

A Neural Network Potential Approach for the study of Phosphodiester Bond Reactivity

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The ability of RNA molecules to self-replicate by template-directed polymerization, together with the central role of RNA in contemporary biology for storing and transmitting genetic information, led to early proposals of RNA as a highly suitable candidate for the first self-replicating molecule. The activation of the mononucleotide phosphate groups would have been essential to facilitate polymerization in a prebiotic environment, while divalent ions were also found to be involved in this nonenzymatic polymerization process. In particular, magnesium ions, the dominant divalent cation in biological systems and the most available in the biosphere, are known to play a fundamental role in RNA stabilization and RNA catalysis ¹.

The most common catalytic pathway involves a two-metal ion-dependent mechanism, proposed to be the general pathway of many nucleases, such as the Ribonuclease H enzyme ². Other nucleases, like the human APE1 enzyme, have been observed to exhibit catalytic activity in presence of a single metal ion ³. As suggested by the RNA world hypothesis, contemporary catalytic polymerization mechanisms were probably preceded uncatalyzed polymerization facilitated by metal ions. Our aim is to understand the role of magnesium ions in the prebiotic formation of phosphodiester bonds.

The study of reactive mechanisms at quantum level is computationally very demanding. Machine learning-generated potential energy models offer efficiency comparable to classical force field models while maintaining ab initio accuracy and enabling submicrosecond simulations. However, their application to complex reactivity in condensed phases presents significant challenges. We employ an active learning workflow for the training of the potential energy models, while enhanced sampling techniques are used to generate reactive structures ⁴. Consequently, we achieve unambiguous characterization of reaction kinetics, thermodynamics, and mechanistic intricacies. The phosphodiester reaction mechanism has been investigated and found to favor a dissociative mechanism involving the formation of a loose, metaphosphate-like state with the assistance of surrounding water molecules ⁵.

Supported by these insights, we investigate the role of magnesium ions in the phosphodiester bond formation mechanism, exploring their impact on the energetic barrier and on the pKa of the phosphate group. These factors could have significantly influenced the reaction rates in a prebiotic environment.

Keywords: prebiotic chemistry, reactivity, neural networks.

¹J. C. Bowman, T. K. Lenz, N. V. Hud, L. D. Williams, et al., *Current opinion in structural biology* 2012, 22, 262.

²G. Palermo, A. Cavalli, M. L. Klein, M. Alfonso-Prieto, M. Dal Peraro, M. De Vivo, *Accounts of chemical research* 2015, 48, 220–228.

³M. M. Aboelnga, S. D. Wetmore, *Journal of the American Chemical Society* 2019, 141, 8646–8656.

⁴H. Wang, L. Zhang, J. Han, E. Weinan, *Computer Physics Communications* 2018, 228, 178–184.

⁵Z. Benayad, R. David, and G. Stirnemann. 2023. doi: 10.26434/chemrxiv-2023-8c1mt