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On the Origin of Single Chirality of Amino Acids and Sugars in Biogenesis

JASON E. HEIN[†] AND DONNA G. BLACKMOND*

Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037, United States

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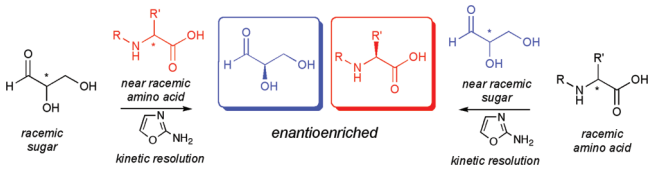
CONSPECTUS



The process of delineating the origins of the chemistry of life starts with the consideration of the molecules that might have existed on prebiotic earth and extends to the discussion of potential mechanisms for assembly of these molecules into informational polymers capable of self-replication and transmittance of genetic information. At some point along this pathway, the property of single chirality emerges as the hallmark of the amino acids and sugars present in biological molecules. In the 20th century, researchers developed abstract mathematical theses for the origin of biomolecular homochirality from a presumably racemic collection of prebiotic molecules. Before the end of that century, experimental findings corroborated a number of basic features of these theoretical models, but these studies involved chemical systems without direct prebiotic relevance. Currently researchers are examining prebiotically plausible conditions that couple chemical and physical processes leading to single chirality of sugars and amino acids with subsequent chemical reactions that enhance molecular complexity. While these studies have been conducted for the most part in the context of the RNA World hypothesis, the experimental findings remain relevant to a "metabolism first" model for the origin of life.

To many chemists interested in chembiogenesis, the synthesis of activated pyrimidine ribonucleotides under potentially prebiotic conditions by Sutherland's group provided a landmark demonstration of what Eschenmoser has described as "an intrinsic structural propinquity" between certain elementary chemical structures and modern biological molecules. Even while some synthetic issues for plausible prebiotic construction of RNA remain unsolved, our work has focused on coupling these synthetic advances with concepts for the evolution of biomlolecular homochirality. Drawing on our own findings as well as those from others, we present an intriguing "chicken or egg" scenario for the emergence of single chirality of sugars and amino acids. Our work incorporates both chemical and physical phenomena that allow for the amplification of a small initial imbalance of either sugars by amino acids or amino acid by sugars, suggesting that an enantioenriched chiral pool of one type of molecule could lead to a similarly enantioenriched pool of the other.

Introduction

Prebiotic chemistry has been defined by Eschenmoser[1] as a special branch of synthetic organic chemistry that aims to define the reactions that may have constituted the chemistry of biogenesis. A number of particular challenges differentiate this research from other investigations in synthetic organic chemistry. Uncertainties in our understanding of the geochemical evolution of Earth make a conclusive definition of "prebiotically plausible reaction conditions" difficult. Further, parameters such as reaction yield, selectivity, and reaction time take on a different meaning when a laboratory experiment is compared with the boundary conditions of time and space on the primordial earth. Despite these difficulties, an accumulation of experimental observations has successfully demonstrated the synthesis of a range of organic building blocks of living organisms, including amino acids, sugars, and nucleobases, under a wide variety of conditions aiming to retrodict the chemistry of the prebiotic world.

One important question that has largely been unaddressed in many studies of potentially prebiotic chemical reactions, however, is the origin of the single-handedness of biological molecules. Molecular and macromolecular

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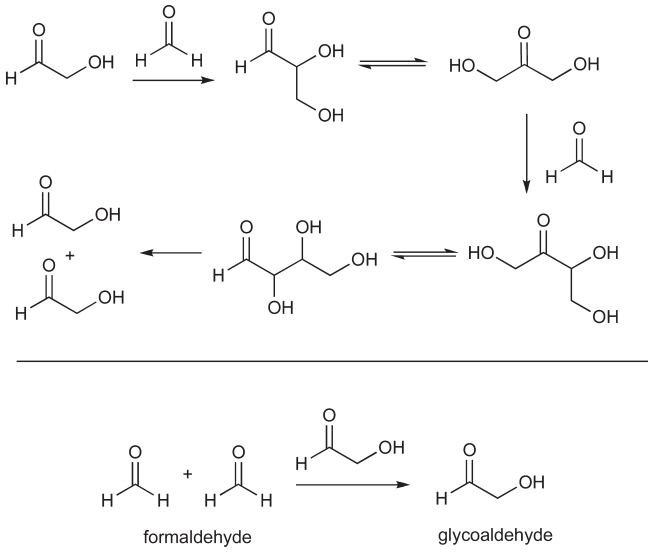
homochirality is a property of all living organisms and would seem to be a prerequisite for life. Theoretical investigations dating back more than half a century have been concerned with how an initial imbalance between left- and right-handed molecules might have been formed initially and then amplified.[2,3] More recently, experimental investigations have yielded several viable models invoking both chemical[4,5] and physical[6,7] mechanisms for amplification of enantiomeric excess. Models for the origin of biological homochirality have recently been reviewed elsewhere;[8,9] the aim of this Account is to weave salient aspects of that story back into ongoing endeavors to demonstrate how the complexity in organic molecules necessary for the development of life might have arisen in chemical reactions under plausible prebiotic conditions. Rather than present a detailed review of the current state-of-the-art in prebiotic chemistry, selected examples are presented of the intersection between studies in prebiotic chemistry and those focusing on the evolution of biological homochirality.

SCHEME 1. The Formose Reaction, Showing the Autocatalytic Role of Glycoaldehyde[11]



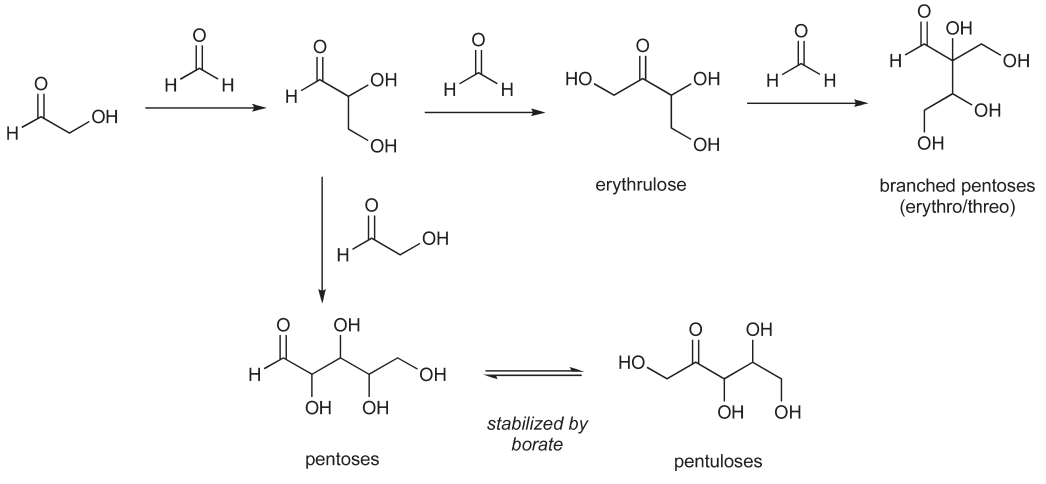
Back to the Beginning: The Formose Reaction

The synthesis of sugars from formaldehyde was discovered by Butlerow in 1861.[10] The simple reaction stoichiometry belies a complex product slate and reaction mechanism. One hundred years later, Breslow[11] revealed the autocatalytic nature of the formation of glyceraldehyde from glycoaldehyde and formaldehyde (Scheme 1). The formation of sugars from simple building blocks has strong appeal for understanding the buildup of complexity in organic molecules, but limitations of this chemistry have been pointed out that raise questions with respect to prebiotic importance, including the inherent instability of sugars and the lack of selectivity in the reactions.[12] However, the formose reaction remains one of the basic tenets of prebiotic chemistry.

Various means of increasing the efficiency and selectivity in the formose reaction have been proposed, including interaction of reacting species with minerals. Benner has proposed a "premetabolic cycle" in which a network of parallel and consecutive reactions adding formaldehyde to glycoaldehyde, glyceraldehyde, and higher sugars in the presence of borate minerals leads to the stabilization of pentoses and pentuloses (Scheme 2).[13]

An unanswered question in all of these studies relates to chirality. In the absence of some form of a homochiral template, these reactions necessarily produce racemic product, and the critical issue of the emergence of homochirality in such reactions is not addressed. Understanding how the

SCHEME 2. Formation of Carbohydrates in Borate-Stabilized Formose Reactions (Abbreviated from Ref 13)



enantiomeric excess of the reaction products might be amplified remains a key point.

Breslow and co-workers recently returned to study of the formose reaction with a focus on understanding how an enantiomeric excess might evolve in these reactions.[14] They showed that L-amino acids catalyze the formation of an excess of D-glyceraldehyde in the formose reaction (Table 1). Intriguingly, among the proteinogenic amino acids, only proline gave the opposite result, producing an excess of the unnatural L-glyceraldehyde, leading Breslow to question whether this amino acid indeed played a role on prebiotic earth. However, an alternative explanation may lie in recent, unrelated studies of asymmetric catalysis by amino acids carried out by our group. We found that the sense of the stereochemical outcome of the α-amination of aldehydes catalyzed by proline is reversed for proline in the presence of organic bases and for proline mixed with salts of acetic acid.[15,16] We then confirmed that the formose reaction carried out under Breslow's conditions with L-proline in the presence of $Bu_4N^+OAc^-$ gave the natural D-glyceraldehyde in excess (Scheme 3).[17] This trend was supported by showing the opposite enantioselectivity using D-proline in the absence and presence of $^tBu_4N^+OAc^-$. This suggests that the relative alkalinity of the environment in which such reactions may have occurred on prebiotic earth may have played an important role in their stereochemical outcome.

TABLE 1. D/L Ratio in Glyceraldehyde Synthesized from the Formose Reaction of Scheme [1] in the Presence of Amino Acids[14]

L-amino acid	D/L ratio
serine	50.3/49.7
alanine	50.8/49.2
phenylalanine	52.2/47.8
valine	52.2/47.8
leucine	54.4/45.6
glutamic acid	60.7/39.3
proline	**28.9/71.1**

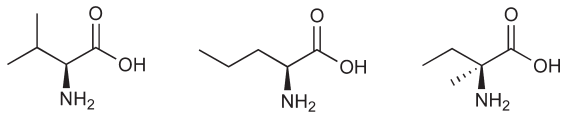
Transfer of Chirality

Enantiomeric excesses toward L-amino acids have been measured in organic materials extracted from a variety of meteorites,[18,19] leading to discussions of an extraterrestrial origin for the symmetry-breaking that ultimately led to the single chirality of biological amino acids and sugars. However, such imbalances have not been shown conclusively for the proteinogenic amino acids in the absence of terrestrial contamination (Scheme 4). Breslow and co-workers have suggested that these observations imply a role for nonproteinogenic amino acids in the origin of homochirality of biological molecules. They studied transamination reactions between α-methylvaline and keto acids in the presence of metal ions, concluding that this potentially prebiotic reaction is capable of transferring the chirality of the nonnatural amino acid to proteinogenic amino acids (Scheme 5).[20] This work supports suggestions that the initial enantiomer imbalance leading ultimately to homochirality on Earth could have been established extratrerrestrially. While this concept might provide a solution to the earthly conundrum, it does beg the question of how and where an imbalance was established outside our planet.

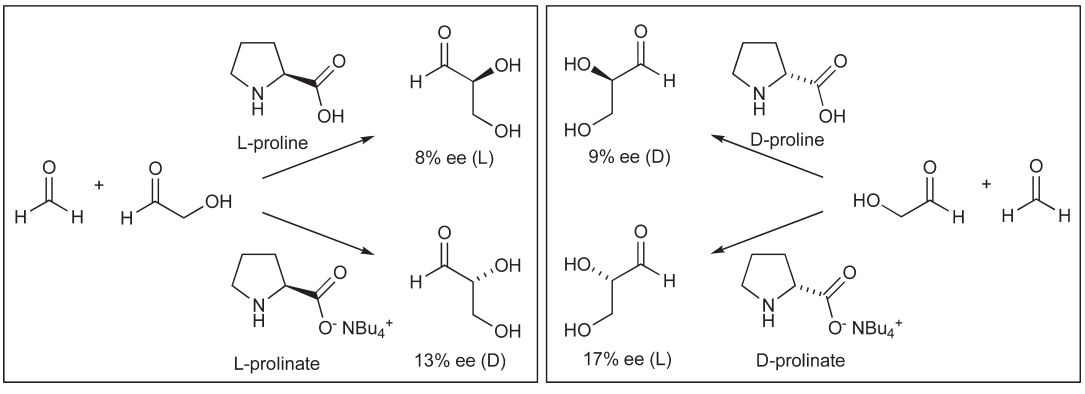
The RNA World

The concept that a simpler self-replicating system capable of transferring genetic information may have preceded our current form of life based on DNA has been a main guiding

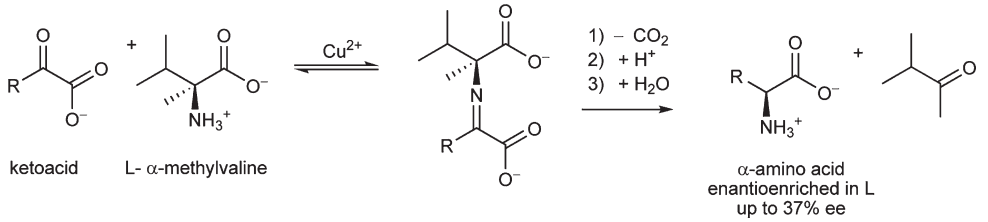
SCHEME 4. Enantiomeric Excess Values Measured from Samples of the Murchison Meteorite[19]



SCHEME 3. Enantiomeric Excess of Glyceraldehyde from the Formose Reaction in the Presence of Proline and Prolinate Catalysts[17]



SCHEME 5. Chirality Transfer to Proteinogenic Amino Acids via Transamination Reactions[20]



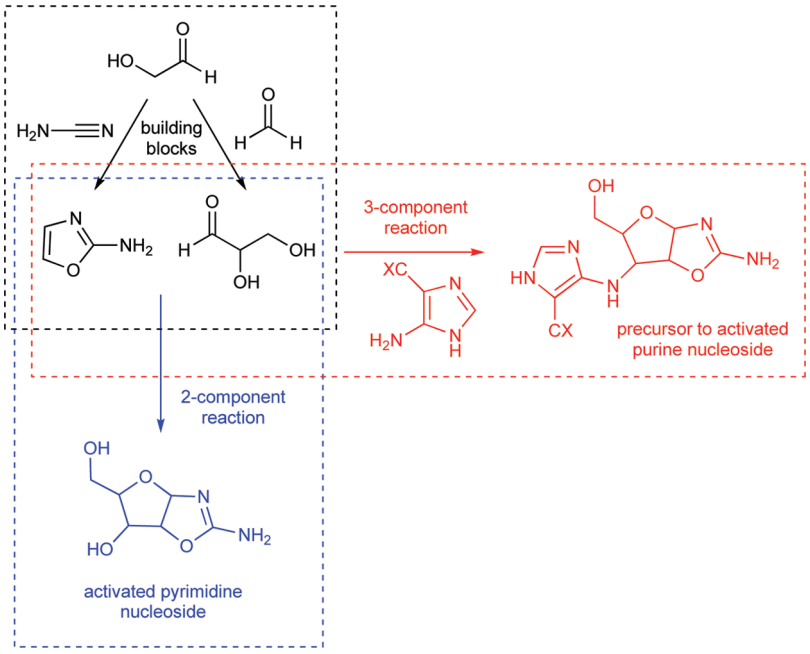
principle of much research in prebiotic chemistry. The "RNA World"[21] hypothesis is based on the fact that RNA is itself both a catalyst and an informational molecule, with the ability to replicate itself and synthesize proteins.[22] Whether RNA arose *de novo* or was itself the result of even more primitive replicative precursors is a subject of much discussion.[23] For years, one of the significant stumbling blocks for proponents of the RNA world was the difficulty in establishing a prebiotically plausible synthesis of RNA from its constituent parts. In particular, the direct addition of nucleobases to ribose is problematic. An elegant solution to this quandary was recently developed by Sutherland and coworkers[24] and Powner et al.,[25] who demonstrated that activated pyrimidine and purine nucleosides may be formed in a prebiotically plausible synthesis. Importantly, this route bypasses the intermediacy of free ribose and nucleobases (Scheme 6). The pyrimidine precursors are formed via a two-component reaction between 2-amino-oxazole and glyceraldehyde, while the analogous purine precursors arise from three-component reactions that add aminoimidazoles to the mix. These findings inject new enthusiasm into research focused on extending RNA-first scenarios to include the replication of nucleic acid macromolecules within constrained boundaries or "protocells".[26]

The Sutherland breakthrough in prebiotic RNA synthesis arose from their careful development and documentation of a stepwise increase in molecular complexity starting from small, high-energy nitrogen-containing molecules and simple aldehydes to produce what has been called a hybrid sugar and nucleobase synthon. However, this scenario contains no mechanism either for symmetry breaking or for amplifying the chirality of the sugar component. As noted by Sutherland, the relevance of this synthesis under prebiotically realistic conditions depends on finding a means of obtaining enantioenriched glyceraldehyde under similar conditions.[27]

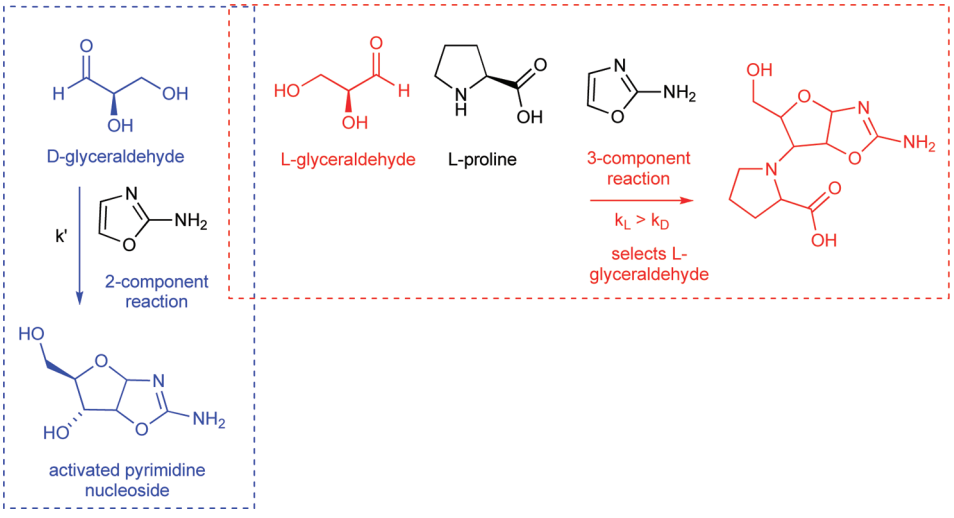
With this challenge in mind, we began studies aimed at addressing how the single chirality of the sugar component of the activated pyrimidine nucleosides might have developed. Based on our findings that amino acids influence the stereochemical outcome of glyceraldehyde in the formose reaction (Scheme 3), we decided to probe how the presence of amino acids might influence the Sutherland reaction of racemic glyceraldehyde and 2-amino-oxazole.[28] With proteinogenic L-amino acids present in the reaction mixture, we found that the resulting ribose and arabinose amino-oxazoline products exhibited notable enantiomeric excesses. Strikingly, addition of L-proline resulted in enantiomeric excesses of up to 80% ee toward the natural (D) nucleoside precursors. Unlike the role of amino acids as selective catalysts for the production of glyceraldehyde in the formose reaction, however, in this case we showed that the amplification of enantiomeric excess occurs via a noncatalytic kinetic resolution: racemic glyceraldehyde reacts with 2-amino-oxazole and the amino acid in a three-component reaction that is analogous to the three-component chemistry described by Powner et al (compare Schemes 6 and 7).[24] In this case, however, the product of the three-component reaction serves as a reservoir in which the natural amino acid sequesters the unnatural sugar, allowing selective production of the amino-oxazolines through the remaining D-glyceraldehyde. Interestingly, the Sutherland group presaged this result in 2006, suggesting that the stereochemical consequences of the glyceraldehyde/2-amino-oxazole reaction should be investigated in the presence of chiral additives.[29]

This kinetic resolution results in an amplification over time of the enantiomeric excess of the glyceraldehyde remaining in the reaction mixture, as shown in Figure 1. Employing the natural amino acid in enantioenriched form facilitates enantioenrichment of the natural sugar present in racemic form because of the competitive three-component reaction with the natural/unnatural combination of amino acid and sugar. Kinetic resolution has been implicated as a mechanism for prebiotic chiral amplification by preferential destruction of one enantiomer of a racemic mixture in a photoresolution process driven by circularly polarized light.[30] However, most chiral compounds exhibit only a very

SCHEME 6. Sutherland's Proposed Prebiotic Route to RNA Precursors from Simple Carbohydrate and High Energy Nitrogen-Containing Building Blocks: Two- and Three-Component Reactions between Glyceraldehyde, 2-Amino-oxazole and Aminoimidazoles Form Pyrimidine and Purine Nucleoside Precursors[23,24]



SCHEME 7. Addition of L-Proline to Two-Component Reaction between Glyceraldehyde and 2-Amino-Oxazole Results in Kinetic Resolution of Glyceraldehyde Attributed to a Selective Three-Component Reaction Analogous to That Shown in Scheme [6]



weak preference in this context, and enantiomeric yields of ~20% ee may be realized only at the expense of ~99% photodestruction of both enantiomers.[31,32] The enantioenrichment observed in the chemical reaction reported here exhibits a greater than 50-fold increase in yield of the desired enantiomer compared with the photoresolution process.

This relationship holds for the opposite combination of natural sugar with unnatural amino acid, as shown in Figure 2. This work thus indicates that the system may proceed effectively as a resolution either of proline by glyceraldehyde or of glyceraldehyde by proline, as long as one or the other is available in nonracemic form. In either scenario, the natural/unnatural combination of amino acid and sugar reacts ca. 2.5 times faster than the natural/natural (or unnatural/unnatural) combination. This result invokes a link between the homochirality of sugars and amino acids and poses a compelling if unanswerable "chicken-vs-egg"

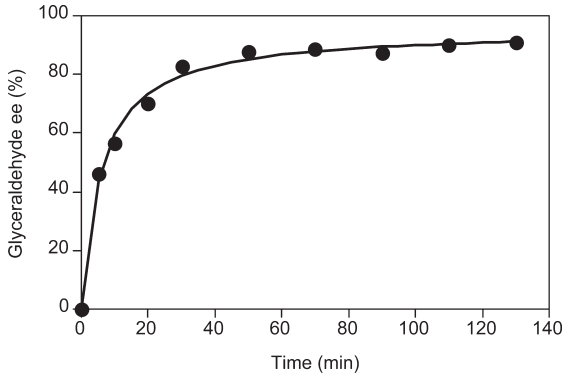


FIGURE 1. Glyceraldehyde enantiomeric excess as a function of time as the reaction proceeds between 1 M racemic glyceraldehyde, 1.2 M 2-amino-oxazole, and 1 M L-proline at ambient temperature in aqueous solution.

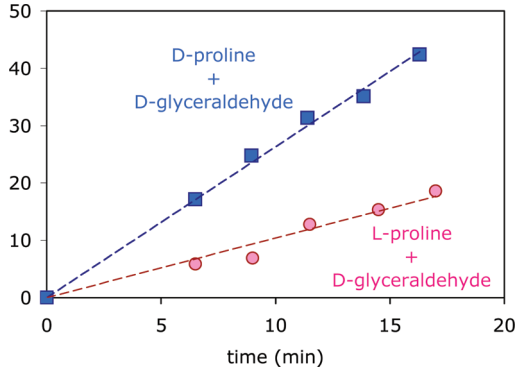


FIGURE 2. Relative rates of conversion of D-glyceraldehyde in the reactions of Scheme 7 carried out separately with L- and D-proline.

question about which came first. In principle, such a resolution could be coupled with other approaches for chiral amplification of either amino acids or sugars.

Scheme 7 suggests that the three component reaction that uses the natural hand of proline to sequester the unnatural hand of glyceraldehyde will be driven by the concentration of proline, and therefore the degree of amplification should be greater at higher proline concentrations. This is confirmed in Figure 3, which shows the glyceraldehyde ee values obtained at low conversions of 1 M *rac*-glyceraldehyde as a function of the initial concentration of L-proline. A kinetic model applying simple elementary step kinetic expressions to the initial reaction rates for both the two component (k') and three component (k_D and k_L) reactions in Scheme 7 yields an expression for enantiomeric excess (eq 1), which allows calculation of an intrinsic selectivity factor $s = k_L/k_D \approx 8$. This represents the true rate difference between L and D-glyceraldehyde in the three-component reaction when it is deconvoluted from the accompanying unselective consumption of glyceraldehyde

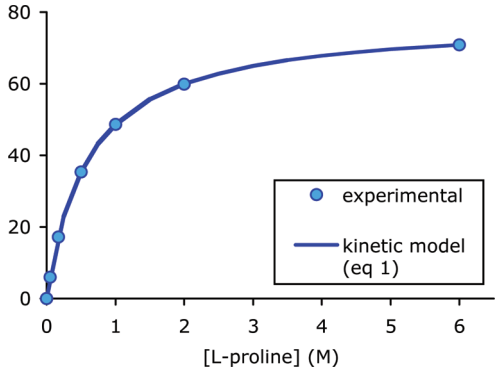


FIGURE 3. Enantiomeric excess of D-glyceraldehyde as a function of initial L-proline concentration in the reactions of Scheme 7 carried out with 1 M *rac*-glyceraldehyde and 1.2 M 2-amino-oxazole.[17]

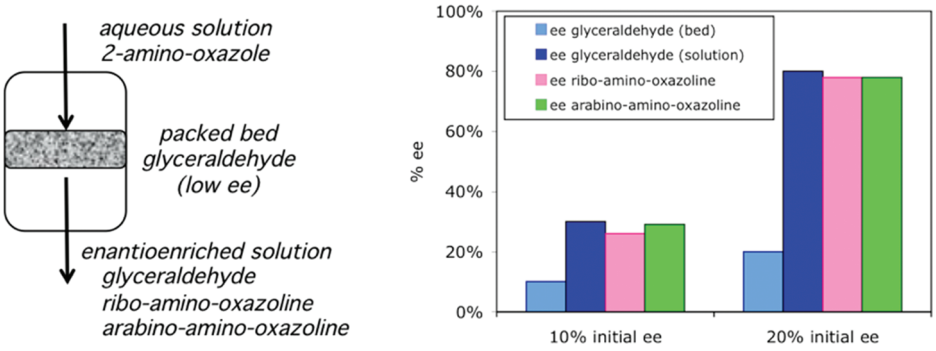
to form the ribonucleoside.

$$\text{ee(D-glyceraldehyde)} = \frac{[\text{L-proline}](k_L - k_D)}{2k' + [\text{L-proline}](k_L - k_D)} \qquad \frac{k_L}{k'} = 1.28\text{M}^{-1}\cdot\text{min} \qquad \frac{k_L}{k_D} = 8.07 \tag{1}$$

Coupling Chemical and Physical Processes

A number of examples illustrate how prebiotic chemistry resulting in amplification of enantiomeric excesses of amino acids and sugars has been aided by physical processes. The selective thermodynamic partitioning of amino acid enantiomers between solution and solid phases has been invoked as a possible prebiotic mechanism for solution phase amplification of enantiomeric excess.[5,33−37] This "eutectic model" has also been explored for sugars, but the high solubility and difficulty in crystallization under ambient conditions led to little success until Breslow and co-workers found that when nearly racemic glyceraldehyde is partially dissolved in water, the solution phase exhibits strong amplification up to ca. 94% ee.[14] Although glyceraldehyde is theoretically nearly infinitely soluble in water, this result was attributed to formation of a 1:1 D/L dimer as a six-membered dioxane ring structure that is nearly insoluble. The precipitation of glyceraldehyde in 1:1 D/L ratio results in enantioenrichment in the solution phase for any system exhibiting a small initial imbalance. The kinetics of forming this "pseudo-eutectic" solution composition were shown to be extremely rapid, with the solution-phase ee enhancement stabilizing in a few seconds after contact of the solid glyceraldehyde with water. The very low solubility of the DL dimer helps to address questions about whether prebiotically relevant concentrations of enantioenriched glyceraldehyde could have been established. Thus partially dissolved nearly racemic

SCHEME 8. Physical and Chemical Amplification of Glyceraldehyde and Amino-oxazoline Enantiomeric Excess[17]



glyceraldehyde in a prebiotic environment might have provided pools of enantioenriched sugar for carrying out chemistry such as the Sutherland reaction.

The DL dimer of glyceraldehyde imparts stability to the racemic precipitate compared with enantiopure glyceraldehyde. We reasoned that this property could be exploited to devise another route to the production of enantioenriched ribo- and arabino-amino-oxazolines via the Sutherland chemistry. We proposed that aqueous solutions of the reactant 2-amino-oxazole passing through packed beds of solid nonracemic glyceraldehyde could preferentially solubilize the enantiomer in excess, allowing the two-component reaction to proceed selectively. This is confirmed in Scheme 8, which shows that formation of the amino-oxazolines occurs preferentially with the enantiomer in excess. Both the solution glyceraldehyde and amino-oxazolines recovered from the packed bed exhibit significant amplification of ee compared with the initial glyceraldehyde ee of the packed bed.[17]

Another method of combining physical and chemical enantioenrichment used in organic chemistry is the preferential crystallization of a less-soluble diastereomer from a mixture of compounds formed in a reaction. This concept of preferential crystallization from enantioenriched mixtures was exploited by Sutherland and co-workers for the products of the two-component reaction of Scheme 6. They showed that ribo-amino-oxazoline precipitates from solution as an enantiopure solid when it is present at ee values over ca. 60% in mixtures of the ribo and arabino compounds.[29] Detailed studies by our group revealed that enantiopure solid ribo-amino-oxazoline could be produced by crystallization from solutions as low as 20% ee.[28] Sutherland and co-workers showed further that the arabino form undergoes a phosphate-mediated interconversion to the ribo form in solution, providing even higher yields of solid enantiopure ribo-amino-oxazoline.[27]

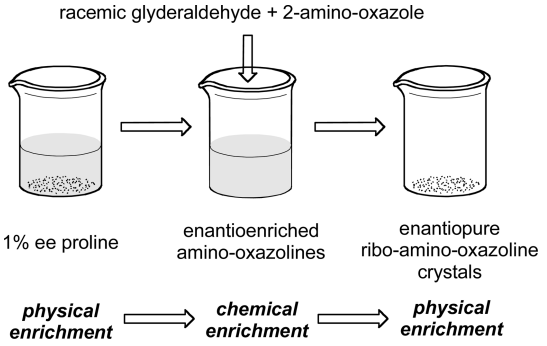
A combination of these physical and chemical amplification processes was demonstrated by our group for the proline-mediated kinetic resolution of glyceraldehyde and concomitant production of enantioenriched ribo-amino-oxazoline.[28] Enantioenrichment of 1% ee L-proline was carried out by mixing in $CHCl_3$, where we had shown previously that a highly insoluble $CHCl_3$-DL-proline cosolvate amplifies the solution phase ee to nearly enantiopure L-proline.[32] Solution phase proline was recovered and mixed with racemic glyceraldehyde and 2-amino-oxazole in aqueous solution to carry out the kinetic resolution and produce enantioenriched ribo- and arabino-amino-oxazolines. The reaction solution was allowed to sit until enantiopure crystals of the ribo-amino-oxazoline appeared. Thus the chemical amplification achieved in the kinetic resolution is augmented by two physical amplification processes: enantioenrichment of the amino acid prior to the resolution, and the selective crystallization of enantiopure ribo-amino-oxazoline following the resolution (Scheme 9).

A likely prebiotic scenario suggests that a complex pool of organic molecules would likely be present in any potential reaction medium. To test the robustness of these chirality amplification processes in multicomponent mixtures, the reaction of racemic glyceraldehyde with 2-amino-oxazole was carried out in mixtures of a variety of different amino acids. Enantiopure crystals of ribo-amino-oxazoline were successfully obtained directly from crude reaction mixtures containing as many as 14 of the 19 chiral, proteinogenic amino acids (Scheme 10).[28] The emergence of molecules of single chirality from complex, multicomponent mixtures supports the robustness of the processes under potential prebiotic conditions.

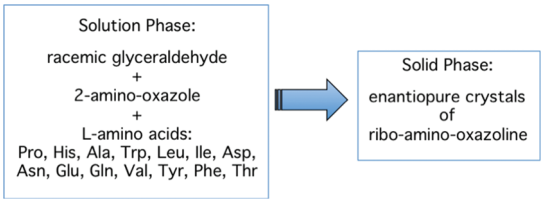
Building Complexity: Single Chirality at the Supramolecular Scale

Single chirality at the molecular level has been the focus of the work described above. Life is based on enantiopure amino acids and sugars incorporated into polymers that

SCHEME 9. Physical and Chemical Amplification of Amino-Oxazoline Enantiomeric Excess[27]



SCHEME 10. Emergence of Enantiopure Ribo-amino-oxazoline Crystals from Complex Mixtures[28]



are capable of self-replicating, transferring information, and creating function. Thus a key to understanding the origin of life lies in understanding the transmission and amplification of handedness from the molecular to the supramolecular level, and extensive research is carried out in this area. The coupling of physical and chemical properties figures prominently in a number of approaches to studying chirality in supramolecular systems. The key role of an interface, air–water or solid crystal–solution, for example, has proven to be critical to directing polymerization or self-organization processes in several examples leading to chiral amplification at the supramolecular scale. The extensive work of Lahav and co-workers has highlighted such effects.[38] For example, they have reported self-organization induced by the achiral glycine at air–water interfaces[39] and have documented asymmetric induction coupled with templating effects to yield enantioselective chain elongation at polymer/solution interfaces.[40] Symmetry breaking in molecular to supramolecular transitions has also been probed recently in the study of monolayers of tartaric acid forming on the surfaces of metal single crystals.[41]

A number of systems have been shown to exhibit strong nonlinear effects in the helicity of growing chiral polymer chains induced by small chiral perturbations in a cooperative effect known as the "sergeant and soldiers principle," dating back to classic early experiments by Green and co-workers on polyisocyanates.[42] The transfer of chiral information to helical polymers via noncovalent interactions has also been observed. Most recently, these effects have been probed in dynamic systems of small molecules that self-assemble via strong intermolecular hydrogen bonds. Meijer and co-workers showed that supramolecular homochirality in noncovalently bonded helical structures may be induced solely by the minute directing influence offered by isotope substitution.[43] This is a striking result that not only confirms the subtle cooperativity leading to chiral amplification that has been demonstrated for polymeric chains but also provides the first thought-provoking examples of these phenomena in noncovalent, self-assembled systems. The participation of the medium in which these interactions take place is often key to achieving chiral amplification at the supramolecular level. Future advances in extending our understanding of the evolution of homochirality from the molecular to supramolecular level will require a combination of experimental and theoretical approaches to probe such systems.

Conclusions

This selection of examples from the literature and from our own work in probing potential prebiotic chemistry for the enantioenrichment of amino acids and sugars provides a few concepts that may be useful for further work in examining the intriguing question of the origin of biological homochirality. First, we may suggest that it may not have been necessary for the prebiotic world to produce pools of enantiopure molecules prior to the building up of molecular complexity. Partial enantioenrichment may have been sufficient to trigger chemical and physical processes such as those discussed here that allow further amplification of enantiomeric excess. Second, these examples suggest that the evolution of enantioenrichment of sugars and amino acids may have been linked to one another, and it remains an open question which came first. Third, the connection between amplification of chirality at the molecular and supramolecular levels is key to the ultimate function of informational polymers leading to life on earth. Fourth, as has been summarized before,[44] the importance of physical phenomena in coaxing enantioenrichment in conjunction with chemical reactions should not be overlooked. It is likely that both physical and chemical processes played essential roles in the evolution of molecular homochirality in early biology prior to the emergence of evolved biochemical capabilities.

BIOGRAPHICAL INFORMATION

Jason Hein was born in Winnipeg, Manitoba, Canada, in 1978. He received his B.Sc. in biochemistry from the University of Manitoba in 2000. He completed his Ph.D. in synthetic organic

chemistry at the University of Manitoba in 2005 as an NSERC PGS Scholar with Professor Philip G. Hultin. He then moved to the Scripps Research Institute as an NSERC postdoctoral fellow jointly with Prof. K. Barry Sharpless and Prof. Valery V. Fokin. In 2010, he became a senior research associate with Prof. Donna G. Blackmond at the Scripps Research Institute. He joined the faculty at the University of California, Merced, in 2011. His current work is aimed at the discovery, design, and study of *N*-heterocyclic carbene organocatalytic reactions. This work centers on deconvoluting systems where multiple catalytic reactions participate simultaneously and focuses on understanding mechanisms of catalyst induction, catalyst deactivation, and autocatalysis.

Donna G Blackmond was born April 19, 1958, in Pittsburgh, PA. She received a Ph.D. in Chemical Engineering from Carnegie-Mellon University in 1984. She is currently Professor of Chemistry at The Scripps Research Institute in La Jolla, CA, and has held professorships in chemistry and in chemical engineering in the US, Germany, and the UK. She has also worked in industrial research in the pharmaceutical industry. She has been a Woodward Visiting Scholar at Harvard University (2002−2003) and a Miller Institute Research Fellow at University of California, Berkeley (2003). Prof Blackmond received the 2009 Royal Society of Chemistry Award in Physical Organic Chemistry, a Royal Society Wolfson Research Merit Award in 2007, and an Arthur C. Cope Scholar Award in 2005 from the Organic Chemistry Division of ACS. She was an invited lecturer at the Royal Swedish Academy of Sciences Nobel Workshop "On the Origin of Life" in 2006. Prof Blackmond's research focuses on kinetic and mechanistic studies of asymmetric catalytic reactions for pharmaceutical applications as well as on fundamental investigations of the origin of biological homochirality.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: blackmond@scripps.edu.
†Present address: Department of Chemistry, University of California—Merced, Merced, CA 95343, USA.

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