycosidic bond between ribose and a nucleobase would result from the reaction of a cyclic free radical derived from ribose with a neutral nucleobase (Fig. 9). Together with a catalytic effect, calcium ions appear to keep all of the OH groups on the same side of the

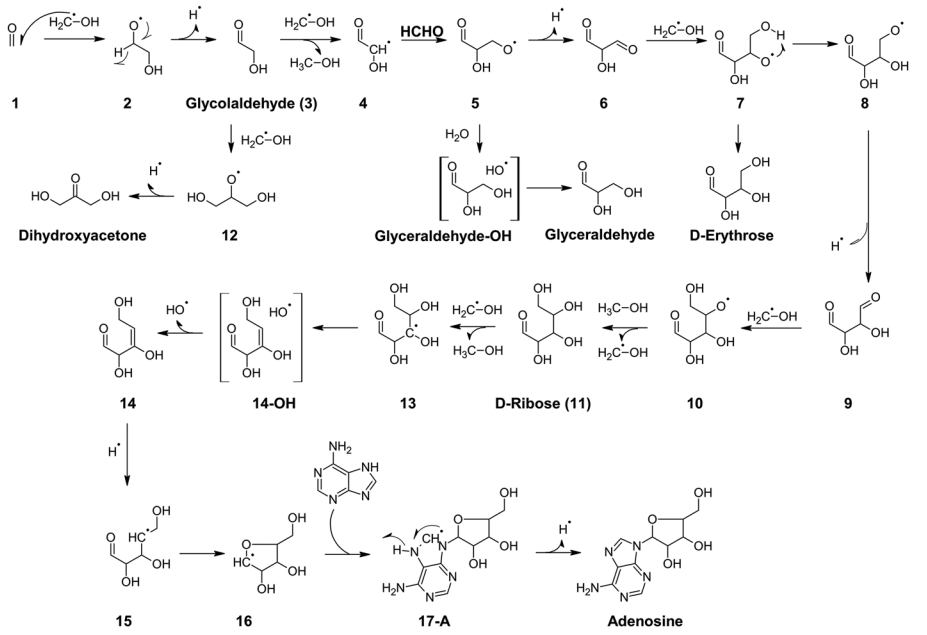

Fig. 9 Putative free radical pathway for the formose reaction along with formation of adenosine resulting from a ribose cyclic radical with neutral adenine. Since this analysis does not include any source of external chirality, both "D-ribose" or "D-erythrose" should rightly be interpreted as *ribo*- or *erythro*- configurations. The presented data can support the prevalence of the *ribo* configuration, yet in the racemic form (see main text). Reproduced with permission from Jeilani and Nguyen (2020). Copyright American Chemical Society

sugar molecule (Fig. 10). This could help explaining why the *ribo*-configuration, and no other configurations, is the favored arrangement. Metals other than Ca^{2+}, such as boron or divalent/trivalent ions present in clays, could play similar roles by coordinating to vicinal *cis*-diols (Ricardo et al. 2004; Nitta et al. 2016; Chen et al. 2021; Franco and Da Silva 2021).

On the other hand, other recent analyses disclose radical mechanisms for enhanced selectivity of ribose-purine condensations (at the N9 position of the nucleobase, while decreasing other ribosylamino isomers), such as cavitational dry–wet cycles that form $H^{\bullet}$ and $^{\bullet}OH$ radicals by water sonolysis (Patehebieke et al. 2021).

In the realm of *asymmetric* formose reactions, the observation of optical activity in supramolecular aggregates (xerogels) is also interesting, as observed by UV irradiation of HCHO at 70 ºC in the absence of catalysts (Stovbun et al. 2019). Chirality was attributed to the formation of elongated helical fibers, for which left-handed and right-handed domains could be detected, i.e. spontaneous segregation of enantiomorphous structures at a supramolecular level. Although the structures of such sugar oligomers were not elucidated and further study will be required, the generation of twisted elements in this puzzling transformation is relevant for materials design by using modified versions of the formose reaction (Delidovich et al. 2014).

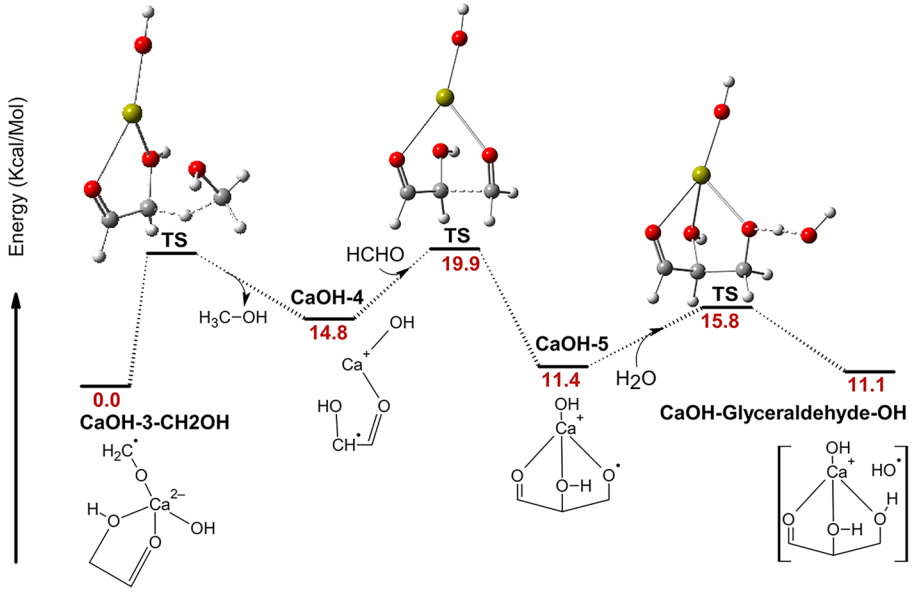

Fig. 10 Potential energy profile (kcal/mol) for the CaOH + -catalyzed formation of CaOH-glyceraldehyde-OH complex. Calcium coordination keeps the orientation of the hydroxyl groups on the same side. Reproduced with permission from Jeilani and Nguyen (2020). Copyright American Chemical Society

Why Ribose?

The stereochemical issue in the formose reaction is as intimidating as its purely chemical grounds. Leaving aside enantiomorphism, *a crescendo* stereo-complexity goes from glyceraldehyde, the first chiral sugar, to hexoses. For aldopentoses there are four possible diastereomeric pairs. Why ribose (or 2-deoxyribose) was selected as the structural component of nucleic acids is far from being evident. *Rac*-ribose is obtained in an extremely low yield (< 1%) from the messy formose reaction. The *ribose problem* has been repeatedly tackled without clear-cut conclusive statements. As noted by Shapiro in the late 1980s: *"The evidence that is currently available does not support the availability of ribose on the prebiotic earth, except perhaps for brief periods of time, in low concentration as part of a complex mixture….One other possibility deserves serious consideration: that RNA was not present at the start of life, but was first produced by biosynthetic processes, and subsequently took on a hereditary function"* (Shapiro 1988).

Enhanced diastereoselection in the formose reaction could have been attained through another prebiotic step, phosphorylation, key to biological evolution indeed (Eschenmoser 2011; Toxvaerd 2013). Starting from glycolaldehyde phosphate (whose synthesis can alternatively occur from a phospho-cyanohydrin derived from HCN), the formose reaction ends up in ribose-2,4-diphosphate as the main pentose (Mueller et al. 1990; Krishnamurthy et al. 1999). In the absence of HCHO, glycolaldehyde phosphate can evolve to a mixture of hexoses, with allose-2,4,6-triphospate as the major product (Fig. 11). Obviously, all products obtained are racemic compounds composed of D- and L-enantiomers. Like in aminoxazole chemistry, *O*-protected or masked sugars, *not free sugars*, would have dictated the syntheses preceding early metabolism. Certainly, a negatively charged phosphate group decreases the rate of enolization (abstraction of acidic protons), thereby diminishing the nucleophilic reactivity of intermediates toward HCHO and other carbonyl groups (Benner et al. 2010).

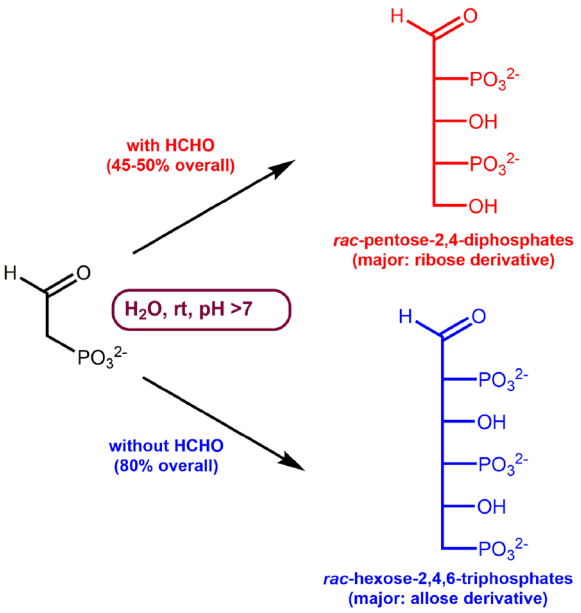

Fig. 11 Selective formose reactions from glycolaldehyde phosphate toward *rac*-ribo and *rac*-allo configurations as the main pentose and hexose, respectively

As inferred from the above-mentioned computational study (Jeilani and Nguyen 2020), the thermodynamic stability of ribose against other aldopentoses could rightly be ascribed to the orientation of all OH groups on one side of the ring, which provides a stronger coordination with metal ions. In fact, the stability constant of the α-D-ribopyranose-Ca(II) complex is larger than that of the remaining aldopyranoses, with the sole exception of α-D-allopyranose that shares an identical arrangement of hydroxyl groups (Angyal 1989). It is worth noting, however, that the coordinating ability of OH groups is more pronounced in a pyranose form (with well-defined equatorial and axial bonds) than in a furanose ring (pseudo-axial and pseudo-equatorial positions in the most stable *E*-conformations), which is however present in nucleic acids. *Rac*-ribopyranose could have undergone a selective interaction with a chiral surface decorated with the appropriate metal ions. An external electric field can also exert an orientational effect of polar groups, thus avoiding the necessity of an inherently chiral surface for enantioselection (Bielski and Tencer 2007). Likewise, a favorable puckered conformation for the β-D-ribose anomer has been invoked to justify ribose's selection in nucleic acids, while for the other pentoses the hydroxyl groups at C-2' and C-3' positions lying above the furanose ring cause steric hindrance with the OH group at C-5' and the nucleobase (Banfalvi 2006).

Ribose would have also benefitted from favorable interactions with biomolecular systems before or after cellular genesis (Sacerdote and Szostak 2005). A ribo-aminoxazoline derivative can easily be obtained from D-ribose and cyanamide at basic pH values (Borsenberger et al. 2004; Springsteen and Joyce 2004). It has been shown that this aminoxazoline degrades more slowly than ribose (*ca.* 70-fold at pH ~ 10, $t_{1/2} > 1$ week), thus being a masked form of the free sugar and hence, susceptible of accumulation due to enhanced stability. This ribofurano-oxazoline crystallizes spontaneously in aqueous solution containing ribose and cyanamide, while the corresponding products derived from other pentoses and hexoses do not. Obviously, this substance generated from enantiomerically pure D-ribose is chiral. Syntheses from *rac*-glyceraldehyde and 2-aminoxazole, or alternatively from D- and L-ribose with cyanamide, yields the racemate, albeit the use of scalemic glyceraldehyde enables the formation of an enantioenriched product (Anastasi et al. 2006). It is well known in carbohydrate chemistry that aldoses react with inorganic cyanates or thiocyanates to afford glyco-oxazolidinones or glyco-oxazolidinethiones, respectively, whereas ketoses often lead to spiranic structures (Grouiller et al. 1988; Kovács et al. 1995). The simplest ketose, dihydroxyacetone, reacts with KOCN, KSCN, or cyanamide giving rise to spiranic bicycles (Saul et al. 2000). The reaction with cyanamide produces a bis(2-aminoxazoline) derivative, which is structurally related to the above-mentioned 2-amino-D-ribofurano-oxazoline (Fig. 12). Remarkably such spiranes are inherently chiral due to axial stereogenicity. Unfortunately, they crystallize as racemic compounds, not conglomerate phases, which impedes spontaneous resolution by crystallization. Diastereomeric resolution proved to be unsuccessful (Saul et al. 2000).

As surprising as it may be, the single-crystal analysis of D-ribose could only be accomplished in 2010 with identification of two polymorphic structures, both exhibiting a significant molecular disorder (Šišak et al. 2010). There are various independent molecules of D-ribose ($Z' = 2$, Form I; $Z' = 3$, Form II), which coexist as β- and α-pyranose anomers, the latter contributing presumably to increase stability through supplementary H-bonding. The fact that D-ribose crystallizes with two (A, B) or three (A, B, C) symmetry-independent molecules, rather than a repetitive single molecule, suggests that one enantiomer does not efficiently fill the unit cell, while anomers (bearing a diastereomeric relationship to each other) of D-ribopyranose with different orientations of axial/equatorial groups, and hence of H-bonds, result in a stable packing. Unlike the behavior in solution, no furanose anomers are detected in the solid-state structure. Accordingly, the DL-racemate could

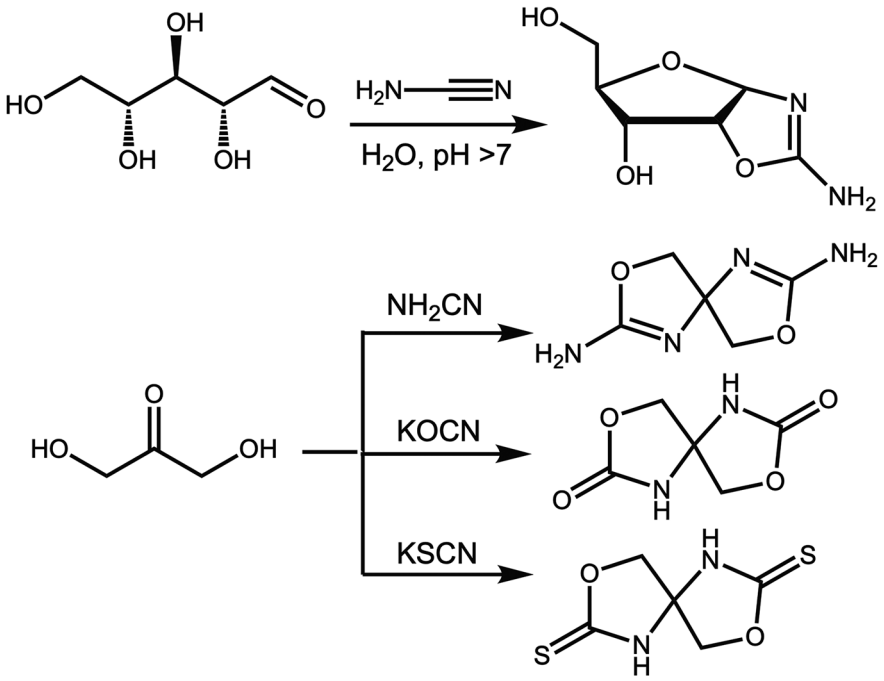

Fig. 12 Top: formation of homochiral D-ribo-aminoxazoline by reaction of D-ribose with cyanamide. Bottom: Similar condensations of dihydroxyacetone with cyanamide and (thio)cyanate salts in aqueous media yielding racemic spiranic compounds

fill the space better. Actually DL-ribose (mix of D- and L-enantiomers) crystallizes and grows much easier than D-ribose. Again, two structures (I and II) have been described for DL-ribose, although the first seems to be a disappearing polymorph, obtained only once (Zandomeneghi et al. 2012). A further re-investigation and DFT analysis of D-ribose and DL-ribose structures (Fig. 13) evidence that intermolecular H-bonding in DL-ribose II leads to a more energetically favored conformational arrangement with less distorted bond lengths and angles than in both D-ribose I and II polymorphs (Patyk and Katrusiak 2014). As a consequence, the racemate constitutes *the only pure form of β-ribopyranose*, consistent with a facile crystallization as well.

If one considers crystallization as an evolutionary event, it could hardly be plausible a structural selection of ribose based on single enantiomers. In stark contrast, sugar racemates circumvent the difficult crystallization of one enantiomorph. On the other hand, the replicating ability of sugar polymers is not limited to pentoses; tetrose- and hexose-based strands can also function efficiently in abiotic models (Eschenmoser 2004; Wachowius et al. 2017; Liu and Sumpter 2018; Kim et al. 2021; Wang et al. 2021). Looking at ribose at the crossroads of homochiral evolution, it is difficult to establish a coherent narrative. One might justifiably ask whether ribose (or 2-deoxyribose) alone would be up to the task; probably the primitive cellular machinery took advantage of the best-fitted chemical derivatives, rather than the native sugars.

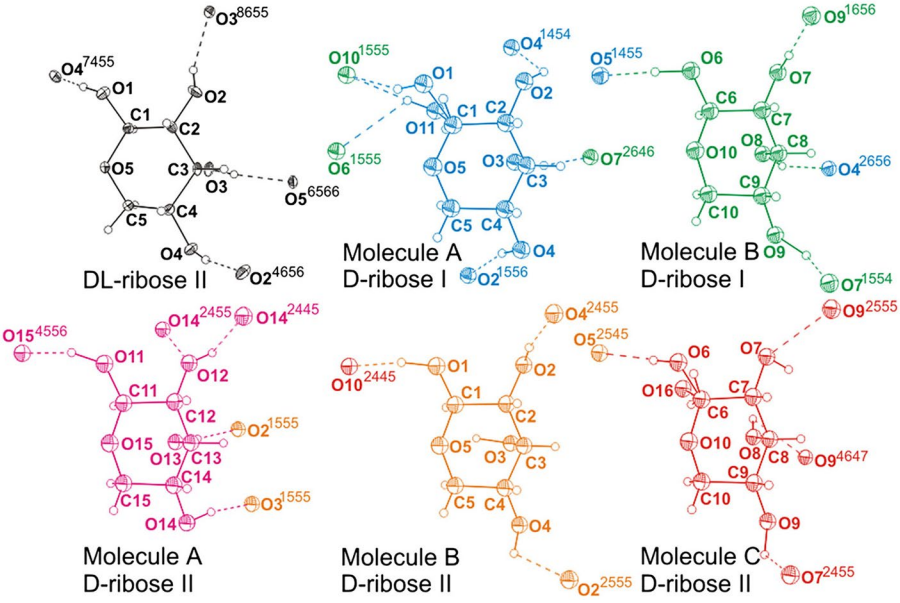

Fig. 13 Intermolecular hydrogen bonding of similarly oriented ribopyranose molecules in DL-ribose II at 295 K, and D-ribose polymorphs at 123 K: Form I contains two independent **A**, **B** pyranose molecules and form II three disordered anomers **A**, **B**, **C**. Reproduced with permission from Patyk and Katrusiak (2014). Copyright Wiley Periodicals Inc

Enantiosymbiosis: the Best of Two Worlds

Accumulated evidence, through theory and experiment, indicates that we could be allowed to introduce herein the term *enantiosymbiosis*, to denote how available homochiral species, lend a helping hand to molecules whose deracemization has proven to be extremely difficult. The amino acid-sugar interaction could thus be foreseen as a bidirectional way to that end. The accidental generation of homochiral bias in such molecules might be transferred to other racemic mixtures via intermolecular interactions in gas or condensed phases, or by forming stable cocrystals. Formation of gas-phase clusters between amino acids and sugars enable the assessment of interaction and recognition mechanisms (Ahn et al. 2001; Nguyen and Fujihara 2018; Murashima and Fujihara 2020). Interactions in solution and identification of stable crystalline complexes between the aforementioned ribo-aminoxaline or spiranes obtained with cyanamide, and racemic and enantiopure amino acids have also been reported recently (Lavado et al. 2019).

The use of amino acids as catalysts to achieve some degree of enantioselection in formose reactions has been documented by different groups during the past two decades (Pizzarello and Weber 2004; Weber and Pizzarello 2006; Breslow and Cheng 2010; Hein and Blackmond 2012; Blackmond 2019). The enantiomeric excesses measured are modest, yet significant, and depend on the nature of the amino acid and experimental conditions. The use of secondary amino acids, like L-proline, gives rise to opposite handedness relative to other amino acids, yielding L-glyceraldehyde (42% *ee*) in the catalytic condensation of HCHO and glycolaldehyde (Breslow and Cheng 2010), while a L-prolinate salt reverted to D-glyceraldehyde (in only 13% *ee*) (Hein and Blackmond

2012). The process is highly influenced by pH values as well and thus, an excess of D-glyceraldehyde is formed by L-amino acids with primary NH_2 groups at acidic pH, while neutral or alkaline conditions lead preferentially to L-glyceraldehyde. L-proline shows the reverse selectivity and catalyzes the synthesis of an excess of L-glyceraldehyde at low pH and excess of D-glyceraldehyde as the pH increases (Breslow et al. 2013). These organocatalytic features can be rationalized in terms of the transition structures suggested for aldol-type reactions involving the formation of enamine intermediates (Fig. 14). Under acidic conditions, primary L-amino acids react with glycolaldehyde producing a *Z*-enamine favored by NH–-O bonding. Then HCHO is brought into the prochiral *Re*-face of the enamine through an additional H-bond with the carboxylic acid group, thereby favoring the formation of D-glyceraldehyde via TS1. At basic pH, HCHO approaches now the *Si*-face to the enamine, because a stabilizing H-bonding with the carboxylate group cannot be established together with the existence of electrostatic repulsion between the carboxylate group and the incipient alkoxide anion, all leading to L-glyceraldehyde through TS3. When L-proline catalyzes the aldol reaction under basic conditions, steric hindrance and the lack of H-bonding direct the stereochemical outcome through the preferred TS2, where HCHO approaches the *Re*-face of the *E*-configured enamine yielding D-glyceraldehyde. On the contrary, an acid medium enables the approach of HCHO to the *Si*-face of the *E*-enamine due to H-bonding with the carboxylic acid group in TS4 leading to L-glyceraldehyde.

Amino acid esters overcome the limitations of zwitterionic species in water and can likewise catalyze the formation of protected and unprotected tetroses at neutral pH. Again, L-proline esters induce discrete enantiomeric imbalances of L-treoses, while esters derived from L-alanine, L-leucine and L-valine favor an excess of D-erythrose or D-threose (Burroughs et al. 2012). Invariably L-proline has been the "silver bullet" since the renaissance of asymmetric organocatalysis in the early 2000s. This proteinogenic amino acid efficiently catalyzes the trimerization of propionaldehyde into six-membered lactols akin to pyranoses, as 1:2 α/β-anomer mixtures, with 33% *ee* at most (Chowdari et al. 2002). Unfortunately, this protocol works well in *N,N*-dimethylformamide (DMF), a suitable solvent in organic synthesis, which is inconsistent with prebiotic aqueous conditions. Direct L-proline-catalyzed cross-aldol reactions can however be performed in phosphate buffer while using sodium dodecylsulfate as surfactant, thereby favoring micellar conditions (Córdova et al. 2002). Among metal prolinates, the environmentally friendly Zn-proline complex proved to be versatile enough in an enantioselective synthesis of D-threose (10% *ee*) starting from glycolaldehyde (Kofoed et al. 2004), as well as in the production of pentoses (with ribose amounting up to 20%) and hexoses from glycolaldehyde and glyceraldehyde (Kofoed et al. 2005). From a mechanistic standpoint, the cross-aldolization benefits from Zn-complexation in ways comparable to other metals in formose reactions. The glycolaldehyde enolate is formed preferentially, while *rac*-glyceraldehyde serves as electrophile. Incubation of ribose with Zn-proline for two weeks gave no sign of epimerization to other aldopentoses. As the reaction progresses, the percentage of tetroses decreases yielding pentoses as the major products, while little or no changes are observed for hexoses. The catalytic cycle is shown in Fig. 15, where the *N/O*-coordinated Zn-proline complex efficiently executes the Lewis acid-catalyzed aldol reaction with glycolaldehyde. Metal coordination to the latter affords a chelating enolate resembling the active site of type II aldolases containing Zn^{2+} as cofactor. The nucleophilic enolate may then attack glyceraldehyde, either with or without coordination with the metal ion. Complexation appears to stabilize the chelate structure leading to *erythro*-configurations in the new C2-C3 bond, i.e. ribose and lyxose (40% yield) with respect to a *threo*-arrangement, producing a lower proportion of arabinose and xylose.

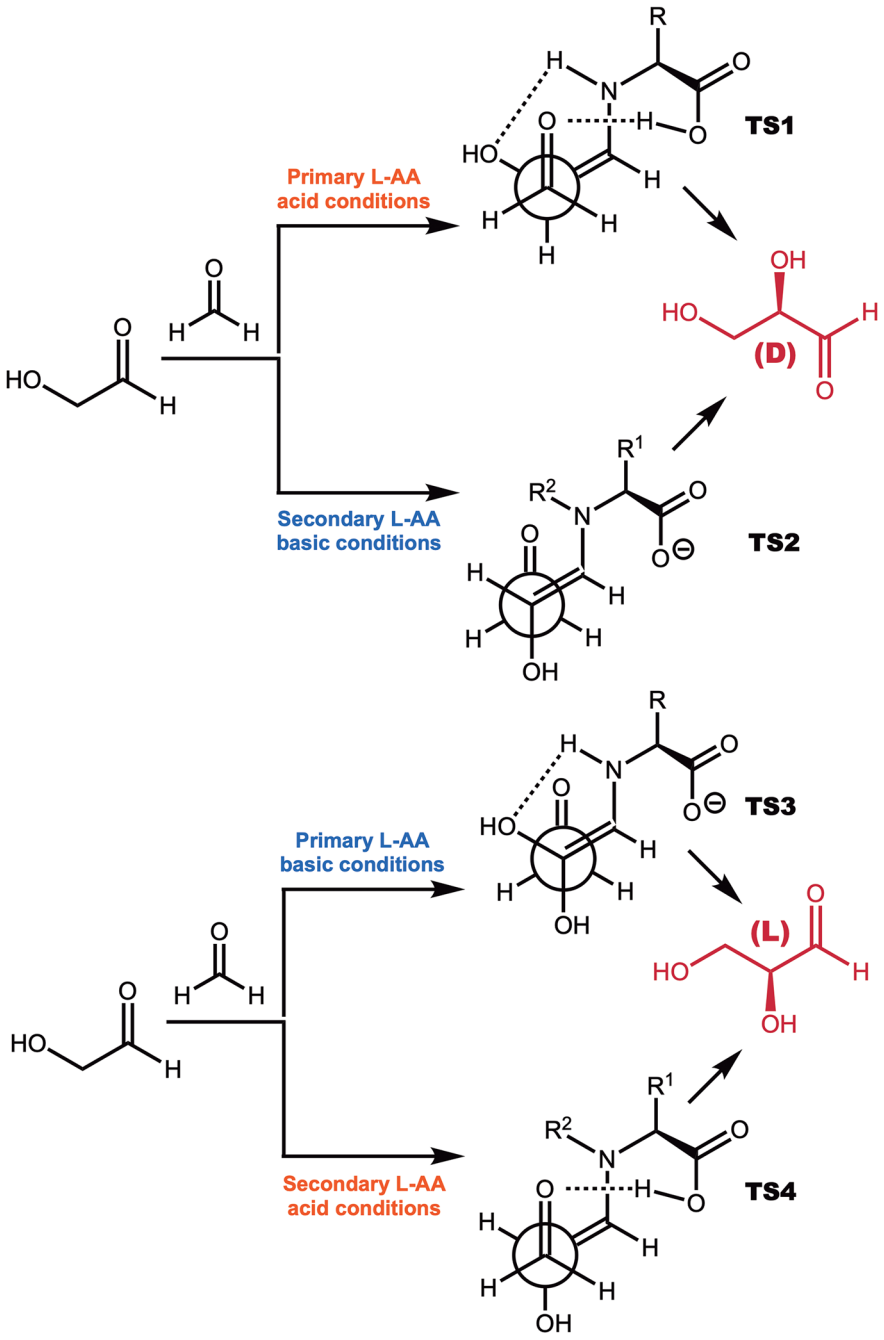

Fig. 14 Proposed transition structures for the amino acid-catalyzed formose reaction between HCHO and glycolaldehyde. Adapted and modified from Breslow et al. (2013)

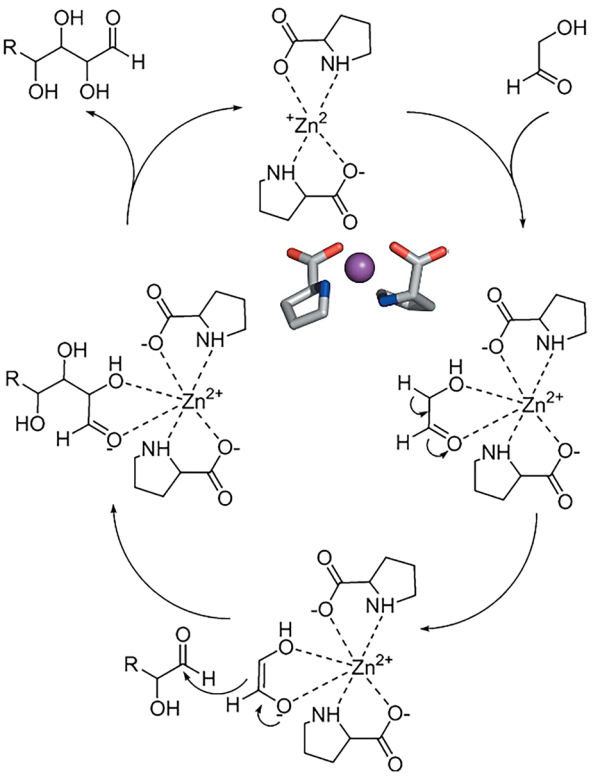

Fig. 15 Mechanistic proposal for the cross-aldol reactions of glycolaldehyde catalyzed by Zn-L-proline complex leading to higher sugars. The 3D structure inserted corresponds to the catalyst where NH and COO groups interact with $Zn.^{2+.}$ Reproduced and adapted with permission from Kofoed et al. (2005). Copyright the Royal Society of Chemistry

An asymmetric version of the aminoxazole variant led to highly enantioenriched sugar derivatives starting from racemic materials in the presence of amino acids with low *ees* (Hein et al. 2011). Thus, L-proline (with an initial 1% *ee*) was added to a mixture of *rac*-glyceraldehyde and 2-aminoxazole and the ensuing reaction gave rise to both D-ribo- and D-arabino-configured aminoxazolines in 20–80% *ee*. On cooling the mixture to 4 ºC, crystallization of enantiopure D-ribo-aminoxazoline crystals occurred. The unnatural L-ribo-aminoxazoline was obtained similarly starting from 1% *ee* of the D-proline enantiomer as catalyst. Notably, L-glyceraldehyde was sequestered by a side reaction that assembles the aminoxazoline and L-proline, thus serving as a kinetic resolution of glyceraldehyde (Fig. 16).

The use of short dipeptides, more hydrophobic than zwitterionic amino acids, yet displaying aqueous solubility, constitutes an interesting catalytic variation for formose reactions. Tetroses can be obtained with good stereoselection, up to 80% *ee* for D-erythrose, employing L-valyl-L-valine as organocatalyst (Weber and Pizzarello 2006). Extension to the condensation of glycolaldehyde and DL-glyceraldehyde yields, in the presence of such a dipeptide, all four pentoses as mixtures of furanose and pyranose structures, along with low yields of tetroses and unidentified byproducts, most likely derived from aldehyde oligomerization (Pizzarello and Weber 2010). Reactions proceeded smoothly at ambient temperature as shown in Fig. 17, where arabinose is the major product followed by lyxose, ribose and xylose. However, the enantiomeric excess varies in magnitude and configuration with respect to the parent catalyst. Thus, with LL-dipeptides, ribose was the only pentose

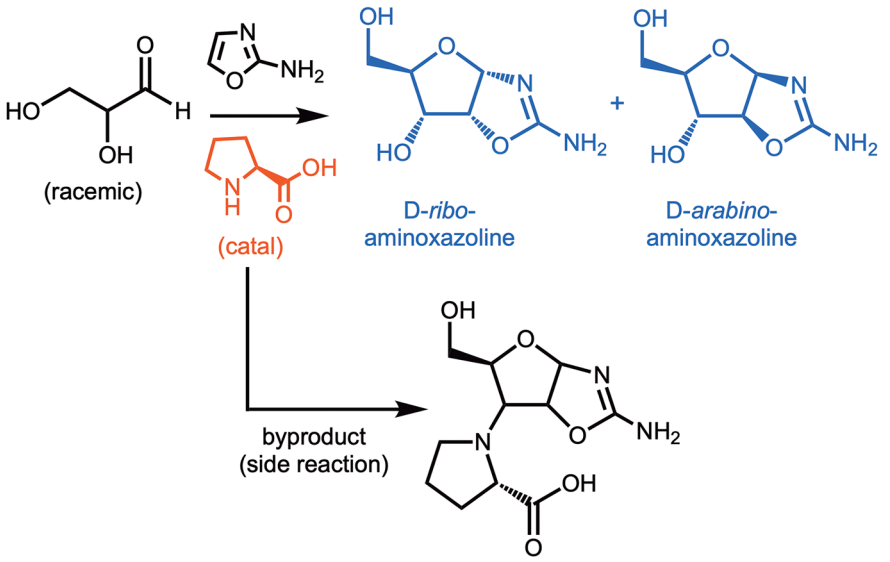

Fig. 16 Generation of enantioenriched RNA precursors from *rac*-glyceraldehyde and 2-aminoxazole catalyzed by L-proline

to have a significant D-*ee* (up to 47%), whereas L-configurations were favoured for lyxose, as high as 66% *ee*, and much lower for arabinose (up to 11% *ee*) with xylose being essentially racemic ($\leq$2% *ee*).

A mechanistic rationale is compulsory to understand the stereochemical selection, where LL-peptides catalyze an enantiomeric excess of D-ribose and L-lyxose, while conversely D-configured dipeptides would induce the formation of L-ribose and D-lyxose. At first glance the chiral intermediates triggered by the catalyst will thus determine the configuration of the C2 and C3 carbon atoms of pentoses. The proposed stepwise route toward tetroses and pentoses would involve a combination of stereoselective intramolecular

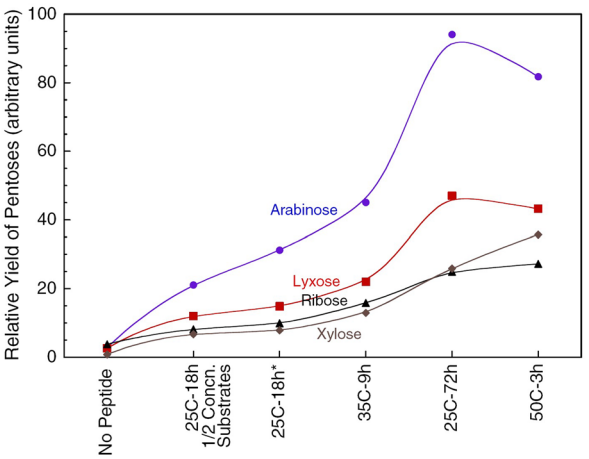

Fig. 17 Temporal and thermal evolution of the synthesis of pentoses catalyzed by L-val-L-val. Reproduced with permission from Pizzarello and Weber (2010). Copyright Springer

cyclization and aldol reaction as shown in Fig. 18. The key element of this rationale is the intermediacy of an imidazolidinone ring formed between the two nitrogen atoms of the peptide and the C1 atom of glycolaldehyde. Reasonably, this heterocyclic intermediate contains a secondary amine plus a carboxylate group, which may adopt the appropriate geometry to act as proton donor–acceptor groups capable of enhancing the nucleophilicity of a vicinal hydroxymethyl group. The latter intermediate could then undergo deprotonation and mediate the subsequent elongation process through the aldol condensation with glyceraldehyde.

This proposal, however, is somewhat problematic. Firstly, it deviates from the expected initial intermediates in amino acid organocatalysis. Moreover, the methylene protons are less acidic than the α-hydrogens involved in aldol reactions. Certainly, the above argument is consistent with general acid–base catalysis typical of enzyme pockets, where the pK_a values of side chain groups within the hydrophobic site are not necessarily the same as those measured in solution (Silverman and Holladay 2014). In aqueous environments the survival of carbanion-like species would be compromised without affecting the stereocontrol and eschewing side transformations. This prompted us to re-investigate an alternative pathway potentially capable of accounting for experimental facts. Our feedback with Prof. Pizzarello was extremely positive and she kindly encouraged further pursuits. Accordingly, the purpose of a theoretical analysis was twofold: (1) whether a favorable pathway could lead to the divaline sugar precursor, and particularly (2) *how the catalyst induces the enantiomeric excess of D-ribose*, which is clearly of prebiotic relevance. A thorough

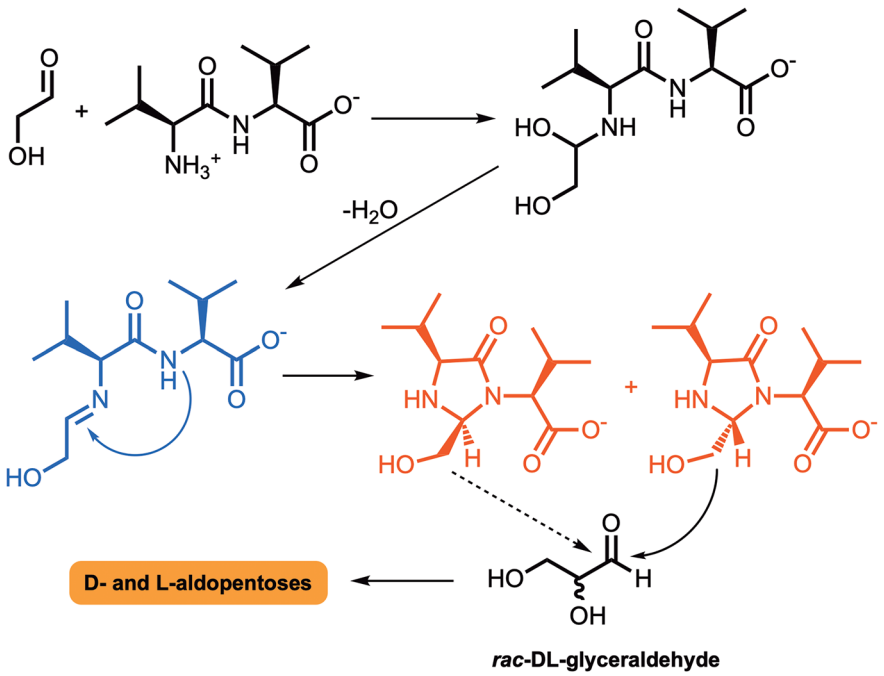

Fig. 18 Proposed mechanistic pathway for the L-val-L-val-catalyzed synthesis of pentose sugars involving the intermediacy of diastereomeric imidazolidinones, according to Pizzarello and Weber (2010)

computational study (Cantillo et al. 2012) was performed with robust M06-2X hybrid functional (Zhao and Truhlar 2008) and the extended 6–311 + + G(d,p) basis set together with inclusion of solvation effects through the SMD model. The initially-formed imine (Schiff base) should have the most stable *E*-configuration. The latter can evolve, by intramolecular attack as suggested, to an imidazolidinone, which is thermodynamically favored by 2.6 kcal/mol. This cyclization however proceeds through a barrier of + 22.5 kcal/mol. The subsequent proton abstraction at the hydroxymethylene group has an extremely high barrier (~ 53 kcal/mol) and formation of the carbanion species is largely disfavored (~ 48 kcal/mol). It seems plausible to conjecture that the asymmetric organocatalysis occurs instead through enamine intermediates (Berkessel and Gröger 2005; Mlynarski and Gut 2012; Dalko 2013). In fact, a *Z*-configured enamine becomes stabilized by *ca*. 3 kcal/mol. Although this species equilibrates with its more stable carbonyl tautomer, the subsequent nucleophilic attack onto glyceraldehyde would take place through the enamine form leading to a new carbon–carbon bond. This addition reaction generates two new chiral centers and should reasonably be the rate-limiting step (Fig. 19).

Accordingly, both the energy barriers and the relative stability of the zwitterionic intermediate affording the different pentoses can be evaluated. However, data did not fulfill the expectations. In contrast to the experiment indicating the prevalent formation of arabinose, the energy barriers favor xylose. Even worse, the D-configuration is not only favored for ribose but also for xylose, thus disagreeing with experiment too,

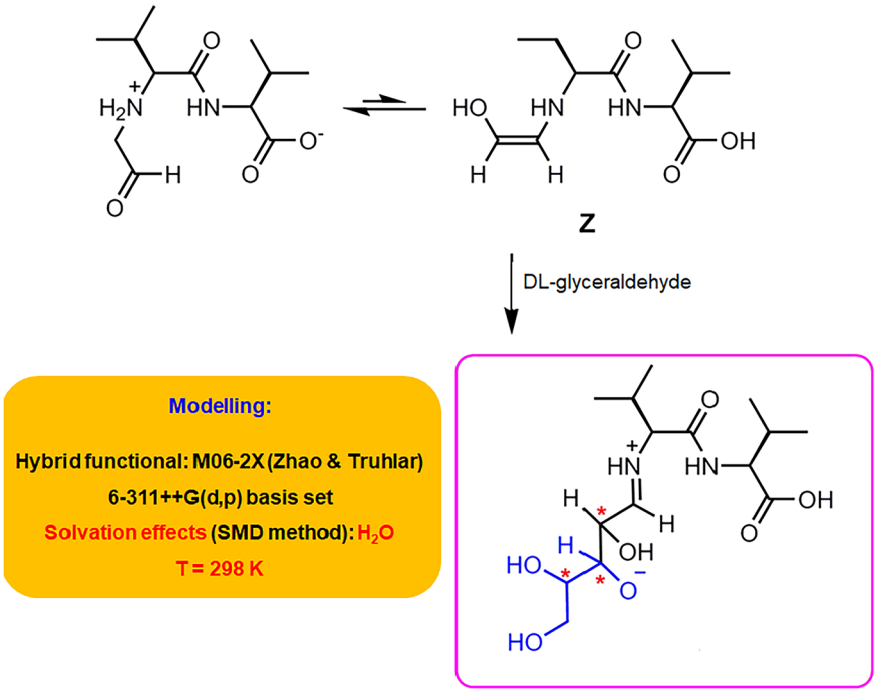

Fig. 19 Prebiotic access to pentoses mediated by dipeptides: step showing the addition of an enaminol intermediate to glyceraldehyde leading to a zwitterionic intermediate with formation of a new carbon–carbon bond

and in addition, no stereoselectivity is predicted for arabinose. Furthermore, the energy barriers are generally low, and especially for xylose (13.4 kcal/mol), inconsistent with the long reaction times (several hours) required for completion under the experimental conditions. Although this discrepancy could be attributed to the theoretical method itself, it could also rule out the addition reaction as the rate-limiting step. The subsequent imine hydrolysis takes place at an sp^2-carbon atom contiguous to the first chiral center and, hence an asymmetric induction may occur in this transformation. To our surprise and, on skipping unnecessary structural details, the corresponding transition structures and minima could be located, and energy data matched all the experimental observations in terms of reaction time and selectivity. Arabinose is actually the most favored pentose and its formation proceeds through the lowest energy barrier. Remarkably, the D-configuration is favored for ribose only, whilst the rest of pentoses exhibit an enantiomeric excess for the L-configuration. In line with the experiment, xylose lacks stereoselectivity as similar energy barriers (22 kcal/mol) were encountered for D- and L-isomers (Cantillo et al. 2012). It is noteworthy that the hydrolysis of the chiral iminium intermediate proceeds through a concerted mechanism (i.e. deprotonation of water by the initially formed alkoxide occurs concomitantly with the nucleophilic attack of the hydroxy group onto the iminic carbon). The catalytic cycle is illustrated in Fig. 20 with a description of the concerted hydrolysis of the iminium ion shown in Fig. 21. A stepwise route could be invoked, but calculations failed to locate the corresponding transition structures. The energy barriers accounting for the experimental range of aldopentose enantiomers are gathered in Fig. 22 for comparative purposes. The fact that one water molecule is involved in proton transfer by the OH group is clearly a salient point as well. Such a transfer lowers the energy barrier by *ca*. 9 kcal/mol relative to the transfer in the absence of water. This observation emphasizes a catalytic action of water in prebiotic syntheses beyond purely solvation effects (Saa and Frontera 2020). Furthermore, catalytic systems, like the ribosome, would have developed similar hydrolytic

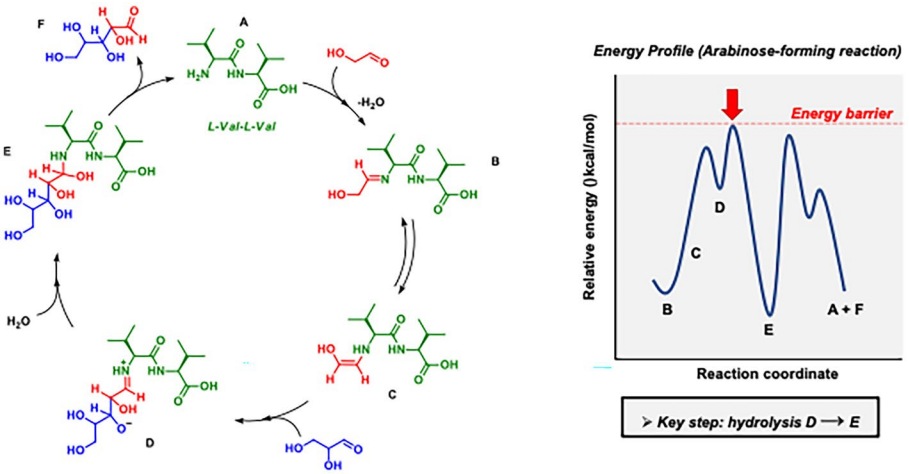

Fig. 20 Catalytic cycle supported by DFT calculations for the asymmetric dipeptide-catalyzed formation of sugar pentoses. The rate-limiting step is actually the imine-hydrolysis reaction (the energy landscape is shown for arabinose formation). The aminopolyol generated after hydrolysis can undergo facile decomposition (lower energy barrier than hydrolysis), thus liberating the dipeptide catalyst

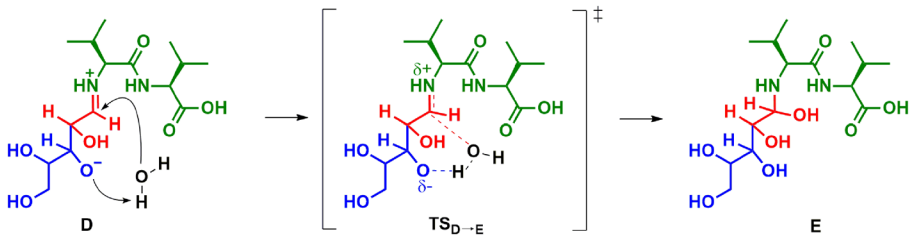

Fig. 21 Concerted pathway and transition structure located for the rate-limiting step (hydrolysis of iminium ion) during the dipeptide-catalyzed synthesis of aldopentoses

mechanisms involving the participation of strong hydrogen bonds, as inferred from the elucidation of the active site for the two reactions of the peptidyl transferase center (Kuhlenkoetter et al. 2011).

In recent times, other groups, Blackmond and associates in particular, have exploited the use of peptides that catalyze the enantioselective formation of discrete formose sugars, like tetroses and glyceraldehyde (Jones et al. 2020; Yu et al. 2021). Thus, enantioenriched glyceraldehyde was obtained from *rac*-glyceraldehyde through a peptide-assisted kinetic resolution. The latter proceeds via a selective reaction between the L-configured partners (LL-peptide and L-sugar) affording an Amadori rearrangement byproduct and leaving D-glyceraldehyde unaffected. The process depends on both the solvent conditions and the structural features of peptides. Good results were obtained in phosphate and carbonate buffers, while borate buffer resulted in low enantioselectivity. Peptide screening revealed that enantioenrichment of D-glyceraldehyde took place with *N*-terminal proline dipeptides, whereas proline alone was unreactive. Moreover, without proline at the *N*-terminus, the enantioenrichment decreased considerably. L-Pro-L-val

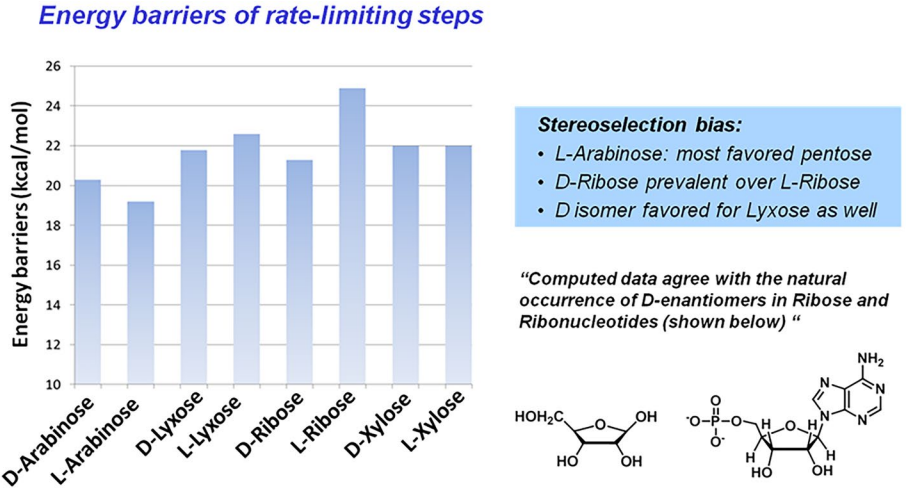

Fig. 22 Summary of energy barriers for the rate-limiting hydrolysis of the ultimate chiral imine derivative, which account for the experimental distribution of aldopentose enantiomers during the L-val-L-val-catalyzed addition of glycolaldehyde to glyceraldehyde

dipeptide gave rise to the best enantioselection (24% *ee*), albeit with a lower conversion with respect to other dipeptides devoid of proline. As mentioned, the central point focuses on the selective interaction of that dipeptide with L-glyceraldehyde that leaves the D-enantiomer untouched (Fig. 23). Under the reaction conditions, glyceraldehyde isomerizes to dihydroxyacetone as well, to a minor extent nevertheless. This isomerization is unselective and occurs with both enantiomers, thereby globally decreasing the selectivity. The extra relevant feature involves the asymmetric synthesis of the enantioenriched dipeptide from nearly racemic precursors by taking advantage of physical processes (*eutectic partitioning*), developed by this group in previous work (Klussmann et al. 2006, 2007). Essentially enantiopure (> 99% *ee*) aqueous valine solutions can be generated from nearly *rac*-valine by mixing low-*ee* valine (partially dissolved) with fumaric acid. This strategy could not be applied to proline, which is highly soluble in water. However, by forming the corresponding LL- and DL-pro-val dipeptides, those diastereomers exhibited a marked difference in solubility. After partial evaporation of a 1:1 mixture, the desired and almost pure LL-dipeptide precipitated.

Not only peptides, but also structurally related amides may serve as potential catalysts compatible with aqueous aldol and formose reactions. A glutamine amide derivative, having capacity as hydrogelator, has been recently harnessed to this end as shown in Fig. 24. The initial material itself can catalyze a model aldol reaction, but does not maintain the gel structure during this transformation. By converting this compound into a Schiff base with benzaldehyde, followed by $NaBH_4$ reduction of the resulting imine, an efficient and stable hydrogelator could be obtained. This substance catalyzed the prebiotic aldol dimerization of glycolaldehyde to give erythrose and threose (Hawkins et al. 2020). Good conversions (up to 76%) and diastereoselectivities (erythrose:threose ~ 1:2 ratio) were observed in neutral aqueous buffers, although unfortunately the enantioselectivity was very low (4% *ee* for erythrose and 10% *ee* for threose at most). The study however unveils new designs of environmentally friendly catalysts that can be tailored for prebiotic-type and related reactions, and are endowed with properties that enable facile purification and recovery.

If amino acids or peptides catalyze the enantioselective formation of sugars, one could conjecture reciprocally that enantioenriched sugars could be recruited as promoters of asymmetric transformations leading to amino acid derivatives. Carbohydrate-based compounds are actually efficient organocatalysts, but the naturally occurring

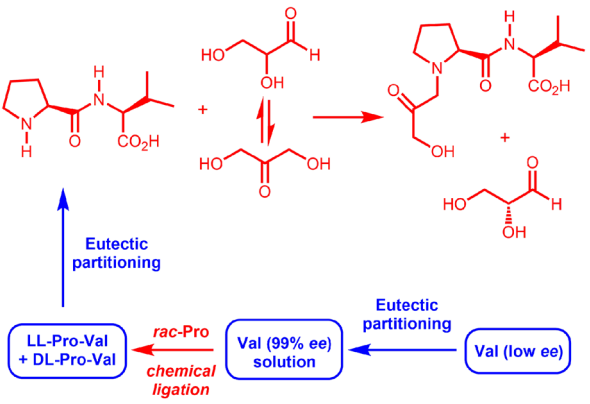

Fig. 23 Combination of physical (marked in blue) and chemical (highlighted in red) processes that enable the kinetic resolution of *rac*-glyceraldehyde with enantioenriched dipeptides. Adapted and modified from Yu et al. (2021)

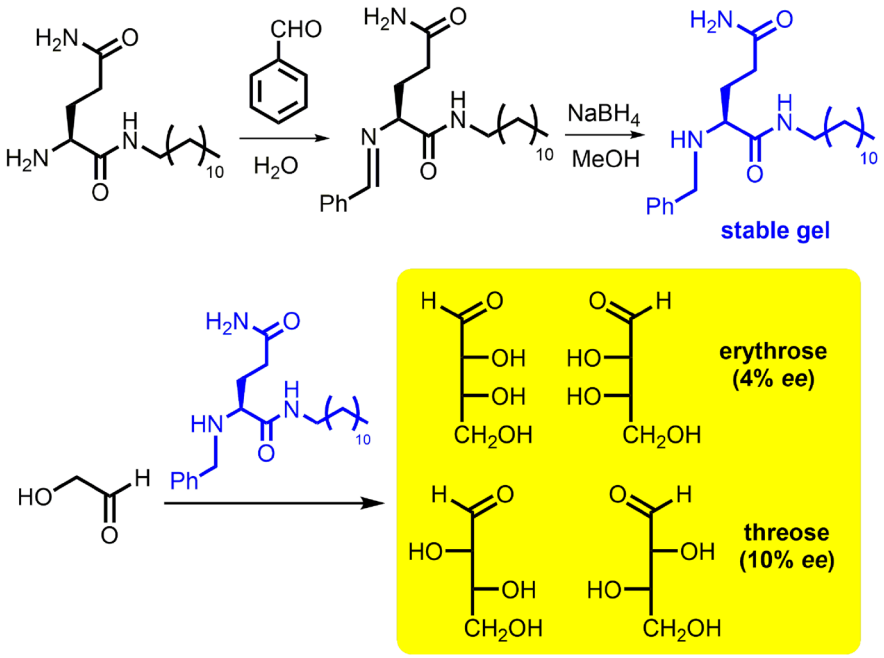

Fig. 24 Design of a catalytic gel, derived from L-glutamine, for glycolaldehyde dimerization affording tetroses

unprotected precursors should be significantly modified to accommodate functional groups (like thioureido moieties) capable of establishing multiple non-covalent interactions (Mishra et al. 2016; Wojaczynska et al. 2021). In absence of such features, including more rigid skeleta, they exhibit poor or null stereoselection.

Parallel to the formose reaction, the prebiotically credible route to amino acid derivatives is indisputably the Strecker reaction. This venerable transformation, dating back to the mid-nineteenth century, leads to α-aminonitriles (whose acid hydrolysis affords α-amino acids) and has become a useful protocol in contemporary synthesis by replacing toxic reagents like HCN, ammonia or cyanates by cyanide surrogates (Kouznetsov and Galvis 2018; Grundke and Opatz 2019; Pimparkar et al. 2021). Notably, the first asymmetric Strecker synthesis catalyzed by a cyclic dipeptides was reported in 1996 (Iyer et al.). Recent research shows that homochiral sugars can induce a certain enantioselection in the de novo amino acid synthesis (Wagner et al. 2017; Legnani et al. 2021). As shown in Fig. 25, homochiral pentoses efficiently catalyze the formation of amino acid amides from α-aminonitriles under basic and mild conditions. Such aminoamides can further be converted into amino acids by hydrolysis. Enantioselection is observed even using catalytic amounts of sugars, as low as 0.025 M and at neutral pH values. In order to identify competing effects, which may otherwise be more realistic than the effect of a single sugar, when the reaction is run with a mixture composed of equal amounts of D-ribose and D-lyxose, as well as equal parts of the four aldopentoses, the enantiomer excess favors the L-configuration. This points to a greater effect of arabinose and lyxose than ribose and xylose. D-Lyxose is the sugar producing in all cases

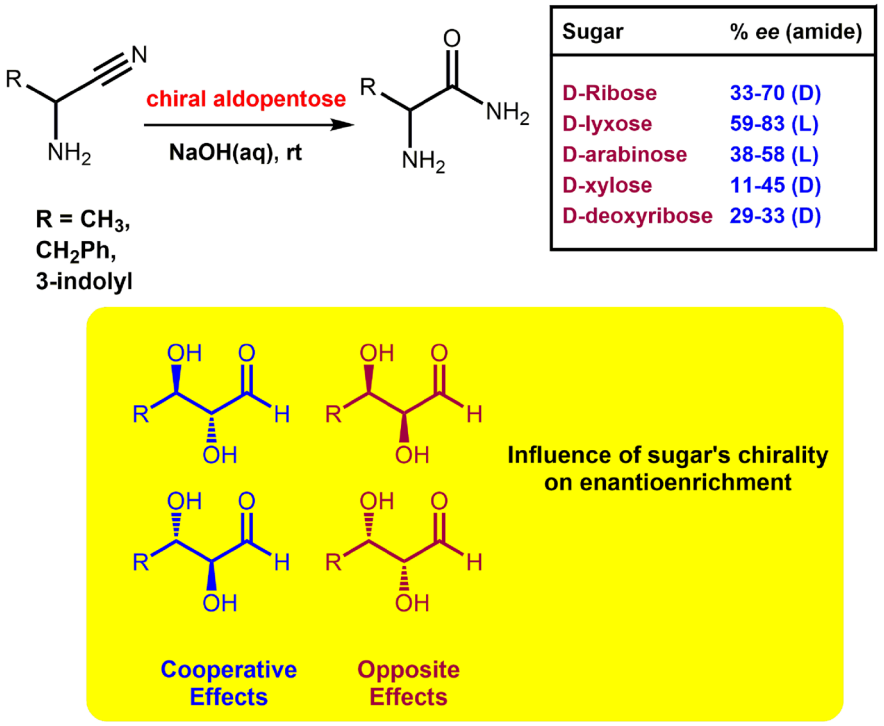

Fig. 25 Enantioselective formation of amino acid amides catalyzed by chiral aldopentoses, each leading to an excess of a given (either D or L) enantiomer. The enantioenrichment is influenced by the configurations of both C2 and C3 atoms of the sugar chain, which can reinforce or diminish the extent of asymmetric induction. Reformulated and modified from Wagner et al. (2017)

the highest *ee* toward L-aminoamides. This study suggests in addition a correlation between the configurational enrichment in the product and the stereochemistry of C2 and C3 carbons adjacent to the sugar carbonyl group. Thus, the (*R,R*) and (*S,S*) configurations for D-ribose and D-lyxose lead to high enantioselectivity than do (*R,S*) and (*S,R*) for D-xylose and D-arabinose, respectively. It appears that C3 has a cooperative effect with C2 in the first cases and an oppositional one for the latter two. This observation has been previously documented in diastereoselective reactions involving acyclic carbohydrate chains, i.e. the synergy of the vicinal stereocenters contiguous to a prochiral center (Avalos et al. 2000, 2001).

Conclusions

The origin of sugar handedness remains unsolved, but science to cope with this research field should not be frustrated. In line with the concept of etiology, as once highlighted by Eschenmoser (2011), the recurring argument that *"we'll never be able to know"*, seems to be an uncomfortable resignation. Experiments and modeling on artificial systems pave the way toward understanding, and surely this suffices as we deal with the subtle details.

Sugars, by virtue of their structure, multiple stereogenicity, and similar reactivity along different isomers, represent many more challenges than those encountered in other natural products. Those of us familiarized with carbohydrates know this chemistry can be both rewarding and disappointing. Syrupy substances, rather than crystalline materials, are often the norm, and syntheses face lengthy protection/deprotection protocols to achieve the desired reactivity and selectivity. How pristine sugars achieved and evolved with a homochiral bias may be a difficult and elusive point. It is conceivable that enantioselection hinged on available resources, and not necessarily on Darwinian fitness. Synthetic biomimetic approaches reveal that artificial scenarios can be as efficient as natural ones in processes like self-assembly, replication or transcription (Bare and Joyce 2021; Mayer et al. 2021; Otto 2022). Regardless of deterministic ingredients of cosmic evolution, it seems plausible the orchestration of biomolecules in pre-metabolic cycles as a necessary condition to exchange matter and energy before the emergence of life. In fact, after finishing this manuscript, the latest release on prebiotic chemistry reinforces this argument. The possibility to grow peptides on non-canonical RNA bases (still found in *t*RNA and ribosomal RNAs) suggests the early existence of an RNA-peptide world (Müller et al. 2022). In this context, synergy, or as we vindicate more precisely, *enantiosymbiosis*, between sugars and amino acids would have occurred. The same could be applied to the interactions of sugars with other chiral metabolites.

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Declarations

Competing Interests The authors declare no competing (financial or ethical) interest on this joint contribution.

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