FROM MESSY CHEMISTRY TO THE ORIGIN OF LIFE. I. Mamajanov[1], [1]Earth-Life Science Institute, Tokyo Institute of Technology, Meguro, Tokyo 152-8550, Japan, irena.mamajanov@elsi.jp

Introduction: In the last 65 years, prebiotic chemistry has been explored in many plausible Early Earth conditions. Biological building blocks have been discovered in the Miller-Urey experiment [1] and at high pressure and temperature in geothermal vent conditions [2]. Some biomolecules have been generated by HCN chemistry [3] and in Fischer-Tropsch-type reactions [4]. Additionally, interesting "life-like properties" such as functioning autocatalysis and self-assembling nucleoside analogs have been discovered in formose reaction [5] and cyanuric acid-triaminopyrimidine coupling [6], respectively. Many of these prebiotic systems share a common feature – they are messy. The systems produce vast multi-component mixtures of compounds through an abundance of reaction pathways. When messy prebiotic systems reach steady state or equilibrium, they produce heterogeneous intractable polymeric structures, dubbed "tar" or "asphalt".

On the contrary, the enzyme-controlled world of biochemistry is characterized by complex yet defined chemical net-works with clearly delineated reaction mechanisms and product diversity. Messy chemistry hypothesis conceptualizes the transition between the uncontrolled prebiotic chemistry and biochemistry through the grasp of methods of organization in chemistry. The open-ended objective of messy chemistry is building a purely chemical system capable of chemical evolution. In the talk, I will discuss several principles of messy chemistry as exemplified by the following experimental and biological models.

Messy Polyesters: Ester bonds are common in modern biochemistry predominantly in the form of triesters of glycerol and fatty acids in lipids. Ester formation has a slightly negative bond energy (~1 kcal/mol under physiological conditions) making this functional group's synthesis facile. Polyesters have been hypothesized to have preceded peptides due to their ease of formation, and this notion is perhaps supported by the demonstrated ability of the ribosome to catalyze alpha-hydroxy acid coupling [7]. We have explored the polyesterification of alpha-hydroxy acids, which are plausibly abundant prebiotic monomers, can be oligomerized to generate vast, likely sequence-complete libraries [8].

Biomimetic Prebiotic Systems: Enzymes are composed of organic, mineral or metal cofactors, agents that actively participate in the reaction mechanism, and folded globular protein or RNA scaffold. The function of the biopolymer scaffold is to specifically bind, and encapsulate substrates while creating a microenvironment suited for reaction progression. When considering enzyme-like prebiotic catalysts, certain small molecules, mineral and metal cofactors are prebiotically plausible unlike high functional proteins and RNA molecules. Could simple polymers substitute RNA or protein scaffold at the early stages of chemical evolution? Such an approach is well established within synthetic biomimetics, where enzyme analogs are commonly synthesized by inserting model catalytic sites within polymeric structures. One of the most well-known structures used for enzyme mimics are dendrimers, regular tree-like macromolecules with an embedded distinct reactive core [9]. Similar to dendrimers, the branched structure of irregular dendritic or hyperbranched polymers (HBPs) results in a multitude of end groups that can bind catalysts and substrates, as well as control the polarity of the intramolecular microenvironment. In contrast to dendrimers, HBPs do not contain a distinct core; have less defined intramolecular cargo space and broad distribution of molecular structures and sizes. Although less controlled functionally, the advantage of HBPs over dendrimers is their straightforward, often one-pot synthesis, whereas dendrimers require multi-step procedures. As proof-of-principle I will describe the capability tertiary amine-bearing HPBs form hydrophobic pockets as a reaction-promoting medium for the Kemp elimination reaction [10] and the ability of HBPs to support metal-sulfide nanoparticles that catalyze redox reactions.

Selectivity in Messy Systems: Gelation is a property of branched polymer related to tar formation. Gelation occurs when a polymer forms large interconnected polymer molecules through cross-linking [11]. We have explored the gel formation in hyperbranched polyester systems under continuous drying and wet-dry cycling associated with environmental conditions, such as dew formation or tidal activities. The results reveal that periodic wetting during which partial hydrolysis of the polyester occurs helps to control the chain growth and delays the gel transition. Moreover, the NMR and mass spec analyses indicate that continuously dried samples contain higher quantities of cross-linked and macrocyclic products, whereas cycled systems are enriched in branched structures**.** Ostensibly, environmental conditions can exert a rudimentary pressure to selectively enrich the polyesterification products in polymers of different structures and properties. At the early stages of chemical evolu-

tion, in the absence of biological machinery, this example of environmental control could have been for selectivity in chemical systems. As expected in marginally controlled systems, the identification of each component of the heterogeneous system has proved challenging, but it is not crucial for concluding [12].

Autocatalysis in Messy Systems: How could complex biocatalysts first have arisen on planet Earth? Previous studies have suggested autocatalytic cycles as a partial answer to this question since such reactions exhibit the life-like property of exponential growth while being composed of relatively simple molecules. However, a question remains as to the likelihood of an autocatalytic cycle forming spontaneously in the absence of highly specific catalysts. We have explored an artificial chemistry model in which such cycles form readily even though the initial conditions of the system involve no direct catalytic processes. Catalytic effects nevertheless emerge as properties of the reaction network. This suggests that the conditions for the formation of such cycles are not challenging to achieve. The resulting cycles solve the problem of specificity not by being small and simple but by being large and complicated, suggesting that early prebiotic metabolisms could have been extremely complex [13].

Heredity in Messy Chemistry: Molecular imprinting technology concerns the formation of particular sites in a polymer matrix with the memory of a template. While the principle is usually applied in the chemical synthetic system, it might apply to prebiotic systems, such as peptide synthesis [14]. Such a process would be simpler, and therefore more prebiotically plausible than nucleic acids systems.

Conclusions: Through above examples and model systems I will outline the messy chemistry origins of life hypothesis, its advantages and challenges.

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