The Conformational Analysis of Brevetoxin A, Brevetoxin B, and Ciguatoxin

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Brevetoxin A, Brevetoxin B, and Ciguatoxin are polycyclic marine neurotoxins produced by the dinoflagellates *Kerenia brevis* for Brevetoxins and by *Gambierdiscus toxicus* for Ciguatoxin. They are biological agents that have been identified as the cause of neurotoxic shellfish poisoning and large-scale food poisoning of non-microbial organisms. These molecules function by binding to voltage-gated sodium ion channels in the fish, creating an extended ion channel opening time at lower membrane potentials. The conformations of these toxins is thought to greatly influence their binding behavior and corresponding toxicity, therefore it is important to research their conformational flexibility. The medium sized rings that make up the structures allow for relative flexibility of the molecule.

The conformational searches of these molecules were performed using the Low Mode and Monte Carlo search methods in a one to one ratio and in both water and chloroform as solvents for each toxin. The potential energy surfaces were exhaustively searched to find the lowest energy structures; the most relevant for research purposes. Ensembles were then generated using XCluster to find geometric similarities.

For the searches regarding Brevetoxin A, 234 structures were found in water and 91 in chloroform. For Brevetoxin B, 105 structures were found in water and 88 were found in chloroform. And for Ciguatoxin, 957 structures were found in water and 2,243 structures were found in chloroform. For each molecule the lowest energy structure found in each solvent model was very similar even though relative energies differed.

Brevetoxin A, Brevetoxin B, and Ciguatoxin all offered both linear and curved conformers. For all molecules, a more linear conformation was favored as the lowest energy structure. The tail of Brevetoxins A and B, rings HIJ and IJK respectively, are rigid with each 6-membered ring adopting a chair conformation, this is also seen with the ABC ring system of Ciguatoxin. Each molecule appears to have a region in the middle of its structure that most greatly influences the conformational flexibility; the EFG ring system in Brevetoxin A, the DE and H rings of Brevetoxin B, and the EFG ring system of Ciguatoxin.

More analysis will be done using XCluster to determine the conformational flexibility of each toxin. Quantum calculations will also be performed with Jaguar to more exhaustively define the lowest energy structures of Brevetoxin A, Brevetoxin B, and Ciguatoxin.