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Growth of proto-peptides by continuous feeding of monomers

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The formation of polypeptides on the early Earth is a long-standing problem in the field of prebiotic chemistry. Although it is generally accepted that amino acids were present on the prebiotic Earth [1,2], a plausible mechanism to form long chain polypeptides is still elusive. Because of high activation energies and formation of side-products, direct peptide bond formation is slow unless elevated temperatures or chemical activating agents are used. Our previous work has described a simple system composed of hydroxy acids and amino acids that is capable of forming peptide bonds under mild conditions [3]. Hydroxy acids form metastable oligoesters in the oscillating (hot-dry/cool-wet) environment and transform into mixed copolymers via the ester-amide exchange reaction. Further analysis of kinetic and activation parameters showed that the ester-mediated pathway enables the amide bond formation by providing a route with lower activation energies [4].

We further interrogated the ability of the ester-mediated reaction, identifying a strategy that enables the formation long chain polymers with peptide backbones. This reaction behaves similarly to chain-growth living polymerization: new monomers add to one end of chains step-by-step without termination. Unreacted monomers were fed to the dry mixture every cycle by an automated “day-night” machine. The feeding composition was found to affect the oligomer distribution. Longer oligomers can be produced more efficiently when only amino acids are fed because of a smaller number of active oligomer chains. This work provides a comprehensive study of the ester-mediated reaction to synthesize amide bonds. This simple reaction is shown to be a robust pathway to synthesize long chain depsipeptides in mild conditions.

References: [1] Miller, S.L. and Urey H.C. (1959) *Science* 130: 245–251. [2] Bernstein, M. P. *et al.* (2002) *Nature* 416: 401–403. [3] Forsythe, J. G., Yu, S.-S *et al.* (2015) *Angew. Chem. Int. Ed.* 54: 9871–9875. [4] Yu, S.-S., *et al.* (2016) *PCCP* 18: 28441–28450.

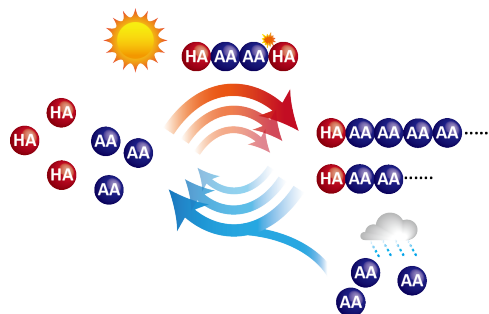


Figure 1 – Production of long chain depsipeptides by continuous feeding during the environmental cycling.