Conformational flexibility of small molecules in different solvent environments

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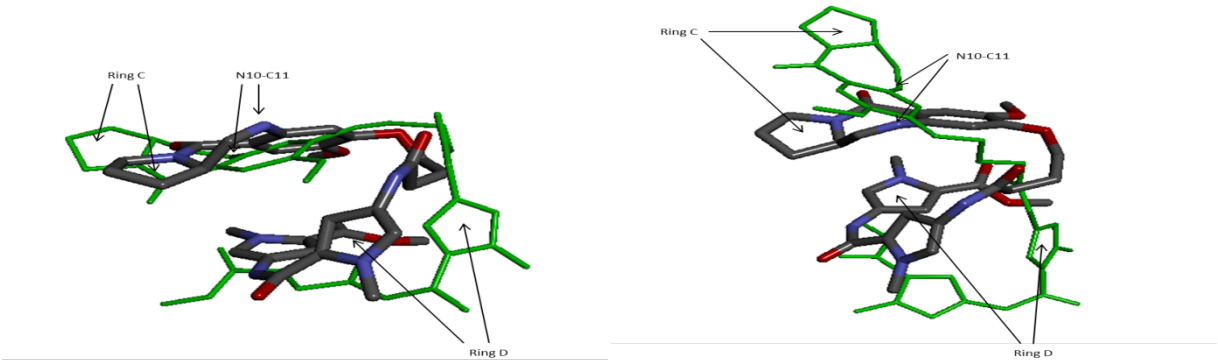
The pyrrolobenzodiazepines (PBDs) are a family of DNA sequence-selective antitumour agents, the best known member of which is anthramycin [1]. They bind in the minor groove of DNA, forming a covalent bond between the electrophilic N10-C11 imine moiety of the PBD and the N2 amino group of a guanine.

GWL-78 and SJG-136 are examples of PBD monomers and dimers, respectively, and the latter agent is presently in Phase II clinical trials in ovarian cancer and leukaemia. This study involves the use of molecular dynamics simulations to study the effect of different solvent environments on the conformation of GWL-78, SJG-136 and anthramycin. Calculations have been carried out using the Desmond 2.2 software [2] and OPLS_2005 force fields [3] with Maestro 9.2 as the Graphics User Interface [4]. 2000 conformations were obtained during 10 ns of simulations, and these were separated into five clusters. The most frequently observed conformations for each cluster were then compared by calculating RMSD values.



Superposition of the most frequent conformations extracted from molecular dynamics simulations of GWL-78 in two different solvent systems. Thick sticks in CPK colours represent the GWL-78 conformation in explicit water with 100 mM NaCl. The thin green sticks show the conformation of GWL-78 simulated in explicit water with 100 mM NaCl, and with an additional H_3O^+ (left)/OH^- ion (right).

Significant conformational changes of these flexible molecules were observed for different pH and salt concentrations, potentially providing information relating to how these molecules interact with DNA prior to the formation of covalent bonds. Our results suggest the importance of the explicit solvent composition for molecular dynamics studies. Further work is required to evaluate whether similar conformational behaviour is observed using different molecular dynamics software and force fields.

References

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