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PREBIOTIC CHEMISTRY

Abiogenic Syntheses of Lipoamino Acids and Lipopeptides and their Prebiotic Significance

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Abstract Researchers have formed peptide bonds under a variety of presumed prebiotic conditions. Here it is proposed that these same conditions would have also formed amide bonds between fatty acids and amino acids, producing phosphate-free amphipathic lipoamino acids and lipopeptides. These compounds are known to form vesicles and are ubiquitous in living organisms. They could represent molecules that provided protection by membranes as well as possibilities for proto-life metabolism . It is here demonstrated that when a fatty acid is heated with various amino acids, optimally in the presence of suitable salts or minerals, lipoamino acids are formed. Magnesium and potassium carbonates as well as iron (II) sulfide are found to be particularly useful in these reactions. In this manner N-lauroylglycine, N-lauroylalanine, N-stearoylalanine and several other lipoamino acids have been synthesized. Similarly, when glycylglycine was heated with lauric acid in the presence of magnesium carbonate, the lipopeptide N-lauroylglycylglycine was formed. Such compounds are proposed to have been critical precursors to the development of life.

Keywords Prebiotic · Proto-life · Lipoamino acid · Lipopeptide · Amide · Membrane

Introduction

Lipid membranes, present in all three biological domains, serve the crucial function of separating chemicals of cellular life from an aqueous environment. A *lipid world* has been proposed as one possibility for how life began (Monnard and Deamer 2002), postulating that proto-life began in a lipid-protected environment. Membranes of all cells are composed of amphipathic phospholipids that contain a phosphate ester of glycerin. One major challenge for theories suggesting such a lipid bilayer for protolife is that phosphate may have been, depending on pH, essentially unavailable for prebiotic chemistry due to its insolubility in the presence of divalent cations that were likely present (Keefe and Miller 1995; Pasek 2008).

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While protolife was eventually able to obtain phosphate for membrane lipids from perhaps various sources, (Schwartz 2006) it may have been unlikely that phosphate was present in the earliest membranes.

Ordering the chemical progression by which protocells evolved has been one of the most vexing problems in origins of life scenarios. One of the most accepted models of protolife is that of the *RNA world*, developed since the discoveries of reverse transcriptases (Temin and Mizutani 1970) and ribozymes.(Cech 1986). However, RNA is a chemically complex compound that would have required exceptional circumstances for formation using difficult to obtain phosphates, a specific monosaccharide and unique nucleic acid bases. Abiotic synthesis may have occurred within protected environments such as in chambers of seafloor vents or inside lipid membranes. While it is likely that an RNA world preceded the current DNA world, RNAs' presence prior to the *peptide world* (defined below) has been seriously questioned (Kurland 2010; Poole 2011).

Peptides are considered by some as central to the origin of life (Carrea et al. 2005). Because of their critical involvement in nearly all life processes, a *peptide world* has been postulated; peptides' necessity early in the development of life seems highly likely. The dehydration condensation of amino acids to form amide bonds has been extensively investigated. Although there is no general agreement as to which conditions might have produced peptides on the prebiotic Earth, numerous conceivable candidate conditions have been described. The formation of peptides from amino acids has included high temperatures (Fox and Middlebrook 1954; Shock 1993; Sakata et al. 2010), wetting/drying cycles (Schwendinger et al. 1995), clays (Fuchida et al. 2014), high pressures (Otake et al. 2011), adsorption (Gururani et al. 2012; Lambert 2008), hygroscopic salts (Lambert 2008; Kitadai et al. 2011), activating agents (Hulshof and Ponnamperuma 1976; Brack 1982), sulfide minerals (Ohara and Cody 2010), and near saturation of water with sodium chloride combined with copper(II) salts (Lahav and Chang 1982; Rode and Schwendinger 1990; Rode et al. 2007).

Cellular membranes are composed of about half lipids and half proteins (Rondel et al. 2009). Cells of many bacterial (Asselineau 1991) and eukaryotic species and possibly archaea (Bodour et al. 2003; Kebbouche-Gana et al. 2009), contain a ubiquitous amphipathic array of lipoamino acids, lipopeptides and lipoproteins. These compounds typically consist of a fatty acid bound to an amino acid by an amide bond. The widespread occurrence in at least two of the three domains is possibly indicative of life's conservation of these biomolecules that have proven to be of significant advantage throughout evolutionary time. Since both a protective membrane and a binding to potentially catalytic transition metals were likely necessary for life's beginnings, lipopeptides provide reasonable and chemically simple candidates for major components of early membranes.

Because the peptide bond is formed by condensation of carboxylate and ammonium groups, it seemed reasonable to this author that lipopeptides could be similarly produced (Ulijn et al. 2002). Reaction conditions that formed prebiotic peptides would have simultaneously formed lipoamino acids and lipopeptides in the presence of sufficient concentrations of fatty acids. This paper has two purposes: to demonstrates the abiotic syntheses of lipoamino acids and lipopeptides using reaction conditions similar to those which have produced peptides from amino acids and to hypothesize the importance of lipopeptides for protolife. Because of its synthetic simplicity and likely relevance to conditions that existed on early Earth, elevated temperatures were selected for synthesizing these compounds under various conditions. Water temperatures above 140 °C can occur below 30 m of water, and elevated temperatures occur around geothermal sites. The products were synthesized by heating fatty acids with either an

amino acid or dipeptide, and then evaluated by infrared spectroscopy. Their esters were analyzed by gas chromatography/mass spectrometry (GC/MS).

Experimental Procedure

L-alanine, ethanol, glycine, iron (II) sulfide, pyrites (FeS_2), magnesium carbonate, potassium carbonate, sodium chloride, stearic acid, sulfuric acid, and black-capped two-dram vials equipped with polytetrafluoroethylene (PTFE) lined caps were purchased from Fisher. Lauric acid and methyl t-butyl ether (MTBE) were purchased from Alpha Aesar; glycylglycine and ethyldodecanoate (LE) from Sigma; thionyl chloride from Fluka; and oxalyl chloride and pyridine from Acros. Zinc sulfide was synthesized from zinc chloride and sodium sulfide, both from Fisher.

Reference compounds were prepared by first forming the acyl chloride of the selected fatty acid using oxalyl chloride and lauric acid (LA) (Adams and Ulich 1920). N-lauroyl glycine (LG) was prepared in 87 % yield by reacting lauroyl chloride with glycine using standard methods (Varasteanu et al. 2011) along with a few drops of pyridine (Montalbetti and Falque 2005). LG was esterified to determine both retention time and mass spectrum of its ethyl ester (LGE) during GC/MS analysis. Similarly, N-lauroyl glycylglycine (LGG) was prepared as a reference by using thionyl chloride (Bauer 1946); the acyl peptide was esterified with ethanol to give N-lauroyl glycylglycine ethyl ester (LGGE).

The GC/MS response was evaluated against commercial LE. Weighed samples were prepared in MTBE and 2.0 μL samples were injected into the GC/MS with the same parameters used with synthesized samples. These gave a quadratic relationship of detected ions (i) to the injected molecules (m) of $i = -7.2 \times 10^{-17} m^2 + 1.9 \times 10^{-4} m$ with an R^2 of = 0.83. The response curve was relatively linear to about 7×10^{11} molecules, at which point about 1.0×10^8 ions were formed. The ion yield here was thus about one ion for each seven thousand injected molecules. Thus, fewer than one in 1000 injected molecules was successfully ionized, as is typical for such electron impact experiments (Millard 1978). All synthesized samples were prepared at concentrations below the saturation level of the detector.

Lipoamino acids were prepared under potential prebiotic conditions following procedures that had generated amide coupling of amino acids to form peptides. Initially, lauric acid was heated with glycine for a week at 140 °C, which produced 0.4 % LG after 14 days; LGE was measured here and elsewhere as percentage of the lipoamino acid ester compared to all lauric acid components in the GC/MS chromatogram. Thus, the LE served as an internal standard by which the yield of LGE could be determined. In order to enhance yields for this reaction, various dehydrating agents were added. In a characteristic reaction, 0.500 mmol of the fatty acid, 0.500–2.000 mmol of the amino acid or dipeptide, and 0.500–2.000 mmol of various salts were added, ground in a mortar, deaerated with N_2 flow for 15 s, sealed with PTFE tape and a black PTFE-lined cap (more thermally stable than white or green), and heated from 100 to 160 °C for a given amount of time ranging from hours to weeks. On removal, the contents were esterified, poured into separatory funnel with equal amounts of MTBE and brine, shaken for 1 min to dissolve the ester in the MTBE, and the organic layer removed for analysis. A wide range of salts, temperatures and reaction times were employed in order to explore the effects on yield. In similar ways N-lauroyl alanine, N-stearoyl alanine and N-lauroyl glycylglycine as well as several other lipoamino acids were prepared using magnesium carbonate and potassium carbonate. In a separate but related set of experiments, various finely ground and screened to less than 0.15 mm transition metal sulfides including FeS, FeS2 and ZnS were heated with lauric acid and glycine at temperatures ranging from 80 to 120 °C.

The esterified samples were analyzed by gas chromatography with mass selective detection (Hewlett-Packard 5890GC/5972MSD). The gas chromatograph was equipped with a 30 m× 0.25 mm Zebron-5HT capillary column (Phenomenex Inc, Torrance, California). The oven temperature was held at 120 °C for 0.5 min and then programmed to 200 °C at a rate of 8 °C/min, then 250C at 4 °C /min and held at this final temperature for up to 35 min. A split mode of injection (50:1) was used. Helium carrier gas flowed at 30 cm/s with the detector and injection port temperatures at 280 and 320 °C respectively. The mass chromatogram and mass spectrum were used for quantitative and qualitative analysis of the reaction products. Acylamino acid condensates' mass spectra were characterized by a molecular ion and /or McLafferty rearrangement ions, and high molecular weight peaks were correlated with structures. Both the GC scans and the MS spectra were output along with the integrated peak areas from the scan. Percentage yields of the lipoamino acid or lipopeptide were determined by integrating MS peak areas of these and comparing against total areas of all fatty-acid-containing peaks. Parent ion peaks were observable with some of the products and the McLafferty peaks were critical for confirming the amide ester products. Retention times and MS spectra of the compounds were compared with those of reference compounds prepared using standard synthetic methods and with NIST98 (1998) mass spectral database. Infrared spectra using a Perkin-Elmer *Spectrum One* in transmission mode were collected using 4 cm^{-1} resolution with quadruple scans between 4000 and 450 cm^{-1} to observe the amide bond.

Results

To determine the feasibility of synthesizing lipomino acids by heating, lauric acid (LA, dodecanoic acid) and glycine (G) were tested. A reference sample of LG was prepared for comparison with the experimental compound. Identification of LGE was straightforward using GC/MS. The strongest MS peak above 50 amu occurred at 145 amu (Fig. 1a), the McLafferty rearrangement cation of the ethyl glycine moiety, and the parent ion peak appeared at 285 amu (the molecular mass of LGE is 285.4 amu).

Initial efforts to produce the condensation product by simply heating the organic reactants in a manner similar to that used to prepare polypeptides yielded very small amounts (<1 %) of product. Since condensation requires removal of water, various dehydrating agents were evaluated. While most gave only marginal increases in yield, $MgSO_4$ on esterification produced up to 6 % of LGE under unoptimized conditions. GC/MS analysis showed the presence of ethyl laurate (LE) with a retention time of 9.1 min and LGE at 18.1 min. The parent ion peak, although small, was present at 285 amu and the McLafferty peak appeared at 145 amu (Fig. 1b). Infrared scans showed amide absorption lines at 3319, 3079, 1647 and 1552 cm^{-1} (Viedma 2000).

Various parameters were analyzed to increase yields. After heating at 150 °C, samples capped in air darkened considerably to deep amber, likely indicating air decomposition. Deaerating samples with N_2 prior to heating decreased the darkening. Decreasing the temperature from 150 to 140 °C essentially halved the amount of product produced in 14 days; small amounts of LGE were obtained at temperatures as low as 120 °C after heating for a month. Visually comparing results of an unground with that of a mixture ground to a fine powder showed the product of the unground sample to be mottled and to decrease yield to one-fourth; therefore, mixtures were pulverized prior to heating. Increasing the ratio of amino acid to lauric acid from 1:1 to 2.5:1 increased the yield from about 4 % by ten times, maximizing at about

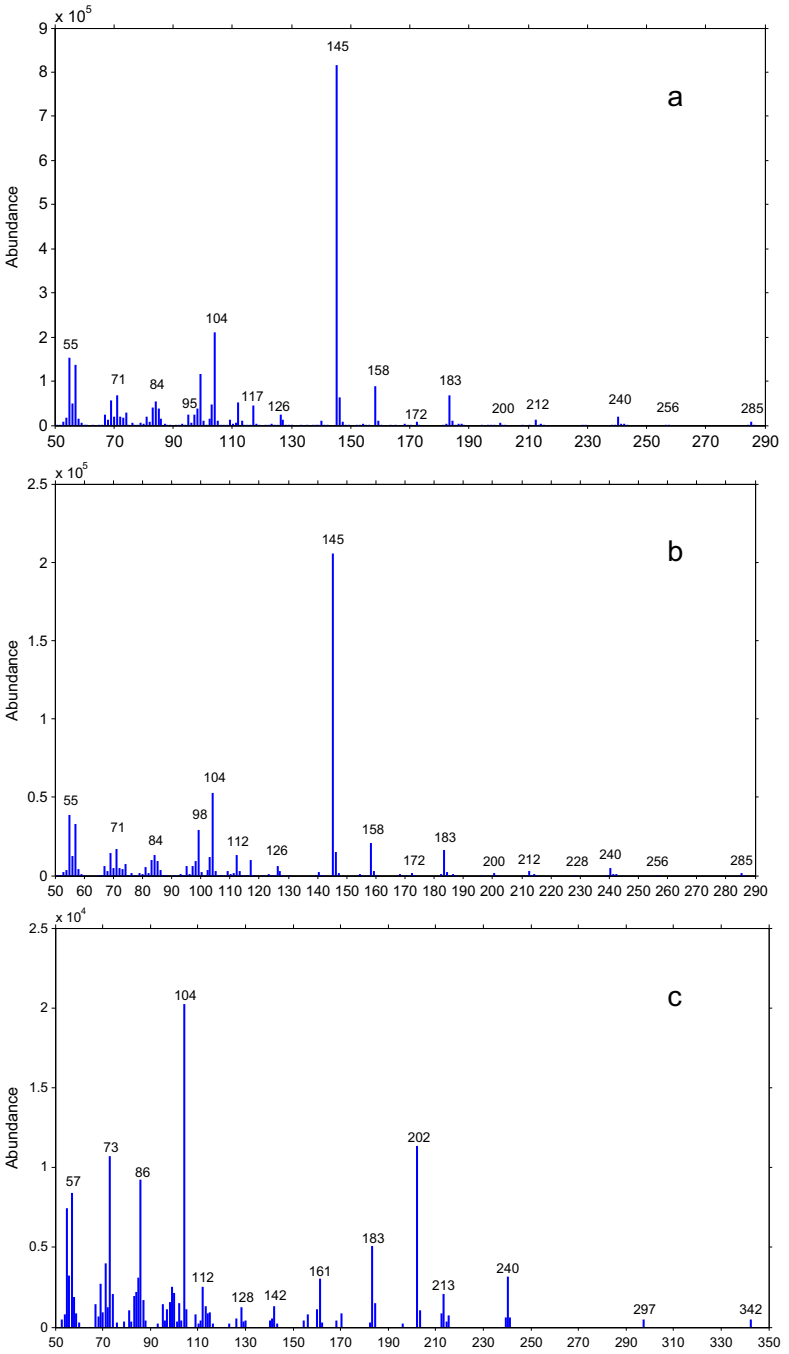

Fig. 1 Mass spectra of ethyl esters of selected lipoamino acids and a lipopeptide. **a & b**: spectra of N-lauroylglycine ethyl ester reference and synthesized with magnesium carbonate, respectively. **c & d**: spectra of N-lauroylglycylglycine ethyl ester reference and synthesized with magnesium carbonate, respectively. **e**: spectrum of L-lauroylalanine ethyl ester synthesized with potassium carbonate. **f**: spectrum of L-stearoylalanine ethyl ester synthesized with potassium carbonate

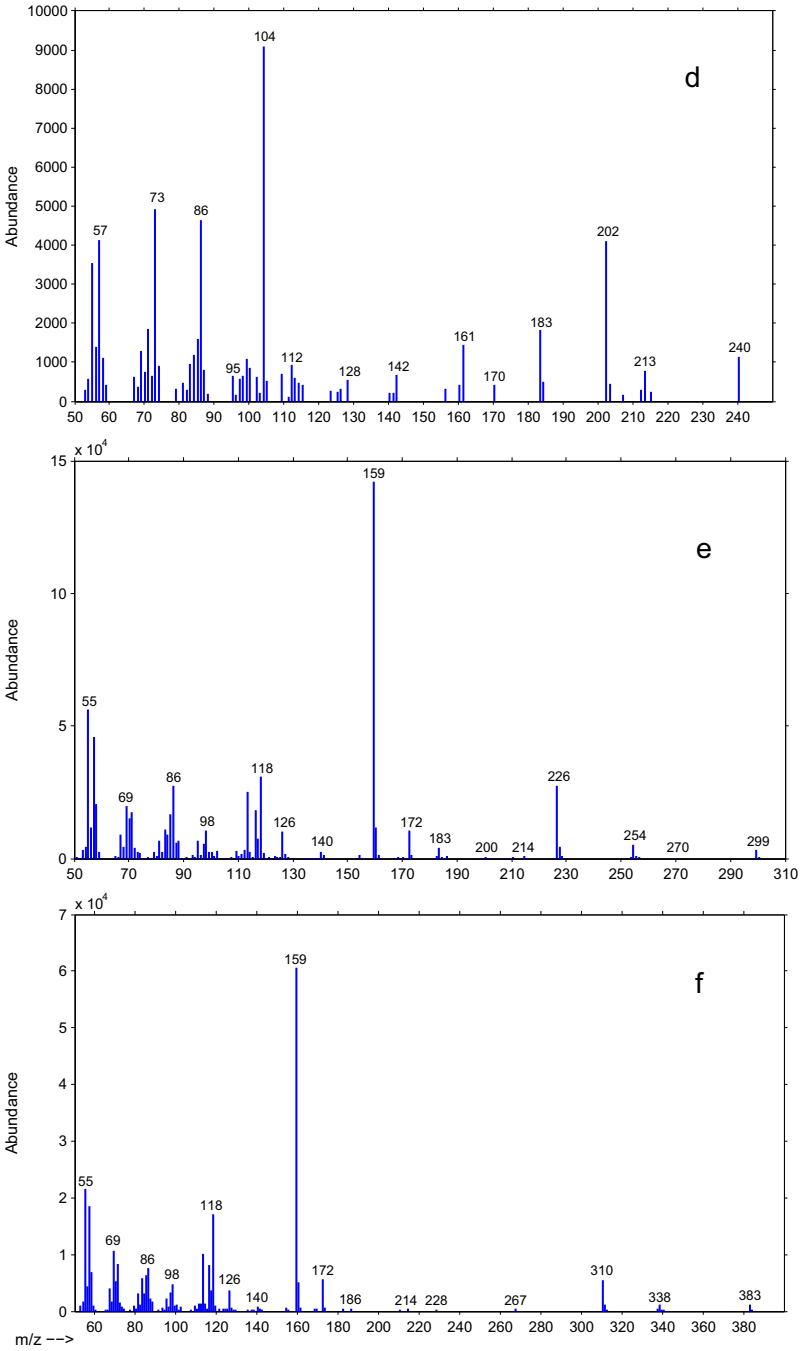

Fig. 1 (continued)

40 % for ratios above 2 to 1 (Table 1). A nearly equimolar ratio of salt to lauric acid provided the best yields (Table 2). Despite carefully controlling preparation techniques, yields of LGE from

Table 1 Percentage yields of N-lauroylglycine ethyl ester as a function of the ratio of glycine to lauric acid

				G to LA	Ratio				
Expt #	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.5	5.0
1	3	6		47					15
2		28	20	51		22			
3		22	35	42		61			
4			1		34		19	33	
5		8	41	47	45	38	38	43	67
6	6	15	21	42	41	32	39	39	53
Average	4	16	24	46	40	38	32	38	45
Stnd Dev	1	9	16	4	5	17	12	5	27

repeated preparations of reacting compounds and even from subdivided samples using the same mixture produced wide ranges of product yields, with standard deviations of 10–15 %.

The demonstrated formation of lipoamino acids implied that lipopeptides could also be synthesized by this method. A reference sample of N-lauroylglycylglycine ethyl ester LGGE) was prepared for comparison against an experimental sample (Fig. 1c). Glycylglycine was reacted with lauric acid along with various salts. Both magnesium carbonate and potassium carbonate produced 11 % of the desired LGGE (Fig. 1d) with a retention time of 30.2 min. The parent ion peak was present at 342 amu (molecular mass of LGE is 342.4 amu) and the McLafferty peak appeared at 202 amu.

The ethyl esters of N-lauroyl alanine and N-stearoyl alanine (Fig. 1e and f, respectively) were prepared in a manner similar to that of LGE, with retention times of 17.5 and 30.5 min, respectively, with McLafferty peaks at 159 amu as expected for alanine. Additionally, numerous other amino acids including aspartic acid, asparagine, glutamine and serine were condensed with lauric and stearic acids, but because of the presence of active functional groups, their MS spectra were more complex due to rearrangements and fragmentations; conventional syntheses have not yet been carried out to confirm them.

As indicated in the Introduction, numerous methods have produced peptides from amino acids. In order to extend experiments that demonstrate the possibility of simultaneous formation of

Table 2 Percentage yield of N-lauroylglycine ethyl ester as a function of the ratio of magnesium carbonate to lauric acid

				$MgCO_3$	to LA	Ratio			
Expt #	0.00	0.12	0.25	0.50	0.75	1.00	1.50	2.00	4.00
1	10		9	7	21	4	36	19	7
2	1		39	36	26	5	18	11	0
3	1	2	9	23	38	37	41	24	
4	1	14	4	30	36	28	30	26	
5	4		19	48	63	37	45	34	20
6	9		13	52	58	43	44	55	4
7	0		33	28	48	15	6	12	0
8			34	14	32	6	2	29	0
Average	4	8	20	30	40	21	28	26	5
Stnd Dev	4	9	14	16	15	16	17	14	8

lipoamino acids and lipopeptides during the formation of peptides, an alternative synthesis was carried out. Ohara and Cody (2010) showed that peptides can be formed simply by heating an amino acid with pulverized metal sulfide minerals. Several sulfides were used in a similar manner to couple lauric acid with glycine. Heating the organics with iron (II) sulfide at 120 °C for 14 days, on esterification produced a 10–15 % yield of LGE, while heating at 100 °C gave a 2 % yield after 25 days.

Discussion

In order to test the possibility of condensing fatty acids with amino acids and thereby combining the lipid and peptide worlds, I chose to heat the reactants. This condition has been used for the formation of peptides and could simulate either geothermal or solar heating on ancient Earth. Because initial mixtures of only a lipid and an amino acid yielded little of the desired product, various dehydrating salts were added with the expectation that these would help in the extraction of water. While magnesium sulfate was found to be advantageous, magnesium and potassium carbonates were found to produce even higher yields of LG, whereas other salts including most that are used as water scavengers gave little enhancement. This corresponds with other recent findings that magnesium salts are superior to those of strontium, barium or lithium for the polymerization of glycine and far superior to salt-free dehydrations (Kitadai et al. 2011). Also, magnesium and calcium carbonates have been shown to increase the formation of alanine oligomers under hydrothermal conditions (Kawamura et al. 2011). The presence of both Lewis acid and Brønsted/Lowry base sites in these salts seems to serve vital roles in enhancing these reactions (Rimola et al. 2007). Temperature and time experiments indicated that higher temperatures up to 160 °C and longer times up to several weeks produced higher yields of the desired acyl amino acids. Alternatively, lower temperatures still produced some LGE, particularly at longer times. Again, these results are in line with those found for the dimerization of glycine by heating (Shock 1993; Sakata et al. 2010). However, in these lipoamino acid experiments the inclusion of salts and sulfide minerals significantly increased yields.

GC/MS of the esterified condensation product of glycine and lauric acid showed a retention time and spectrum essentially identical with a reference LGE. Similarly, the infrared spectrum showed absorption bands that confirmed formation of the amide bond in this product (Fox and Harada 1960; Viedma 2000). Likewise, GC/MS of LGGE synthesized using a salt showed both the same retention time and spectrum as LGGE prepared by standard methods. Table 1 indicates that an excess of G is beneficial, with yields of LGE reaching a maximum at a ratio of G to LA of about 2.0 and thereafter remaining relatively constant. This need for excess G may be due to the concurrent formation of diglycine and/or of glycine anhydride (diketopiperazine), neither of which was evaluated. While product yields were significantly increased by optimizing several parameters, yields from comparable batches were inconsistent and varied widely. It seems likely that this random error occurred because of the heterogeneous nature of the reaction mixtures. Although lauric acid melts around 40 °C, which would provide a liquid medium for reaction, both G and the various salts or minerals would have remained as solids. Grinding and sampling likely produce a range of particle sizes, some with more surface area or active sites available for interaction with the reactants; no effort was made to select particle sizes. Without access to a salt surface, the fatty acid or amino groups may be unable to readily form an amide bond. As can be seen from Table 2, the reaction yields increase with an increasing ratio of salt to fatty acid up to a maximum at a ratio of about 0.75 salt to LA and decreases thereafter. It is unclear whether the salt is behaving as a co-reactant or as a catalyst.

The strong amide bonding of two essential prebiotic species—peptides and fatty acids—could help explain how protolife first became encapsulated and provided protection for development of the *RNA world*. Assuming the presence of abiogenic amino acids and fatty acids in appropriate geological conditions on early Earth, lipopeptides would have formed alongside peptides. With these amphipathic compounds, protolife would have had the dual advantages of the biophysical and biochemical characteristics of these substances: a membrane boundary as well as peptides that could serve biochemical processes. Numerous authors have recognized the necessity of both peptides and lipids for the formation of the protocell (Monnard and Deamer 2002; Bywater 2009; Egel 2009).

The likelihood that lipopeptides provided a mode by which the abiogenic chemistry of protolife could have evolved is indicated by numerous observations: 1) as demonstrated, lipoamino acids and lipopeptides can readily form under the same conditions as peptides; 2) salts and acids of lipopeptides have been shown to combine with cationic surfactants to form vesicles (Ambuehl et al. 1993) as well as liposomes (Epand et al. 1998), while lipopeptides alone form lamellar structures (Douy and Gallot 1986; Gallot and Diao 1992); 3) although current life forms all have membranes composed of phospholipids, it is unlikely that protocells could have had the means to acquire phosphates; since lipopeptides are phosphate-free amphipathic compounds, they could have provided protective membranes for protocells without the need for phosphate; 4) lipopeptides are surfactants that do not require the three-carbon glycerol molecule currently found in membranes of all three domains; removal of glycerol from the earliest forms of life helps to resolve the differences in membrane chemistry between Archaea on one hand and Bacteria and Eukarya on the other (Glansdorff et al. 2008); 5) reactive side chains of peptides covalently attached to the lipids could have provided centers on which various metabolic functions could occur; 6) intriguingly, when grown under phosphate-limiting conditions, the lipoamino acid N-acyl onithine has been found in the membrane of the bacterium *Deleya marin*, replacing the phosphate-containing N-acyl phosphatidylethanolamine with N-acyl ornithine whose structure is comparable to the lipid it replaces (Yagi et al. 1997); the replacement of standard phospholipids by this lipoamino acid in a contemporary life form demonstrates both the feasibility of lipopeptides as capable alternatives for forming the lipid bilayer and the possible preservation of lipopeptides as relics due to their primordial necessity; and 7) rather than using the standard means of translation of RNA to proteins, some peptides are produced directly from other proteins via non-ribosomal peptide synthesis (NRPS); these NRPS's fascinatingly and instructively produce a range of lipopeptides (Roongsawang et al. 2010). These several observations combine to form a unifying picture that points toward a resolution for how lipopeptides of protolife, during what may be called the chemical lipopeptide era, could have served as precursors to the biological *RNA world*.

Along with heating, it remains to be seen if other methods that have been used to produce peptides under potential pre-biotic conditions can also be shown to produce lipopeptides. I am currently exploring some of these alternative methods as well as the kinetics and thermodynamics of this reaction.

Conclusion

Using elevated temperatures that imitate geothermal or solar energy input on prebiotic Earth, lipoamino acids and a lipopeptide have been synthesized by heating in a manner that parallels reactions that have been used to synthesize peptides. Conditions in the prebiotic world suitable for forming peptides from amino acids are likely to have concomitantly produced lipoamino acids and

lipopeptides. Certain salts, particularly magnesium sulfate, magnesium carbonate, potassium carbonate and iron (II) sulfide, enhance yields by at least an order of magnitude compared with salt-free reactions. Lipoamino acids and lipopeptides are surfactants that behave in a manner similar to phospholipids found in cellular membranes. They may represent vestigial biomolecules of prebiotic organisms. Since they do not include phosphate, these surfactants could have provided protolife with a suitable membrane that avoided the need for unobtainable phosphate. With the potential encapsulation provided by lipopeptides along with the probable rudimentary metabolism inherent at peptide surfaces, lipopeptides are likely to have been critical for prebiotic development. A *lipopeptide era* is proposed in which these compounds allowed biochemical evolution of physically protected and chemically active protolife.

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