Molecular mechanisms of phosphoester bond formation in abiotic conditions with reactive neural network potentials

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RNA, with its dual ability to store genetic information and catalyze chemical reactions, stands as a pivotal molecule in the quest to understand the origins of life: the earliest life forms might have relied solely on RNA[1]. However, the process of RNA polymerization, crucial for life's emergence, poses a formidable challenge in the absence of enzyme catalysts[2]. To shed light on potential mechanisms to expedite this reaction under abiotic conditions, a deeper comprehension of the uncatalyzed reaction mechanism is crucial. Experimental data remains sparse and inconclusive, while computational approaches face numerous hurdles. Factors such as significant entropic effects, involvement of solvent molecules, and the myriad of collective variables possibly involved in the reaction coordinates pose formidable challenges[3]. Neural network potentials offer a promising avenue, because they are in principle capable of addressing these obstacles by leading to reactive force fields with quantum accuracy[4]. However, their application to complex reactivity in condensed phases presents significant challenges.

We introduce a robust workflow to train such potentials, leveraging active learning of reactive structures through enhanced sampling methods, which is combined to the now well-established concurrential learning approach. Utilizing these models now enabling submicrosecond simulations, we employ enhanced sampling techniques, most notably transition path sampling, which enables to discern between various reaction pathways without presuming specific reaction coordinates. Consequently, we achieve unambiguous characterization of reaction kinetics, thermodynamics, and mechanistic intricacies[5]. Our findings favor a dissociative mechanism over an associative one, indicating the formation of a metaphosphate transition state with direct involvement of water solvent molecules. These insights not only rationalize previous ambiguous experimental results but also elucidate the temperature-dependence of the reaction rate, offering avenues for the design of more efficient abiotic catalysts and activating groups.

Keywords: Reactivity, Neural Networks, Enhanced Sampling, Free Energy Surface.

[1] K. Ruiz-Mirazo, C. Briones, and A. de la Escosura. Chemical reviews, 114(1):285–366, 2014.
[2] SCL Kamerlin, J. Florián, and A. Warshel. ChemPhysChem, 9(12):1767–1773, 2008
[3] F. Duarte, J. Åqvist, N. H Williams, and SCL Kamerlin. Journal of the American Chemical Society, 137(3):1081–1093, 2015.
[4] H. Wang, L. Zhang, J. Han, and E Weinan. Computer Physics Communications, 228:178–184, 2018.
[5] Z. Benayad, R. David, and G. Stirnemann. 2023. doi: 10.26434/chemrxiv-2023-8c1mt