Divergent prebiotic synthesis of pyrimidine and 8-oxo-purine ribonucleotides
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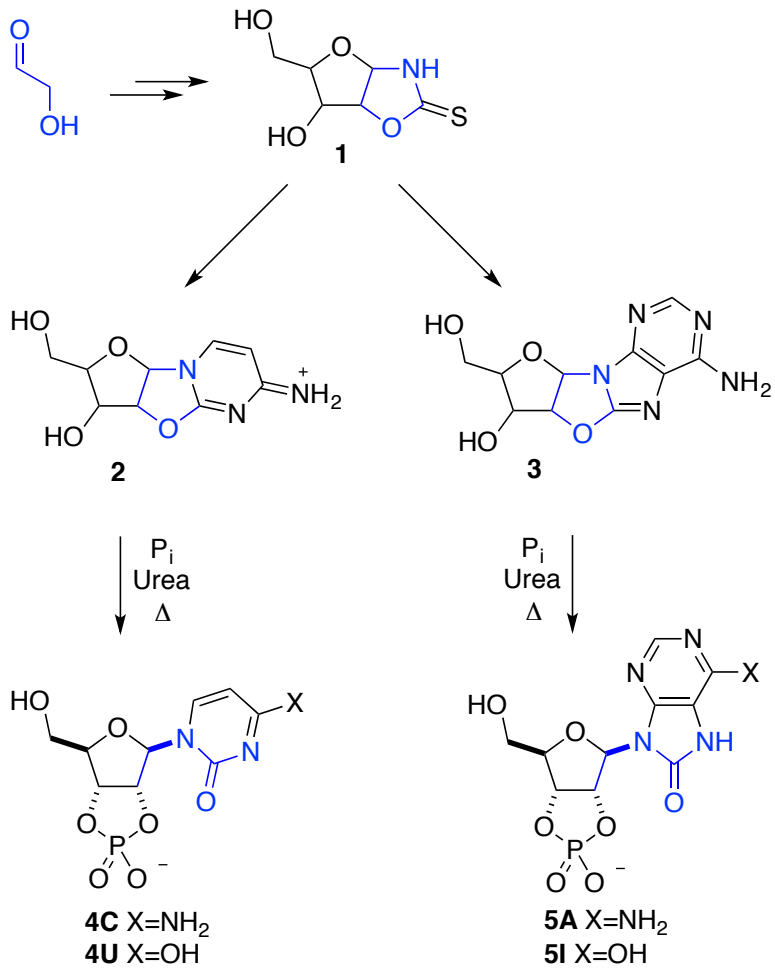
According to Dr. Matthew Powner from University College London (UK), a central issue for origins of life research is to elucidate the roots of biochemical information transfer, which underpins Darwinian evolution, inheritance, replication, and genetically encoded catalysis in life.

Dr. Powner believes that RNA is the leading candidate for the first biopolymer of life, due to its dual biological role in information transfer and catalysis, as well as the deep-seated evolutionary history of non-coding RNAs (for example, 16S and 23S ribosomal genes, tRNA genes and nucleotide binding domains are amongst the most conserved genomic regions in both microbial and non-microbial taxa).
"Accordingly," said Dr. Powner, "the 'RNA World' – an evolutionary period, before DNA and coded proteins, when biological genotype and phenotype were both maintained in RNAs – is the leading model for the origin of Darwinian evolution on Earth, but this model is contingent upon realizing the prebiotic synthesis of a pool of activated RNA monomers – The 'Molecular Biologist's Dream'".

Dr. Powner added: "Although prebiotic nucleotide synthesis has been investigated for more than 50 years an adequate solution to this problem remains elusive. Recently, remarkable progress has been made towards this challenge, but to date all syntheses have only accounted separately for pyrimidine or purine nucleotides."

He continued: "During my PhD with Prof. John Sutherland at the University of Manchester (UK), we developed a chemical strategy to synthesize the canonical pyrimidine nucleotides, cytidine and uridine, by a robust prebiotically plausible route (Powner et al. *Nature*, **2009**, *459*, 239–242). This was an important step towards understanding the origins of RNA, however two classes of RNA monomer are required to synthesize RNA, pyrimidines and purines. Although we had elucidated a robust synthesis of the pyrimidine nucleotides, there was no complementary purine synthesis. In fact all reported purine syntheses are contingent on unstable complex sugars, low yielding reactions, unselective transformations, large pH fluctuations, and, importantly, all operate under conditions that are incompatible with pyrimidine synthesis."

The issue of selectivity, rebranded as clutter, has surfaced as a major concern for those working in the area of prebiotic chemistry. Recently, however, Dr. Powner's group has resolved several major outstanding selectivity issues inherent to their previous work by demonstrating that their pyrimidine synthesis (as well as proteinogenic amino acid synthesis) can be controlled by the sequential crystallization of the essential prebiotic precursors, even from highly complex aqueous mixtures (Islam et al. *Nat. Chem.* **2017**, *9*, 584–589). "Remarkably, we found that the order of crystallization of nucleotide precursors predicted the order of reactions required to selectively build the canonical nucleotides, and these discoveries further emboldened us to revisit and revise our pyrimidine synthesis strategy," remarked Dr. Powner.



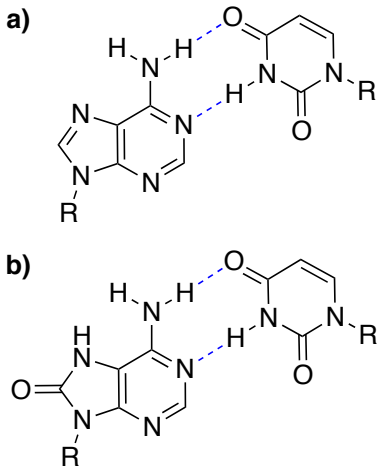
Scheme 1: Divergent synthesis of pyrimidine (**4C**, **4U**) and purine (**5A**, **5I**) nucleotides on a single oxazole sugar scaffold (**1**).

An essential element of the selection strategy required to orchestrate nucleotide assembly from complex mixtures was *in situ* synthesis of a molecular

chaperone, 2-aminothiazole, which contains a key sulfur atom that allows it to tracelessly direct ribonucleotide synthesis. Dr. Powner explained: "Exploiting the same rationale, that sulfur compounds or moieties could act as traceless directing groups, we considered how sulfur might be used to introduce the plasticity, controlled and site-specific activation required to divergently synthesize both purine and pyrimidine heterocycles on one single sugar scaffold. We focused our strategy on conformationally restricted, tethered purine assembly (Powner et al. *J. Am. Chem. Soc.* **2010**, *132*, 16677–16688; Powner et al. *J. Am. Chem. Soc.* **2012**, *134*, 13889–13895) to overcome the chemo-, regio- and stereo-selectivity problems inherent to nucleotide synthesis."

According to Dr. Powner, the paper in *Nature Communications* resolves the mutual incompatibility of purine and pyrimidine synthesis for the first time (Stairs et al. *Nat. Commun.* **2017**, 8, 15270), by recognizing that 8-oxo-purines, rather than the canonical purines, reveal an underlying generational parity to pyrimidine nucleotides. "We then exploited this equivalence to develop, through a single set of congruent reactions, a divergent synthesis of pyrimidine and 8-oxo-purine nucleotides from a common oxazoline precursor (**1**) (Scheme 1)," explained Dr. Powner. He continued: "Our divergent synthesis concurrently delivers regiospecific *N*1-pyrimdine and *N*9-purine glycosidation, and the β-*ribo*-stereochemistry of RNA to both purine and pyrimidine nucleotides."

"The simplicity and parity of our divergent reaction pathways attest to the unrealized potential of 8-oxo-ribonucleotides (**5**)," said Dr. Powner. He concluded: "The generational relationship between pyrimidine (**4**) and 8-oxo-purine (**5**) nucleotides opens the exciting possibility that 8-oxo-ribonucleotides may have acted as information carriers at the outset of biology (Scheme 2). Accordingly, we provide a new perspective on the original RNA molecules that would have harbored the first step of biology, and a simple chemical solution to delivering both purine and pyrimidine nucleotides at the origins of life."



Scheme 2: a) Watson-Crick base pair between adenine and uracil moieties. **b)** Watson-Crick base pair between 8-oxo-adenine and uracil moieties.

Biosketches

Shaun Stairs was born in the UK and received his undergraduate degree from the University of Cambridge (UK). He continued at Cambridge for his PhD under Dr. Finian Leeper developing new click chemistry methodologies for cell surface glycan labelling. He later undertook post-doctoral research with Dr. Matthew W. Powner at University College London (UK) where he worked on the prebiotic chemistry of purine nucleotides. His research interests encompass the origins of life, nucleotide and carbohydrate chemistries, green chemistry, 'click' and bioconjugation chemistrys and medicinal chemistry.

Arif Nikmal was born in Kabul (Afghanistan) in 1989 and came to the U.K. in 2004. He received his B.Sc. in Chemistry in 2011 and M.Sc. in Chemical Research in 2012 at Queen Mary University of London (UK). He then joined University College London (UK) to conduct his doctoral studies under the supervision of Dr. Matthew W. Powner. His scientific interests include prebiotic chemistry and organic chemistry.

Dejan-Krešimir Bučar obtained a B.Sc. in chemistry under the supervision of Dr. Ernest Mestrović at the University of Zagreb (Croatia), and a Ph.D. in chemistry from the University of Iowa (USA) under the guidance of Prof. Leonard R. MacGillivray. He then started his independent research career as a Royal Society Newton International Fellow at the University of Cambridge (UK), where he was kindly hosted by Prof. William Jones. While in Cambridge, he was also a Bye-Fellow at Sidney Sussex College. He recently joined the Department of Chemistry at University College London (UK) as UCL Excellence Fellow and lecturer. His research interests mainly evolve around molecular cocrystals and their applications.

Shao-Liang Zheng received his Ph.D. degree in Inorganic Chemistry under the supervision of Professor Xiao-Ming Chen at Sun Yat-Sen University (P.R. of China) in 2003. He then worked with Professor Phillip Coppens at the State University of New York at Buffalo (USA) as research scientist, emphasizing photocrystallographic studies of host-guest crystals. He joined Harvard University (USA) in 2009, where

he is currently the Director of X-ray Laboratory and Lecturer in Department of Chemistry & Chemical Biology. His interest is applications of advanced crystallography in chemistry and materials science and crystallography education.

Jack W. Szostak received his B.Sc. from McGill University (Canada) in 1972, and then under the supervision of Prof. Ray Wu his Ph.D. from Cornell University (USA) in 1977. He moved to the Sidney Farber Cancer Institute and Harvard Medical School (USA) in 1979, and then to Massachusetts General Hospital (USA) in 1984. He is an Investigator of the Howard Hughes Medical Institute, Professor of Genetics at Harvard Medical School, Professor of Chemistry and Chemical Biology at Harvard University, and the Alex Rich Distinguished Investigator at Massachusetts General Hospital. He is a member of the National Academy of Sciences and the American Philosophical Society, and a Fellow of the New York Academy of Sciences, the American Academy of Arts and Sciences, and the American Association for the Advancement of Science and has been awarded the National Academy of Sciences Award in Molecular Biology, the Sigrist Prize from the University of Bern, the Medal of the Genetics Society of America, Harold Urey Medal from the International Society for the Study of the Origin of Life, the Albert Lasker Basic Medical Research Award and the Nobel Prize in Physiology or Medicine.

Matthew W. Powner obtained his MChem in Chemistry at the University of Manchester (UK) in 2005, and then his PhD in Organic Chemistry working with Prof. John D. Sutherland in 2009. He continued his research at Manchester as an EPSRC Doctoral Prize fellow, before moving to the laboratory of Prof. Jack W. Szostak as postdoctoral fellow at Massachusetts General Hospital (USA). He joined University College London (UK) in 2011, where he is currently

Reader in Organic Chemistry. His research interests include the origins of life, photochemistry, nucleotide, peptide, lipid, and carbohydrate chemistries, green chemistry, ribozymes, multicomponent reactions, chirality and crystal engineering.