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Chance and Necessity in Biochemistry: Implications for the Search for Extraterrestrial Biomarkers in Earth-like Environments

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Abstract

In this paper, we examine a restricted subset of the question of possible alien biochemistries. That is, we look into how different life might be if it emerged in environments similar to that required for life on Earth. We advocate a principle of chance and necessity in biochemistry. According to this principle, biochemistry is in some fundamental way the sum of two processes: there is an aspect of biochemistry that is an endowment from prebiotic processes, which represents the necessity, plus an aspect that is invented by the process of evolution, which represents the chance. As a result, we predict that life originating in extraterrestrial Earth-like environments will share biochemical motifs that can be traced back to the prebiotic world but will also have intrinsic biochemical traits that are unlikely to be duplicated elsewhere as they are combinatorially path-dependent. Effective and objective strategies to search for biomarkers, and evidence for a second genesis, on planets with Earth-like environments can be built based on this principle. Key Words: Origin of life—Biomarkers—Exobiology—Extraterrestrial life—Prebiotic chemistry. Astrobiology 14, 534–540.

1. Introduction

DESPITE TREMENDOUS ADVANCES in the last 60 years, biological science still lacks a theory of life, perhaps with the sole exception of the universal principle of Darwinian evolution. Precisely, the search for a theory of life is one of the fundamental drivers behind the field of exobiology, or the study of life beyond Earth (Lederberg, 1960). Indeed, nothing would advance further our understanding of life than finding a second genesis.

One of the outstanding issues in exobiology is how to identify alien life without previous knowledge of its nature or composition. We excel at finding Earth life because we base our technology on terrestrial biochemistry, but it is entirely different to search for a form of life whose biochemistry is unknown. In this paper, we consider how different life might be if it emerged in environments similar to that required for life on Earth. In a sense, we are asking what the range of possible biochemical outcomes are if the history of life on Earth were to be rerun many times. Clearly, our approach does not address questions of life in environments very different from Earth. Life in liquid methane on Titan, if it exists, would not necessarily follow the biochemical principles addressed here (Benner *et al.*, 2004; Lunine, 2009). Similarly, we do not address other exotic chemistries for life (*e.g.* Bains, 2004; Benner *et al.*, 2004; Schulze-Makuch and Irwin, 2006), but we focus on life that lives in environments of liquid water with energy and mineral sources similar to the energy and mineral sources available on Earth.

2. A Common Chemistry at the Origin of Life

Lovelock (1973) first pointed out that biological processes, in contrast to abiotic ones, do not make use of the range of all possible organic molecules. Instead, biology is built from a selected set. This idea has received considerable attention in the recent literature as a method for the search for life (McKay, 2004; Davies *et al.*, 2009; Lunine, 2009; Shapiro and Schulze-Makuch, 2009; McKay, 2010). In the case of Earth life, the selected set of biochemical monomers are the 20 amino acids, the five nitrogenous bases, and the monosaccharides, fatty acids, and simple lipids (see, *e.g.*, Nelson *et al.*, 2004). McKay (2004) labeled this pattern of biological selection the ‘‘LEGO principle’’—in analogy with the children’s toys called LEGO blocks.

The building blocks of Earth’s life are only partially a reflection of prebiotic chemistry. Ten of the protein amino acids as well as some of the five nitrogenous bases are found in carbonaceous chondrite meteorites and can be synthesized

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prebiotically (Oró and Kimball, 1961; Stoks and Schwartz, 1979; Cronin *et al.*, 1993; Miller, 1993; Robertson and Miller, 1995; Nelson *et al.*, 2001; Pizzarello and Shock, 2010; Callahan *et al.*, 2011). The prebiotic frequency and abundance of these compounds is not random but determined by thermodynamic principles. The chemically simple compounds are typically the most abundant, and as shown by Higgs and Pudritz (2009) there is a correlation between Gibbs free energies of reaction and the observed rank in abundance of the 10 prebiotic amino acids in carbonaceous chondrites.

The relative abundance of the chemically simplest monomers implies a small number of stable structural isomers available at the time of the origin of life (Fig. 1), as best exemplified in the case of the amino acids (Cleaves, 2010). For example, there is only one structural isomer for C2 amino acids (glycine) and four isomers for C3 amino acids; however, the number of possible isomers increases exponentially thereafter. If life originates elsewhere under chemical conditions that resemble those of prebiotic Earth, then a similarly limited ''chemical space'' ought to be available to form the first biomolecules. The result ought to be an incipient biochemistry similar to the earliest biochemistry on Earth. Once life sets hold, the original set of chemically simple building blocks will be augmented by incorporation of new and more complex monomers—either naturally available or through biosynthesis—by evolutionary processes. As more complex isomers are incorporated, the number of choices increases (*e.g.*, Cleaves, 2010, Fig. 2 for the amino acids); thus it is unlikely that on different worlds the same monomers would be chosen (Fig. 1).

Hence, biochemistry is in some fundamental way the sum of necessity and chance; there is an aspect of biochemistry that is an endowment from prebiotic processes plus an aspect that is invented by the process of evolution. As a result, life in Earth-like environments always starts off with a similar set of LEGO blocks as determined by prebiotic availability—this represents the necessity. This initial set is later expanded based on evolutionary history, functional utility, and metabolic compatibility, which will be different in different worlds—this represents the chance. The former is likely to be common, if not universal, while the latter cannot be duplicated elsewhere, as it is combinatorially path-dependent.

3. Common and Unique Biochemical Traits in Earth-like Planets

Earth life universally uses phospholipids as main components of cell membranes. However, it seems improbable that such complex molecules were available in prebiotic Earth (Deamer *et al.*, 2002). On the other hand, phospholipids contain long-chain amphiphilic molecules, the fatty acids, which are similar to the long-chain acids extracted from carbonaceous meteorites (Fig. 2) (Deamer, 1985; Deamer and Pashley, 1989; Deamer *et al.*, 2002). These simple meteoritic amphiphiles form membranous vesicles in aqueous solutions that could have been the earliest precursor of modern biological membranes (Deamer *et al.*, 2002). Hence, while phospholipids might be an evolutionary invention intrinsic to Earth life, self-enclosure with amphiphilic molecules could represent a universal biochemical trait stemming from the prebiotic world (Deamer and Pashley, 1989; Deamer *et al.*, 2002).

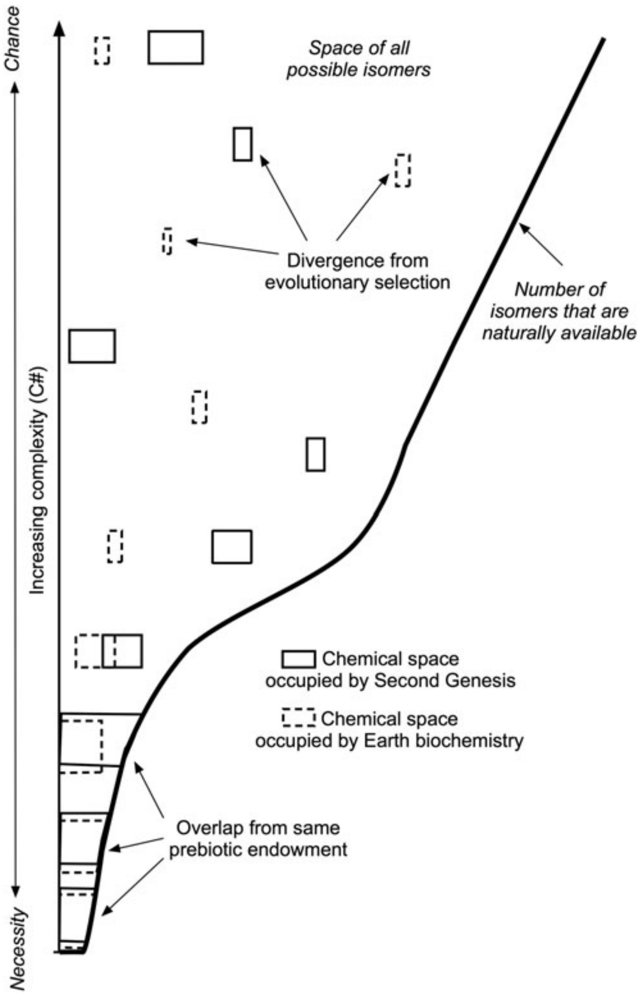

FIG. 1. Chance and necessity in biochemistry. Squares represent the chemical space occupied by a given biochemistry (*e.g.*, Earth life, second genesis) as a function of molecule complexity (carbon number). The total chemical space is defined by the number of possible building blocks that are naturally available. Structurally and chemically simple building blocks (small carbon numbers) have a small number of possible isomers and therefore define a narrow chemical space. In addition, these simple building blocks are the most frequent and abundant in the prebiotic world. Hence, incipient life has few structural isomers to choose from, and these simple building blocks ought to be universal biochemical traits (prebiotic endowment or *necessity*). As life evolves, the original set of building blocks is augmented by incorporation of more complex compounds. This expands the available chemical space—life has more structural isomers to choose from—and the probability that independent biochemistries choose the same building blocks decreases (evolutionary divergence or *chance*).

All life on Earth shares the same set of 20 protein amino acids. As noted by Philip and Freeland (2011), this set covers an optimal chemical space that allows a broad range of protein functionalities. However, this is not the only optimal set, and Philip and Freeland (2011) showed that other combinations equally cover the chemical space. Ten of the 20 amino acids in Earth biochemistry are commonly found in meteorites and can be synthesized in prebiotic

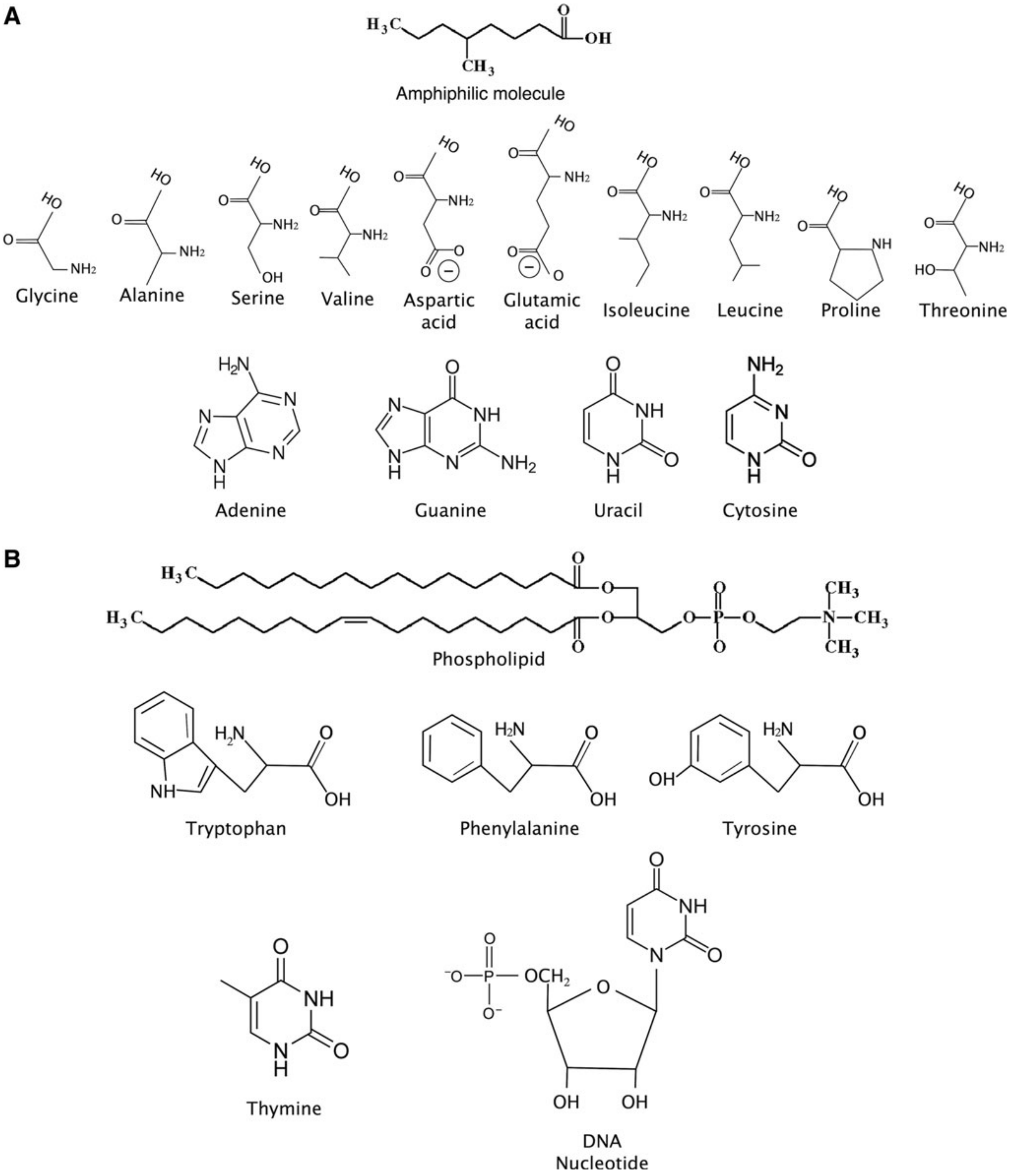

FIG. 2. (**A**) Biochemical building blocks that could be common, if not universal, in Earth-like planets with life. These are the most frequent and abundant monomers in meteorites and in simulated prebiotic chemistry. (**B**) Examples of widespread biochemical traits in Earth life that were invented by the process of evolution and could be intrinsic to our planet only.

chemistry (Weber and Miller, 1981; Higgs and Pudritz, 2009; Cleaves, 2010; Philip and Freeland, 2011). Of those, the chemically and structurally simple ones are particularly frequent and abundant (Higgs and Pudritz 2009; Cobb and Pudritz, 2014). The role of these simple amino acids in Earth's biochemistry is therefore an endowment of the prebiotic world and could represent a necessary and universal biochemical trait of life in other Earth-like environments. Later, incorporation of more complex amino acids in Earth's biochemistry, such as the aromatic ones (Trp, Tyr, Phe),

TABLE 1. EXPECTED COMMONALITIES AND POSSIBLE DIFFERENCES BETWEEN THE BUILDING BLOCKS OF EARTH LIFE AND A SECOND GENESIS

Earth and Second Genesis	*Only Second Genesis*
Self-enclosure with amphiphilic molecules	Different set of complex amino acids
Gly, Ala, Asp, Glu, Ser, and Val	L-sugars only
Homochirality	D-amino acids only
α-amino acids	Hypoxanthine and xanthine in nucleic acids
α-helix and β-sheets	No thymine
RNA bases (A, C, U, G)	

must have occurred in response to environmental conditions by way of evolution and natural selection, resulting in the final set of 20 fundamental amino acids. The set of more complex amino acids would therefore represent evolutionary adaptations specific to Earth life and likely to be different in other Earth-like environments (Fig. 1).

The proteinogenic amino acids of Earth life share two additional features: all proteins are composed of L-amino acids, and all of them occur in the α-configuration. Homochirality has long been recognized as a distinct, and perhaps necessary, feature of biochemistry. However, D-amino acids are equally capable of forming catalytic proteins (Milton *et al.*, 1992), and the D-form of the simple amino acids is also found naturally in meteorites (except for glycine, which is achiral). Hence, while homochirality likely represents a universal biochemical trait, it is not possible to anticipate the preference of life toward a specific stereoisomer. With respect to the position of the amino group, α-amino acids appear to predominate in CM and CR carbonaceous chondrite meteorites, whereas β-, γ-, and δ-configurations dominate in CI, CV, and CO types (Burton *et al.*, 2012). It has already been shown that β-peptides with the amino group bonded to the β carbon rather than the α carbon can fold into complex three-dimensional structures (Appella *et al.*, 1996; Seebach *et al.*, 1996). However, β-, γ-, and δ-configurations of chemically simple amino acids are not abundant in meteorites (except for β-alanine) or in simulations of prebiotic chemistry (Cleaves, 2010; Burton *et al.*, 2012; Pizzarello *et al.*, 2012), which implies that early β-peptides would cover a very small chemical space compared to α-peptides. In addition, β-, γ-, and δ-peptides would have a larger diversity of possible structural configurations (*e.g.*, β^2- and β^3-peptides), would be chemically more complex than α-peptides, and would lack glycine, which is a key conformational amino acid in α-peptides, as well as one of the most abundant amino acids in the prebiotic world. As such, while alternative protein backbones with β-, γ-, and δ-amino acid residues cannot *a priori* be ruled out as part of alternative biochemistries, the selectivity of Earth life toward α-amino acids is likely not accidental but a reflection of the type of chemistry available at the time of the origin of life, and as such it might be a universal trait (Weber and Miller, 1981; Cleaves, 2010).

Regarding the bases in nucleic acids, purines are the most widely distributed *N*-heterocycles in nature (Rosemeyer, 2004), and both adenine and guanine are found in meteorites (Callahan *et al.*, 2011) and frequently produced in simulated prebiotic chemistry (Oró and Kimball, 1961; Barks *et al.*, 2010). Hence, like the abundant prebiotic amino acids, the central role of adenine and guanine in biochemistry is likely not fortuitous but a reflection of prebiotic availability and a likely universal motif of biochemistry in other Earth-like environments (Fig. 2). The same might apply to the pyrimidine bases uracil and cytosine. Uracil is the only base found in meteoritic material (Stoks and Schwartz, 1979), and it can be produced in plausible prebiotic conditions together with cytosine (Robertson and Miller, 1995; Nelson *et al.*, 2001). In fact, uracil is formed from cytosine by hydrolysis; therefore the chemistry of both bases is tightly linked. A summary of expected commonalities and differences between the building blocks of Earth life and a second genesis is shown in Figure 1.

The above also has implications for reconstructing the environmental conditions at the time of the origin of life on Earth. Biochemical traits of extant organisms are often used to infer likely properties of the initial Darwinian ancestor (IDA) and the environment where it originated. For example, the use of cytosine, thymine, uracil, adenine, and guanine in DNA and RNA can be viewed as the result of adaptive pressures for life starting in environments exposed to sunlight (Mulkidjanian *et al.*, 2012). These bases are relatively stable compared with plausible alternatives in the presence of UV light (Serrano-Andrés and Merchán, 2009). As such, the selective advantage of these bases makes sense in scenarios where life originates on land (Mulkidjanian *et al.*, 2012), not at deep marine vents (*e.g.*, Russell *et al.*, 1993, 1994). However, with the exception of thymine, the rest of the bases are frequent and relatively abundant in prebiotic chemistry and in meteorites. If the universal use of cytosine, uracil, adenine, and guanine in RNA were due to prebiotic endowment (*necessity*), then their presence in the IDA would be independent from the environment where life originated. On the other hand, thymine, which is only present in DNA, could have been a late incorporation to substitute uracil, as an adaptation to minimize errors in transcription and to chemically stabilize the genetic message by making the phosphodiester backbone less susceptible to hydrolysis and damage caused by UV radiation (Jonsson *et al.*, 1996). This would represent an evolutionary adaptation of the IDA in response to a specific selective pressure (*chance*). As such, thymine could represent a biochemical motif that is indicative of a specific type of environment and inherent only to Earth life.

4. The Search for Extraterrestrial Biomarkers

If life on Earth-like planets always starts off with a similar set of building blocks, this would place constraints on how different other biochemistries can be, and we could use these constraints to inform the search for biomarkers. Mars, Europa, and Enceladus are the only places in the Solar System where biochemistry similar to that of Earth life might have evolved. While Mars today is an extremely cold and dry planet, conditions in the past were more benign (McKay and Davis, 1991), including the existence of habitable environments compatible with Earth life (Grotzinger *et al.*, 2014). Europa and Enceladus are prime destinations to search for life amid the presence of liquid water below a thick icy crust in both moons. In the case of Enceladus, evidence of liquid water is direct, from measurements of a plume of interior materials that are being released directly into space (Hansen *et al.*, 2006; Waite *et al.*, 2009). In the case of Europa, evidence is indirect, based on the distortion of Jupiter's magnetic field induced by the transit of the moon, suggesting a salty subsurface ocean, and on the detection of salts on the surface of the moon, seemingly originating from the freezing of internal fluids escaping through cracks in the icy crust (Khurana *et al.*, 1998; McCord *et al.*, 1998).

We can devise efficient strategies to search for biomarkers in these worlds based on the principle that biochemistry is the result of both necessity and chance. Life on Mars, Europa, or Enceladus ought to have incorporated at least some of the canonical prebiotic amino acids and nucleobases into its biochemistry. Arguably, the presence of these compounds in a sample cannot, by itself, be used as a biomarker. However, some individual and collective properties of these compounds could be used as a diagnostic for life. For example, the frequency of amino acids in meteorites is controlled by thermodynamic processes (Higgs and Pudritz, 2009), with the simplest and more stable ones being more abundant. However, the relative abundance of the same amino acids in biological systems is largely controlled by biosynthetic pathways, according to evolutionary processes. Biosynthetic pathways can promote the synthesis of complex amino acids over simple ones to optimize protein function and stability. As a result, the relative ratios of the prebiotic amino acids in a sample can in principle be used to distinguish between meteoritic and biological sources (Fig. 3).

A common chemistry at the origin of life also implies that some emergent properties of large biomolecules in Earth life could be common on other planets. For example, despite the presence of different amino acid configurations in meteorites (Burton *et al.*, 2012), there are compelling reasons why life would preferentially select the α-configuration (Cleaves, 2010), in which case the α-helix and β-sheet structures resulting from the polymerization of α-amino acids would also represent universal biochemical motifs.

Finally, while Earth life and a second genesis might share some of the prebiotic amino acids, the complete set of proteinogenic amino acids will likely be different and unique. However, the set would be homochiral, and this is perhaps one of the most universal biochemical properties of life (Bada and McDonald, 1995). Yet the preference of life toward a specific stereoisomer cannot be, in principle, anticipated. Other biochemical traits of Earth life that appear to be products of evolution such as the incorporation of thymine in the DNA structure (and the DNA structure itself); the specific selection of complex amino acids; or the use of phospholipids, sterols, and hopanoids in cell membranes cannot be assumed, *a priori,* in other biochemistries. Their presence in an extraterrestrial sample, however, would be indicative of convergent evolutionary trends.

5. Conclusions

In this work, we propose the principle of chance and necessity in biochemistry; there is an aspect of biochemistry that is an endowment from prebiotic processes, plus an

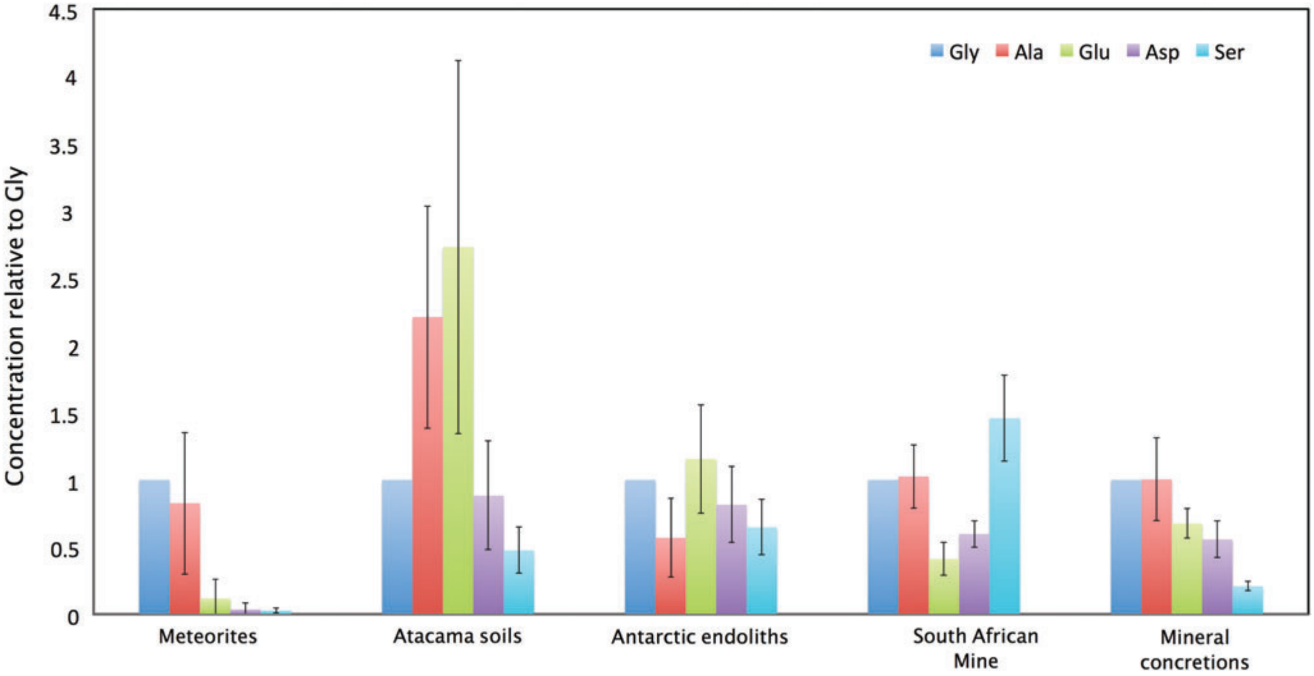

FIG. 3. Differences in the frequency and relative abundances of the simplest α-amino acids found in meteorites (abiotic) and in different terrestrial samples (biogenic). While the same amino acids can be found in meteorites and in life, their relative abundances are different. Different patterns in the relative abundances of these prebiotically abundant building blocks could potentially be used as a biomarker. Amino acid concentrations in meteorites were obtained from Cronin and Pizzarello (1983), Ehrenfreund *et al.* (2001), and Martins *et al.* (2007). All other data were obtained from Aubrey (2008). Color images available online at www.liebertonline.com/ast

aspect that is invented by the process of evolution. The former is likely to be common, if not universal, while the latter cannot be duplicated elsewhere, as it is combinatorially path-dependent. Effective and objective strategies to search for biomarkers in Earth-like planets can be built based on this principle.

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Abbreviation

IDA, initial Darwinian ancestor.

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