EXAMINE RECENT ADVANCES IN CREATING CHIRAL ORGANIC COMPOUNDS

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Abstract- Chirality is a central feature in the evolution of biological systems, but the reason for biology's strong preference for specific chiralities of amino acids, sugars, and other molecules remains a controversial and unanswered question in origins of life research. Biological polymers tend toward homochiral systems, which favor the incorporation of a single enantiomer (molecules with a specific chiral configuration) over the other. There have been numerous investigations into the processes that preferentially enrich one enantiomer to understand the evolution of an early, racemic, prebiotic organic world. Chirality can also be a property of minerals; their interaction with chiral organics is important for assessing how post-depositional alteration processes could affect the stereochemical configuration of simple and complex organic molecules. In this paper, we review the properties of organic compounds and minerals as well as the physical, chemical, and geological processes that affect organic and mineral chirality during the preservation and detection of organic compounds. We provide perspectives and discussions on the reactions and analytical techniques that can be performed in the laboratory, and comment on the state of knowledge of flight-capable technologies in current and future planetary missions, with a focus on organics analysis and life detection.

Keywords— Chirality, Homochirality, Origins of Life, Organics, Minerals, Biosignatures, Life Detection, Prebiotic Chemistry, Enantiomeric Excess.

PREBIOTIC CHEMISTRY, CHIRALITY, AND THE ORIGINS OF LIFE

(i) Chirality, Homochirality, and Enantiomeric Excess- Characterizing the organic chemical composition on planetary bodies is a key component in the search for habitable environments and evidence of extinct or extant life. The field of prebiotic chemistry focuses on how simple organic precursor compounds could have been synthesized and how they could have evolved into complex, functioning biomolecules, such as nucleic acids, peptides, and proteins. These building block precursors were likely required to carry out metabolic reactions and the information storage and transfer necessary for the maintenance and replication of living organisms. Molecules can be arranged in three-dimensional space from a single point source (i.e., at a carbon atom). When a carbon atom has four distinct functional groups attached to it (i.e., is sp^3 hybridized), the molecule can exist as one of two possible three-dimensional shapes, and that carbon atom is termed a "chiral center". Molecular chirality or handedness whereby a molecule is not superimposable on its mirror image, is a property that is of great interest in the field of prebiotic chemistry. Chiral molecules are optically active; that is, they rotate plane-polarized light in opposite directions depending on their chirality. Enantiomers of chiral molecules possess identical chemical and physical properties, with the exception of how they interact with other chiral molecules or electromagnetic radiation. Thus, chirality can affect various properties of important molecules, such as amino acids and sugars (Figure 1, including: molecular self-assembly, asymmetric reactions/reactivity, molecular recognition and replication, and light, or spin polarization. Homochiral polymers are a result of the preference for one enantiomer over the other; biology on Earth has evolved to use homochiral proteins and nucleic acids, which are made up of L-amino acids and D-sugars, respectively, although there are rare exceptions. Notably, life generally relies on L-amino acid and D-sugar monomers for metabolic functions as well. L- and D- are stereochemical designations for discerning enantiomeric pairs of amino acids and sugars, and are described in more details. Without a seed (i.e., a solid catalyst or already chiral reactant) that can induce asymmetry, chemical reactions will synthesize products in racemic mixtures, i.e., an equal mix of both enantiomers. Enantiomeric excess (ee) reflects the abundance of one particular enantiomer over the other and can be determined as a ratio of the observed specific rotation of the mixture over the specific rotation of the pure enantiomer, typically calculated as $ee = [(L - D)/(L + D)] \times 100$. For example, an enantiopure product will have 100% of one enantiomer and 0% of the other, and racemic mixtures have ee of 0%, as there is no excess of one enantiomer over the other.

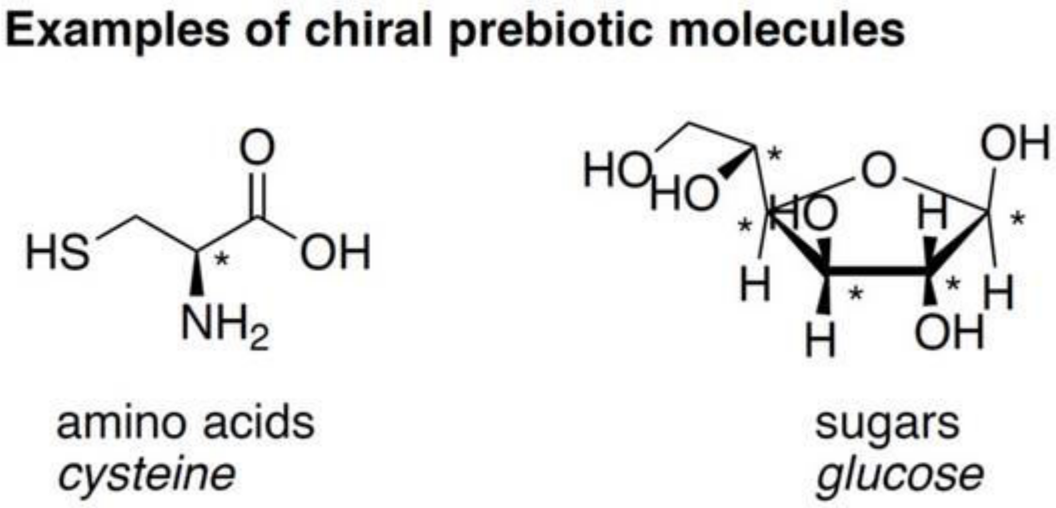

Figure 1- Amino acids and sugars are examples of chiral molecules relevant to prebiotic chemistry

(ii) Chirality in a Prebiotic Context- Before life arose on Earth, nucleosynthetic reactions occurring in the interstellar medium created elements that formed primitive organic compounds. These organic compounds can be preserved in asteroids and comets and are delivered to Earth within carbonaceous chondrite meteorites. Homochirality and the amplification of the enantiomeric imbalance resulting in the observed chirality of biological polymers has been hypothesized to have originated from either terrestrial or extraterrestrial processes before abiogenesis (i.e., the origins of life) or afterwards as a consequence of biological evolution. Among the prebiotic hypotheses, there are theories that propose either stand-alone or deterministic processes. For example, the autocatalytic mathematical model developed by Frant proposed that homochirality was amplified through the catalysis of a starting compound, which repeatedly synthesizes itself in one structural configuration while excluding the other. Additionally, amplification in terrestrial environments of ee could have occurred with the aid of chiral reactants or substrates, as this has been demonstrated to promote the synthesis of specific enantiomers. The effect of circularly polarized light and other energy sources, such as galactic cosmic rays (GCRs), on the chirality of organics is also well studied. While prebiotic molecules of interest are generally synthesized in racemic mixtures, moderate abiotically synthesized ee have been measured in meteorites and references therein. The organic composition of meteorites, specifically of hydroxy acids, typically demonstrate racemic composition and, in some cases of amino acids and sugar derivatives, meteoritic organics demonstrate an ee approaching that observed in biology.

(iii) Enantiomeric Excess as a Biosignature- Enantiomeric excess (ee) of organic molecules has been proposed as a biosignature based on our observations and knowledge of molecular biochemistry on Earth. However, it remains to be observed whether ee is a robust indicator of life, given that it is unknown (1) if abiotic processes can generate significant enantiomeric excess such that it would be mistaken for a false positive for life detection; (2) whether the chemical evolution of near-homochiral polymers was required for life to evolve (if not, lack of ee could lead to false negatives); (3) if such chemistry is a requirement for all life or just Earth-like life; or (4) that biological systems always utilize a single enantiomer for building functional polymers. To expand on the fourth point, it remains possible for extraterrestrial life to rely on homochiral polymers of various chiralities; for example, perhaps it could use a protein composed of D-amino acids for one function and another composed of L-amino acids for another. Terrestrial life does this to some extent in that it incorporates only L-amino acids for building proteins, but uses D-amino acid monomers for various functions; bacteria also use both D- and L-amino acids for the production of peptidoglycan , and some bacterial strains have even been demonstrated to be capable of growing using D-amino acids and L-sugars.

ORGANIC CHIRALITY

(i) Point/Molecular Chirality- There is various types of chirality that organic molecules can possess; some different types are shown in Figure 2 (as illustrated by the amino acid alanine, Figure 2a). Point or molecular chirality is chirality that is based around an atom, such as carbon. Molecules that have atoms where each functional group attached to it is distinct are termed chiral. For carbon, this typically means that the carbon atom has four different groups attached. Compounds that are mirror images of one another but cannot be superimposed through rotation are termed enantiomers; those that are non-superimposable, non-mirror images are termed diastereomers (example shown in Figure 2b).

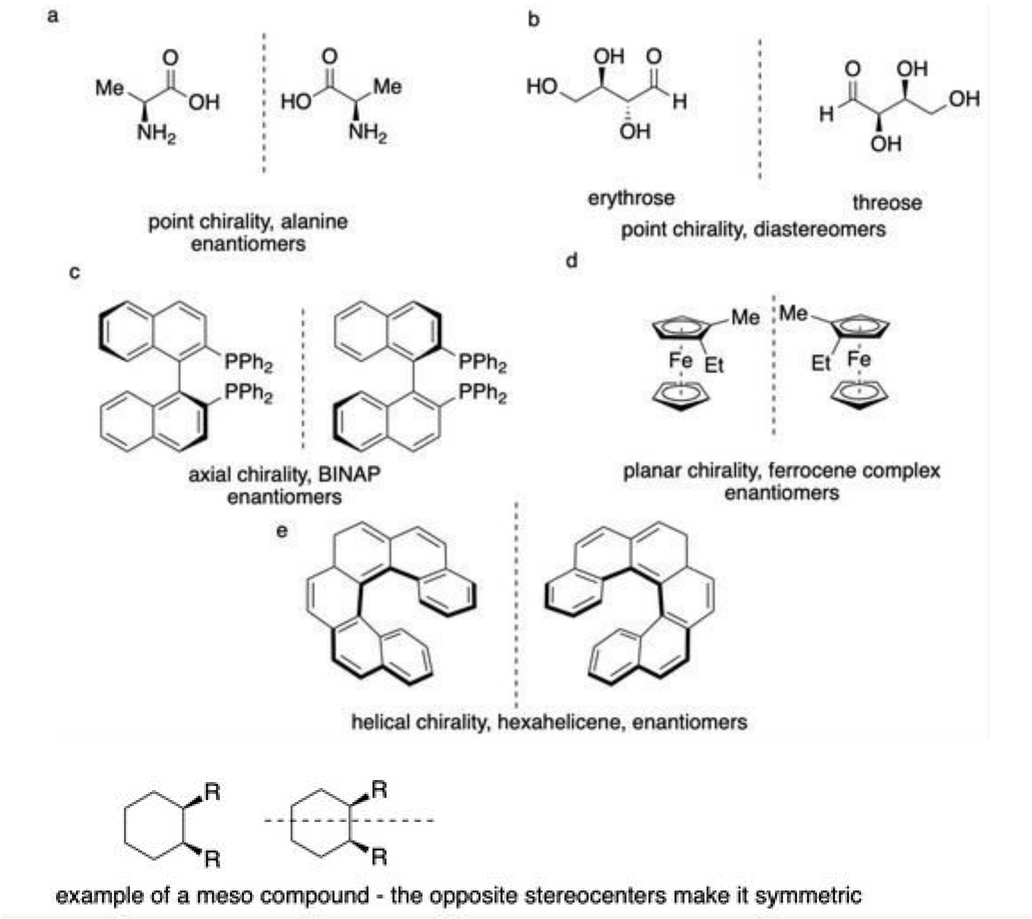

Figure 2- Examples of point/molecular chirality in organic molecules. (**a**) Enantiomers of the amino acid alanine. (**b**) Diastereomers of erythrose (**left**) and threose (**right**). (**c**) Axial chirality exhibited by BINAP enantiomers. (**d**) Planar chirality of the enantiomers of a ferrocene complex. (**e**) Helical chirality of hexahelicene enantiomers

Often, enantiomers are described by their absolute configuration as R (rectus, right) or S (sinister, left). The difference between R and S involves assigning priority to the different substituents and determining whether the identified lowest to highest priority groups follows a clockwise direction (designated R) or counterclockwise direction (designated S). This method is also called the Cahn–Ingold–Prelog rules in organic nomenclature. The D/L designation is often used for sugars and amino acids; however, these do not directly line up with the R/S designation. In a Fisher projection of the molecule (for example, a sugar), the second to last carbon determines whether the molecule is D or L. If the hydroxyl group is on the left, the sugar is L, and if the hydroxyl group is on the right, the sugar is D. While the majority of chirality discussed in the context of origins of life is point/molecular chirality, there are other types of chirality that organics can possess, including axial, helical, and planar chirality, which we discuss below.

(ii) Heteroatom Chirality- This work will primarily focus on point/molecular chirality relevant to carbon; however, other atoms can be chiral, including P, N, and S, which are common heteroatoms in organic compounds. Additionally, other atoms within the carbon group, e.g., Ge and Si, can exhibit chiral structures. In the case of heteroatoms, P, N, and S in their neutral form would typically need a lone pair of electrons and three different substituents attached to be considered chiral. A key for maintaining this configuration (i.e., chirality at the heteroatom) is to limit inversion around the lone pair. This is known as pyramidal inversion and, in the specific case of N, it is known as amine inversion. Amine inversion occurs rapidly at and below room temperature, and the N does not exhibit a chiral center. These are known as fluxional reactions and allow the enantiomers to racemize, which means pure enantiomers cannot be isolated. During amine inversion, in the transition state, there are three substituents arranged in the plane (co-planar) around the N atom, and the lone pair of electrons occupies an out-of-plane p orbital. Therefore, the structures containing chiral heteroatoms are often rigid or bulky, limiting the rate of inversion and giving rise to enantiomers. Phosphine (PH_3) and chiral sulfur-containing compounds, such as sulfites, sulfoxides, sulfonium salts, and sulfinic esters, also undergo the same inversion as amines, but the rate at room temperature is much lower. Therefore, chiral P-phosphines and appropriately substituted chiral S compounds are optically stable at room temperature.

(iii) Additional Forms of Chirality- Molecules possessing features related to axial, helical, and planar structure can also impart chirality in compounds that do not possess point chiral or stereogenic centers. Axial chirality is achieved when symmetry exists looking down an axis of a molecule; this commonly occurs in 2,2′-disubstituted biaryls and dissymmetrically substituted allenes. Examples of axial chirality include the organophosphorus compound, 2,2′-bis (diphenylphosphino)-1,1-binaphthyl), or BINAP and 2,2′-dihydroxy-4,4′,6,6′-tetramethylbiphenyl. In both examples, axial chirality is due to restricted rotation as a result of steric hindrance (Figure 2c). Helical chirality is based on twisting in 3D space, as demonstrated in the aromatic compound hexahelicene (Figure 2d). Similar to axial chirality, steric strain promotes the existence of a stereogenic axis, giving rise to chiral forms in helically chiral structures. Planar chirality is a system where the 2D structures are not superimposable. They contain two dissymmetric, non-coplanar rings that cannot be easily rotated (e.g., metallocenes including ferrocene, Figure 2e).

ORGANOMETALLIC SYSTEMS RELATED TO CHIRALITY

Organometallic compounds, whereby a carbon atom is covalently bonded to a metal, play important roles in enantioselective organic synthesis and methodology, industrial synthesis, materials science, nanotechnology, pharmaceuticals, and medicinal research, and in prebiotic and metabolically relevant systems and references therein. Organometallic reagents can be used in other reactions as reagents e.g., R-MgBr (where R = alkyl, allyl, aryl, or vinyl group) for Grignard reactions and catalysts, i.e., Pd and Ni compounds for Heck reactions. Cross-coupling reactions are a notable type of organometallic reactions where two organic fragments are coupled together with the use of a metal catalyst, such as the Suzuki reaction. Cross-coupling reactions and the use of precatalysts are powerful techniques that can be used to form C-C, C-N, and other C-X bonds, e.g., to synthesize materials relevant to all fields of chemistry. While there are a significant number of different cross-coupling techniques, far more often than not, the techniques have not been explored for selectivity. Table 1 lists some of the examples where the reactions are enantioselective. In addition to interest in bioactive-starting materials relevant to the pharmaceutical industry, some cross-coupling reactions could have relevance in prebiotic environments. For example, the copper-mediated cross coupling of cyanide and acetylene synthesized the amino acids: arginine, aspartic acid, asparagine, aspartate, glutamine, glutamate, and proline. Many proteins are associated with organometallic complexes or metalloenzyme cofactors, as they assist with the stabilization of their structure and support other vital biochemical reactions and references therein. Organometallic compounds have been demonstrated to catalyze the polymerization of peptides and proteins. The metal ions stabilize spectator ions during peptide formation within their ligands and the amino or carboxyl group of amino acids is protected during peptide synthesis. Recently, there have been several reports of metal-organic compounds in meteoritic organic matter that have implications for understanding parent-body interactions with origins of life implications. A study by Ruf and colleagues surveyed 61 meteorites over a wide range of petrologic types. They found dihydroxymagnesium carboxylates $[(OH)_2MgO_2CR]^-$ in the soluble organic fraction that could be associated with metamorphic events, such as thermal alteration and shock events. These types of organometallic anion complexes had not been identified in meteorites prior to this study. Another study looked at the soluble organic fraction of 44 meteorites and found a novel homologous series of sulfur magnesium carboxylates. They appear to be thermally stable and their abundance was correlated with increasing thermal maturity. Smith and colleagues looked at the origin of cyanide in the CM2 Murchison meteorite and found that it was primarily bound (and subsequently released) as iron cyanocarbonyl ($[Fe^{II}(CN)_5(CO)]^{3-}$ and $[Fe^{II}(CN)_4(CO)_2]^{2-}$) organometallic complexes. These results suggest that cyanide in the form of iron cyanocarbonyl complexes could be a source for free cyanide delivered by meteorites and potentially be a precursor to catalytic centers of early enzymes, such as Fe hydrogenases. Below, we describe mineral chirality and how organic reactions can impart chirality in organic-mineral systems in the context of prebiotically relevant environments.

CONCLUSION

Homochirality is of great interest and importance to prebiotic chemistry as well as those researching the origins of life. Chirality is an important property observed in both organic materials and mineral structures and these structural properties have implications for reactivity and analysis. Understanding both organic and mineral chiral systems is relevant for prebiotic chemistry, as the origins of life had to occur in a geologic context of some kind. We have described asymmetric organic reactions as well as mineral alterations that involve chiral systems to emphasize their relevance to geological processes and highlight the diversity in their applications. Lastly, we recommended some future research directions in the field of chiral organic and mineral systems, in particular, technological and scientific advancements that include: (1) Identifying additional chiral organics and chiral minerals that could be used as biosignatures; (2) focusing on geologically and astrobiologically relevant reactions and systems; and (3) designing instruments that can be modified for spaceflight and remote operation to further the search for life on other worlds.

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