

## Abstract

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The driving force of assembly formation of caffeine in water and dissociation of these assemblies in 8 M urea has been studied using molecular dynamics as the tool. All the simulations have been conducted in an isothermal isobaric ensemble where, temperature at 298 K and pressure at 1 atm. As the first step, a reliable force field for caffeine was developed and validated. The potential model yielded upon fine-tuning force field parameters of caffeine showed a very good agreement with experimental results such as enthalpy, diffusion coefficient etc. After the validation, newly developed force field for caffeine was used in all the subsequent simulations.

Two simulations, one in water and the other in 8 M urea, each containing a ladder of eighteen caffeine molecules were run for 4 ns and at the end, their structures were compared. Comparison of these structures revealed that formation of assemblies of caffeine in water while disperse of caffeine molecules in 8 M urea. This was evidenced by the variations of DOP and SAS parameters as a function of simulation time. Interaction energy of caffeine-caffeine indicated that separation of caffeine molecules from each other in 8 M urea while aggregation of caffeine molecules in aqueous media. Variation of interaction energy of caffeine-solvent in 8 M urea with time showed that favorable binding of urea and water with caffeine while this interaction was higher than the interaction energy of caffeine-water in water medium, indicating that entropic influence in the dissociation of caffeine aggregates in 8 M urea. Accumulation of urea around caffeine was clearly seen by the prominent peak in the RDF of urea and also by the reduction of caffeine diffusion in 8 M urea. The investigation of number of hydrogen bonds of caffeine confirmed that interaction of caffeine with urea and water is largely mediated through hydrogen bonds.

The association free energy of caffeine indicated that formation of assemblies in water is energetically favorable. Though dissociation energies are not reflecting the dissociation is energetically favorable, but the change of entropy in 8 M urea with time indicated that dissociation of assemblies is mainly governed by the entropy. Also the affinity of urea to bind with caffeine gives a considerable weight. The dipole moment analysis also indicated that dimer formation is facilitated by the proper alignment of dipole moment of caffeine molecules.