pH- and pressure dependent tautomeric and conformational equilibria

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Knowledge of conformational and tautomer preferences of a molecule is essential to understand its behavior in solution and its mechanism of action in the body. The accurate pH-dependent characterization of the conformational and tautomer equilibria of ionizable species in aqueous solution is a challenging task even for well-known compounds such as the neurotransmitter histamine that is involved in the regulation of multiple physiological functions like gastric acid release and in immune system responses. The prediction of physiologically relevant protonation states and preferred conformations in solution under various conditions including pH and pressure/temperature variations is therefore important not only for drug discovery but also for understanding biochemical processes of a vast number of lifeforms that are accommodated to extreme conditions such as near deep oceanic black smokers. High pressure and/or temperature may affect the protonation patterns of biomolecules like nucleobases, leading to fundamental questions regarding the robustness and universality of the genetic code.

Because of the rapid conformational changes and the fast proton transfer between multiple tautomeric forms, it is difficult to elucidate such problems experimentally, especially under extreme conditions. We here present a computational approach, supported by experimental data, to overcome this problem with the goal to characterize the complete spectrum of tautomeric and underlying conformational states. Conceptually footed in the methodology employed within the SAMPL2 and SAMPL5 prediction challenges for tautomer equilibria [1] and partition constants, [2] we here combine exhaustive tautomer and conformational sampling followed by GIAO-NMR and vibrational frequency calculations in aqueous solution for model systems such as histamine and nucleobases. Solvent effects on energies and spectroscopic parameters in quantum-chemical calculations are considered using the polarizable continuum model (PCM) and the embedded cluster reference interaction site model (EC-RISM) integral equation theory. This methodology has been demonstrated to provide accurate estimates of thermodynamic quantities and spectroscopic features in solution even for high pressure solvents. [2,3] As a key result, we obtain the contributions of all accessible states to the molecular ensemble as a function of pH and pressure as well as their respective relevance for understanding experimental FTIR and NMR spectra.

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