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Influence of Nucleic Acid Intercalators on Model Proto-Nucleotide Supramolecular Assemblies

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The observations that the nucleobases of RNA do not assemble in water as free bases or as mononucleotides presents a significant challenge to the proposal that RNA was the first genetic polymer of life.[1] We are investigating two potential solutions to this problem: 1) that certain prebiotic molecules facilitated nucleic acid polymerization by acting as nanometer-scale surfaces that stabilized base pair formation through non-covalent interactions (the ‘molecular midwife’ hypothesis), and 2) that RNA has evolved from an ancestral polymer that contained nucleobases that had an intrinsic ability to base pair at the monomer level (the hypothesis RNA is the product of evolution). Previously, small molecules that are known to intercalate between the base pairs of DNA and RNA have been shown to facilitate oligonucleotide polymerization and enhance the stability of duplexes with incompatible backbones,[2-3] results that lend support to the molecular midwife hypothesis. It has also been demonstrated that four plausibly prebiotic heterocycles that are similar in structure to the extant nucleobases of RNA base pair in aqueous solution at the monomer level to form linear supramolecular assemblies,[4-6] results that lend support to the hypothesis that the earliest nucleic acids contained different bases. We are now investigating the potential for known nucleic acids intercalators, as model midwife molecules, to alter the supramolecular structures formed by self-assembling model proto-nucleobases. In the absence of intercalators some of these model proto-nucleobases/nucleotides form assemblies that are microns in length (Fig. 1A). The introduction of cationic intercalators, such as ethidium, to these samples shorten the linear assemblies to discrete fibers of remarkably uniform length (Fig. 1B). In contrast, when purine is added to a solution containing proto-nucleobases/nucleotides that form shorter fibers (Fig. 1C), the assemblies are lengthened and appear to be extremely straight (Fig. 1D). The possible physical underpinnings of these observed phenomena and their potential relevance to the origins of nucleic acids will be discussed.

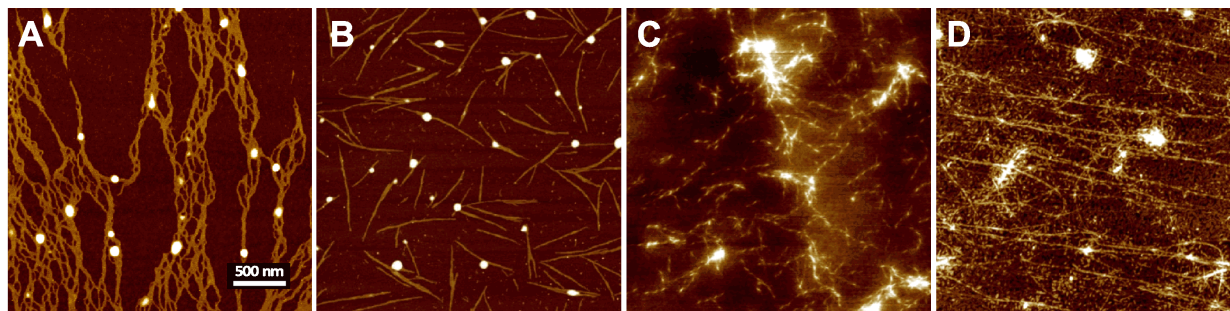


Figure 1 (A) AFM image of 2,4,6-triaminopyrimidine mixed with hexanoic acid-modified cyanuric acid. (B) Sample A after the addition of 1 mM ethidium. (C) AFM image of assemblies formed by melamine-ribosyl-monophosphate and barbituric acid-glucosyl-monophosphate. (D) Sample C after the addition of 50 mM purine.

[1] Engelhart AE and Hud NV (2010) *Cold Spring Harbor Perspect. Biol.* 2: 10.1101/cshperspect.a002196. [2] Horowitz ED *et al.* (2010) *Proc. Natl. Acad. Sci. USA* 107: 5288-5293. [3] Cafferty BJ *et al.* (2016) *Chem. Comm.* 52: 5436-5439. [4] Chen MC *et al.* (2014) *J. Am. Chem. Soc.* 136: 5640-5646. [5] Cafferty BJ *et al.* (2016) *Nature Commun.* 7. [6] Li C *et al.* (2016) *PCCP* 18: 20091-20096.