THE PREBIOTIC QUEST FOR RIBONUCLEOSIDE SYNTHESIS

Soumitra Athavale 25 Feb. 2016

LIFE'S QUINTESSENTIAL BUILDING BLOCK

The origin of life remains a daunting, unsolved puzzle. At the base of this overarching topic, the question of abiotic synthesis of bio molecular precursors, namely lipids, nucleotides, sugars and amino acids, stands as a challenge to the scientific community. Advances in molecular biology in the last sixty years illustrated the dual potential of RNA as a driver of hereditary and metabolic functions, leading to the suggestion that RNA may have played a central role in the early chemical evolution of life and served as a crucial informational polymer of the prebiotic age.[1] This hypothesis elevated ribonucleosides to be the most important targets for prebiotic chemists. However, absence of modern day synthetic techniques and protecting group methodologies on the primordial earth also make them the most challenging targets in prebiotic chemistry.

THE CLASSICAL DISCONNECT

An intuitive retrosynthetic analysis of nucleosides reduces these structures to sugars and nucleobases. This strategy was enforced by two seminal discoveries: Butlerow's formose reaction for sugar synthesis,[2a] and, Oro's purine synthesis from hydrogen cyanide.[2b] It was hoped that optimizing these two pathways and assuring the supply of ribose, purine and pyrimidine bases would pave the way for their ligation towards ribonucleosides (Figure 1). Pioneering work by Orgel[3] set the stage for the discovery of nitrogen heterocycles from cyanide and related molecules. On the other side, the classical formose reaction that gave a combinatorial explosion of multiple sugars had to be tamed to provide

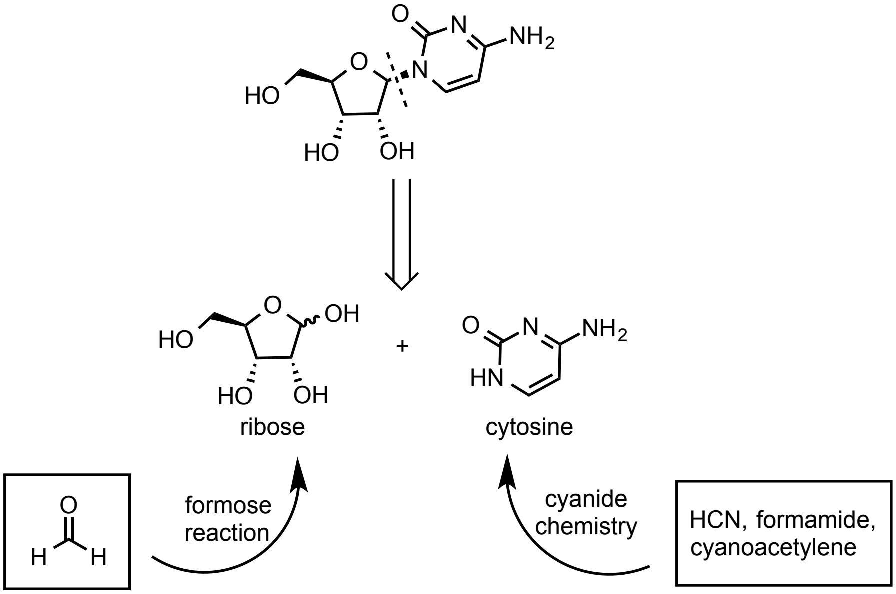

Figure 1. Classical approach to prebiotic ribonucleoside synthesis

product stability and selectivity.[4a] Eschenmoser[4b] and Benner[4a] recognized the ability of phosphate and minerals to control the formose reaction. Consequently, cyanide and formaldehyde chemistry seemed predisposed for nucleobase and sugar production respectively.

NEED FOR ALTERNATIVES

However, the subsequent *N*-glycoside bond formation was recognized as a serious challenge. This issue amongst other concerns in the previous steps, magnified the need for alternative strategies for ribonucleoside synthesis.[5a] Orgel's suggestion that sugar-aminooxazolines may be potential ribonucleoside precursors[3] was revisited in the past decade by Sutherland and co-workers who demonstrated a radically different strategy for pyrimidine-ribonucleoside synthesis.[5b] The route involves simultaneous assembly of a nascent sugar-nucleobase structure from simple organic precursors and circumvents the *N*-glycosidic bond challenge altogether (Figure 2).

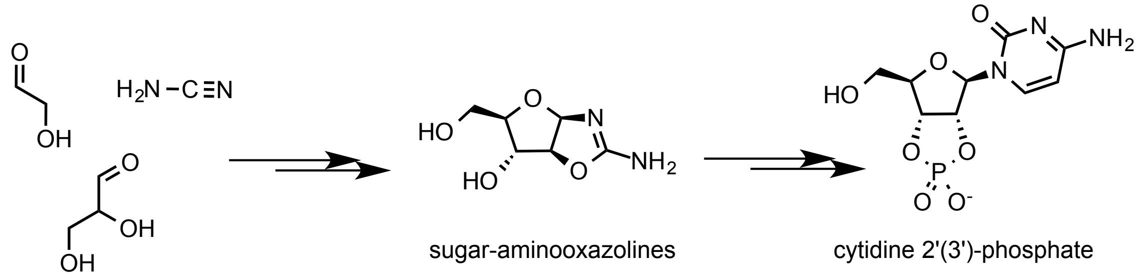

Figure 2. Synthesis *via* sugar-aminooxazolines

SUMMARY

Two major hypotheses describe the prebiotically plausible abiosynthesis of ribonucleosides. After more than fifty years of investigation, a convincing 'prebiotic total synthesis' still remains elusive. The varied aspects of ribonucleoside synthesis also provide a lens through which challenges in prebiotic chemistry can be illustrated. These challenges stand to test the ingenuity and imagination of organic chemists and promise to reveal as yet unknown universal chemical principles that guided constructive chemistry on the primordial earth.

REFERENCES

(1) Gilbert, W.; *Nature*, **1986**, *319*, 618.
(2) (a) Butlerow, A; *Liebigs Ann. Chem.,* **1861**, *120,* 295. (b) Oro, J.; *Nature,* **1961**, *191,* 1193.
(3) Orgel, L. E.; *Critical Reviews in Chemistry and Biochemistry,* **2004**, 99.
(4) (a) Kim, H.; Ricardo, A; Illangkoon, H.; Kim, M.; Carrigan, M.; Frye, F; Benner, S; *J. Am. Chem. Soc.,* **2011**, *133,* 9457. (b) Mueller, D.; Pitsch, S.; Kittaka, A.; Wagner, E.; Wintner, C.; Eschenmoser, A.; *Helv. Chim. Acta.,* **1990**, *73,* 1410.
(5) (a) Powner, M.; Sutherland, J.; Szostak, W.; *Synlett,* **2011**, *14,* 1956. (b) Powner, M.; Gerland, B.; Sutherland, J.; *Nature,* **2009**, *459,* 239.