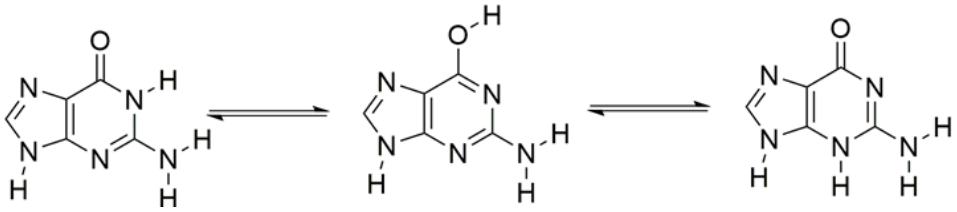
Tautomerism of nucleic acid building blocks at ambient and extreme conditions

Lukas Eberlein, Nicolas Tielker, Stefan M. Kast

Fakultät für Chemie und Chemische Biologie, TU Dortmund, Germany

Extreme conditions such as high hydrostatic pressure or temperature as exhibited at deep sea hydrothermal vents, where water can exist either in liquid or in a supercritical form, influence structure and behavior of biologically active molecules. Knowledge of their environmentally modulated conformational, tautomeric and protonation state preferences is essential to understand their behavior in solution and mode of action in the organism. An accurate pH-, temperature- and pressure-dependent characterization of these properties in solution is of vital importance but poses a challenge to both experiment and theory even for well-studied compounds such as nucleic acid building blocks. Experimentally, rapid conformational changes and the fast proton transfer between multiple tautomeric forms make elucidating these equilibria cumbersome especially under extreme conditions, while the theoretical task is complicated due to the environmental effect on both electronic structure and solvent distributions.

We here predict tautomeric and conformational equilibria of natural and non-natural nucleobases in water under various environmental conditions by the methodology employed within the SAMPL blind prediction challenges for tautomers, distribution coefficients and acidity constants [1-3] of small molecules. Solvent effects on energetics and spectroscopic parameters in quantum-chemical calculations are considered using the "embedded cluster reference interaction site model" (EC-RISM) developed by us, which has been demonstrated to provide accurate estimates of thermodynamic quantities and spectroscopic features in solution even for high pressure solvents [4]. Refining the EC-RISM workflow with a coupled-cluster extrapolation, which allows treatment of electron correlation effects with high accuracy, is used to further improve the quality of tautomer predictions.



We obtain the contributions of all accessible states to the molecular ensemble as a function of pH, pressure and temperature as well as their respective relevance for understanding experimental NMR spectra. Preliminary results indicate remarkable tautomeric stability of natural nucleobases which could hint at tautomerism being an evolutionary relevant chemical optimization target.

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[4] R. Frach, P. Kibies, S. Böttcher, T. Pongratz *et al.*, *Angew. Chemie Int. Ed.* **2016**, *55*, 8757-8760.