



Free Energy Calculations of Phenothiazine Dyes in Homogeneous and Micro-Heterogeneous Media

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Keywords: Phenothiazines, Aggregation, Methylene Blue, Free Energy, Molecular Dynamics.

INTRODUCTION

Photosensitizers (PS) are light-sensitive chemical compounds that have been used in several areas. In medicine occurs the most promising application of PS in Photodynamic Therapy (PDT), a therapy for neoplastic diseases. Upon irradiation, PS can be promoted to excited states and induce the formation of reactive oxygen species (ROS) such as singlet oxygen ($^1\text{O}_2$),¹ and are responsible by the cell death.² However, the aggregation of PS can decrease the photochemical efficiency of these compounds. In this work, we used molecular dynamics simulations to investigate the molecular aggregation of phenothiazine derivatives: Methylene Blue (MB), a well-known phenothiazine dye and DO15. Both compounds present desirable properties for PS in homogeneous and micro-heterogeneous media.

METHODS

Molecular dynamics simulations were carried out for monomers and dimers of PS. Cubic cells were build with 4000 solvent molecules in NPT ensemble using GROMOS 53a6 force field. The micro-heterogeneous solutions were modeling adding urea in aqueous media. The properties was obtained in a running-length of 20 ns. Free energy of solvation was estimated by using the Thermodynamic Integration (TI) method. All simulations were performed using GROMACS 4.5 suite.

RESULTS AND DISCUSSION

The free energy computed using TI for the dimer formation process in water at 298K produces a value of $-114.9 \text{ kJ}\cdot\text{mol}^{-1}$ for ΔG_{dimer} , with ΔH_{dimer} and $T\Delta S_{\text{dimer}}$ being -91.2 and $23.7 \text{ kJ}\cdot\text{mol}^{-1}$ respectively. These values are in line with the ones computed for the same process using several distinct solvation methods and reproduce the experimental finding that dimerization in water is mostly driven by enthalpy. For urea aqueous solutions, MD simulations reveal a clear preferential solvation effect of urea in both monomeric and dimeric forms of MB. In 2M urea a The number of molecules over the first solvation shell. Calculations for the $\Delta\Delta H$ shift when adding urea presented a clear enthalpic contribution of 14.0 kJ mol^{-1} favoring the monomer. Qualitatively, this result is in agreement with experimental observations.³

CONCLUSIONS

Structural analysis of the solutions indicate a increasing density of urea molecules around MB at high concentrations. Preliminary results suggests that the methodology overestimates the desestabilization effects of urea in MB monomers. Comparing to the water, the energetic cost to solvate the dimer is higher than solvate the monomers in water/urea mixtures, in a enthalpic point of view. Further calculations for DO15 molecule are necessary in order to understand its molecular mechanism of aggregation and the impact of urea on the stabilization of these dimers.

ACKNOWLEDGMENTS

The authors acknowledge CAPES and UFABC for financial support.

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XVIII Simpósio Brasileiro de Química Teórica – SBQT 2015
Pirenópolis – GO, 22-25 Novembro de 2015

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