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RNA's Thermodynamically Favored Position on Ice

Maximilian Bloom
University of Puget Sound

Steven Neshyba
University of Puget Sound

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Maximilian Bloom and Steven Neshyba*

University of Puget Sound Chemistry Department
1500 N. Warner St., Tacoma, WA 98416
mbloom@pugetsound.edu
nesh@pugetsound.edu
*Principal Investigator

Abstract

Previous molecular dynamics (MD) work simulated an 8-nucleotide RNA strand on ice, speculatively concluding RNA is stabilized by hydrogen-bonding with the ice's crystal lattice[1]. That conclusion is investigated by studying a simpler RNA dinucleotide, simulated using GROMACS[2] MD computer-simulations. Umbrella sampling results indicate that the most thermodynamically stable position for the RNA to bond is to the uppermost layer of the ice crystal's basal plane.

Introduction

The RNA World Hypothesis postulates RNA was the first self-replicating informational polymer, central to the origin of life. Self-replicating RNA ribozymes likely did not originate in room-temperature water, because RNA strands spontaneously cleave (hydrolyze) in that environment. Supercooled liquid water (-20°C) slows hydrolysis, sufficient for self-replication. The surface of ice at the same temperature may stabilize the RNA as much or more than water. This is investigated using Umbrella Sampling, a MD technique to find the relative energy minima.

Objectives

- Determine what causes RNA strands to lay flat on the ice
- Determine what stabilizes RNA on ice relative to liquid water at the same temperature
- Find the most stable position(s) for the RNA on the surface of ice

Materials and Methods

- Python 3 with libraries (Matplotlib, NumPy, SciPy, MDAnalysis, and NGLView)
- GROMACS 2020.3, TIP4P-D water model, periodic boundary conditions, timestep of 1 fs
- RNA in figure 2 modeled using Spartan Molecular Modeling 2020
- Umbrella sampling to find the Gibb's energy profile, used 40 * 20ns simulations
- 300ns selection from 1 microsecond simulation used to create contour diagram
- Simulations at -10°C for contour diagram, and at -15°C for Gibb's energy diagrams

Results

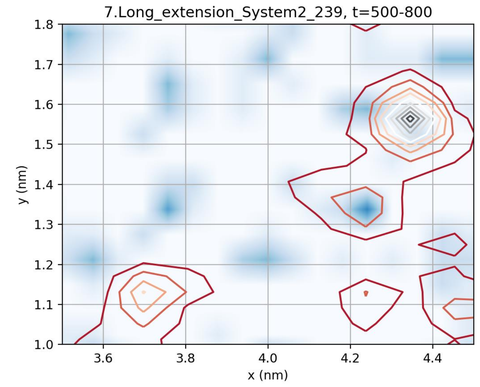


Figure 1. (above) Top-down view of ice. Contour diagram of the x-y position of the anionic phosphate oxygen in the middle-last third of the simulation. The amount of time spent in a location is indicated by color, with grey being the most favored. The blue shading represents the ice molecules.

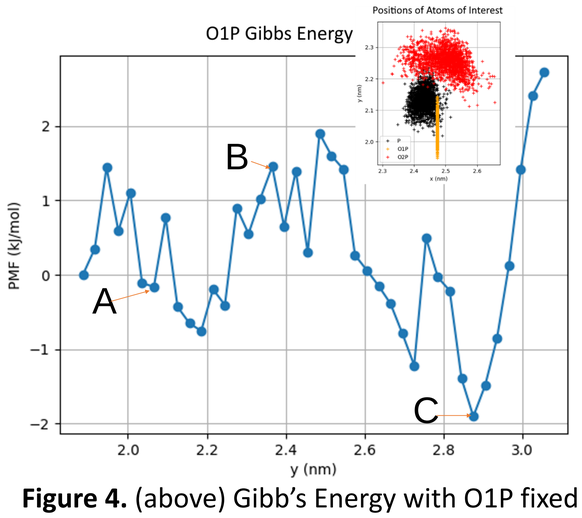


Figure 4. (above) Gibb's Energy with O1P fixed down. Energy Minima at "A" and "C". Positional scatterplot superimposed.

Figure 2. (right) Depiction of the studied C-C dinucleotide, hydrogen bonding to an 'up-buckle' ice molecule. Atoms are colored as follows: P (orange), O (red), H (white), N (blue), and C (gray).

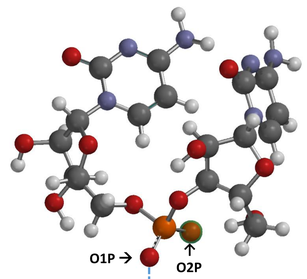


Figure 3. (right) Depiction of hexagonal ice crystal structure. Hydrogen in black, oxygen in white.

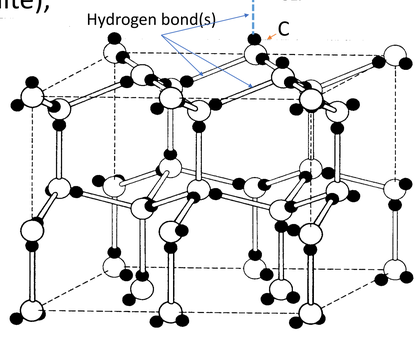
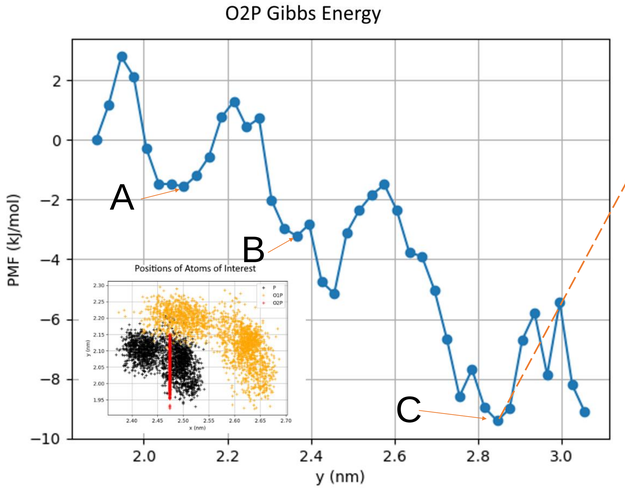


Figure 5. (below) Gibb's Energy with O2P fixed down. Shows additional local energetic minimum at interstitial position "B".



Conclusions

- RNA rapidly configures itself on the surface of ice to allow for the anionic phosphate oxygens to bond with the ice, no matter the starting orientation of the RNA molecule above the ice.
- O2P and O1P both bond to the ice when unconstrained. When O2P is bonding to ice, additional interactions between the nucleotides and the ice led to different behavior vs O1P.
- The most stable position is when anionic phosphate oxygens (O1P and O2P) accept a hydrogen bond from the top ice crystal layer, specifically an 'up-buckle' ice molecule.

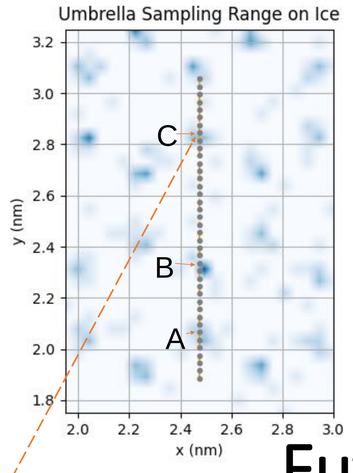


Figure 6. (left) Top-down view of ice. Blue shading highlights ice lattice positions. Grey dots indicate starting positions for each of the 40 umbrella sampling simulations used to gather statistics for calculating the potential of mean force and the Gibb's free energy. The anionic phosphate oxygen was fixed in the x dimension, and umbrella sampling was performed in the y-dimension across a repeating ice crystal pattern. A and C represent points on top of 'up-buckle' ice molecule, and B is on top of a 'down' ice molecule. 'Up-buckle' ice molecules, such as A and C, are hypothesized to be stable positions for the ice based on Gibb's energy profile.

Future Directions

Nucleotides as the cause of O2P's behavior could be investigated by simulating the phosphate backbone alone on ice. Investigating other combinations of nucleotides and longer strands could build a framework for RNA's behavior on ice. This could be used to judge to likelihood of the RNA World on Ice hypothesis. This work could also be expanded by finding the 2-dimensional Gibb's energy surface to confirm the most stable position on ice.

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References

1. Gladich, I.; Berrens, M. L.; Rowe, P. M.; Pereyra, R. G.; Neshyba, S. Solvation and Stabilization of Single-Strand RNA at the Air/Ice Interface Support a Primordial RNA World on Ice. J. Phys. Chem. C 2020, 124 (34), 18587–18594.
2. Abraham, M. J., Murtola, T., Schulz, R., Páll, S., Smith, J. C., Hess, B., Lindahl, E. GROMACS: High performance molecular simulations through multi-level parallelism from lap-tops to supercomputers. SoftwareX 1–2:19–25, 2015.