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New molecular mechanics force field for caffeine: A molecular dynamics simulation study

Rangana Sanjeewa and Samantha Weerasinghe
Department of Chemistry, University of Colombo, Colombo 03

Hydrophobic interactions determine the shape and the functionality of biological systems. However, chemical denaturants such as 8M urea disrupts these hydrophobic interactions. Experimental and theoretical studies have been conducted to understand the effects of chemical denaturants on hydrophobic interactions. Molecular dynamics simulation is the best tool that one can apply to study atomic kevel description of denaturing of biological molecules. However, due to the size of biological molecules it would be computationally expensive to conduct a detail study of unfolding/denaturing effect of chemical denaturants.
It had been found, experimentally, that caffeine forms aggregates in aqueous medium and disperse those aggregates in 8M urea. Since its smaller size it would be an ideal candidate for molecular dynamics simulation study. However, accuracy of simulation results entirely depends on the quality of the force field used. Despite the many studies that have been done on caffeine, a suitable force field is yet to be developed. The present work focused on the development of a molecular mechanics force field for caffeine in aqueous and co-solvent media.
A new molecular mechanics force field was developed for the caffeine molecule by considering atom types, structural and chemical properties of it with the use of molecular simulation methods. Experimental properties of caffeine in water and caffeine in aqueous urea solutions were incorporated to validate the new force field.

Property		**Experimental**	**This work**
Enthalpy/ kJ mol^{-1}		3.432 ± 0.042	3.428 ± 1.621
Diffusion coefficient/ 10^{-9} m^2 s^{-1}	Water	0.773	0.816 ± 0.412
	0.8 m Urea	-----	0.725 ± 0.242
No. of H bond of caffeine		4	4.2 ± 0.53

At the end, aggregation of caffeine in water and dispersion of caffeine molecules in 8M urea, which were found in laboratory experiments, were demonstrated clearly using two; four nanoseconds long molecular dynamics simulations. A new parameter, *distance-order-parameter (DOP)*, was introduced to indicate the aggregation/dispersion of solute molecules in the solvent.

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