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## Phosphorylation in Urea-Rich Eutectic Solvents

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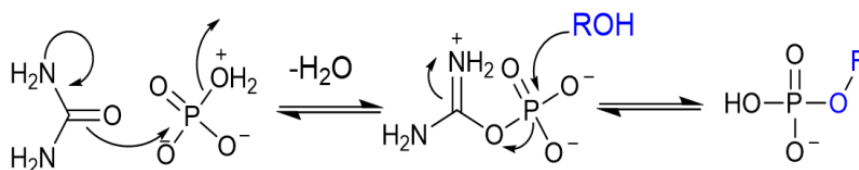
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**Introduction:** Phosphate is an essential component of DNA, RNA, and a range of metabolic compounds throughout biochemistry. On a prebiotic Earth, phosphate may have been equally valuable, providing nascent prebiotic molecules robust aqueous solubility and relatively thermodynamically stable chemical bonds. Nevertheless, the participation of phosphate in the earliest stages of the origin of life has been questioned due to major issues regarding its geochemical availability and chemical reactivity. On a prebiotic Earth, phosphate would have strongly associated with divalent cations in solution (primarily magnesium, iron, and calcium) to form insoluble precipitates that could have prevented phosphate from being incorporated into developing biochemical systems. In addition, the phosphorylation of nucleosides, a dehydration reaction, is thermodynamically unfavorable in aqueous environments. Recent work has focused upon addressing these issues of phosphate availability and reactivity through the utilization of urea-catalyzed phosphorylation (Figure 1) in eutectic solvents [1,2] or in the presence of borate.[3]

**Results and Discussion:** We are exploring urea-catalyzed phosphorylation in eutectic solvents, including prebiotically plausible eutectic solvents that are rich in urea. In eutectics consisting of urea, ammonium formate, and water (UAFW) high degrees of phosphorylation are observed with ribonucleosides or glycerol when evaporatively heated in the presence of soluble phosphate salts. Additionally, in the presence of  $\text{MgSO}_4$ , water insoluble hydroxylapatite ( $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ ) can be utilized as a phosphorylation source. Most recently, we have begun to explore additional eutectic solvents that were inspired by the UAFW eutectic system. Some of these solvents are showing significant improvements in phosphorylation of nucleosides, giving phosphorylation yields in excess of 80% under moderate heating.

These results demonstrate the ability of urea-rich eutectics to access urea-catalyzed phosphorylation in a liquid environment, and to mobilize previously sequestered phosphate for these reactions.[2] Overall, this work shows a prebiotic chemical path to phosphorylation of nucleosides that overcomes two of the major barriers to phosphorylation, helping support phosphate as a potential participant in the synthesis of biopolymers during the earliest stages of the origins of life.

**References:** [1] Gull M, Zhou M, Fernandez FM, Pasek, MA (2014) *Journal of Molecular Evolution*, 78, 109-117. [2] Burcar BT, Pasek MA, Gull M, Cafferty BJ, Velasco F, Hud NV, Menor-Salvan C (2016) *Angewandte Chemie International Edition*, 55 (42), 13249-13253. [3] Hyo-Joong K, Furukawa Y, Kakegawa T, Bitá A, Scorei R, Benner, SA (2016) *Angewandte Chemie International Edition* 55 (51), 15816-15820. [4] Steinman G, Lemmon RM, Calvin M (1964) *Proceedings of the National Academy of Sciences USA* 52, 27-30.



**Figure 1** – Proposed mechanism for urea-catalyzed synthesis of phosphate esters. [4]