Conformational Exploration of the Impacts of Solvent, Chirality, and Ring Fusion on Sulfated Neurosteroids

D. Nicole Smith, Julia A. James, Lisa Gentile, and Carol A. Parish
Chemistry Department, University of Richmond, Richmond, VA 23173

Ionotropic glutamate receptors (iGluRs) have been shown to play a key role in ischematic stroke cascade, schizophrenia, and other neurodegenerative diseases, like Alzheimer's, Parkinson's, and Huntington's. There are currently very few experimental structures of iGluRs. Therefore, in order to understand more about the binding behavior, two neurosteroids that are known to bind and modulate iGluRs, pregnenolone sulfate (PS) and 3α-hydroxy-5β-pregnan-20-one sulfate (PregaS) were examined through conformational searches. The original goal was to perform a conformational search of the steroids in water using the Low Mode Monte Carlo (LMMC) conformational search algorithm, but after reviewing the preliminary results, it was determined that the search should be expanded to take into account the possible affect of the solvent. In order to adequately explore all conformational possibilities, more searches were also conducted using the pure Low Mode (LM) and the Large-scale Low Mode (LLMOD) methods. By using a variety of algorithms and starting each search from a different point on the potential energy surface, it was more likely to achieve an exhaustive search of available conformational space. Also, because of the uncertainty of the location of the binding site each conformational search was conducted in a variety of solvent environments. Water, the original solvent, was utilized to model a hydrophilic environment while chloroform and octanol were used to model less polar (than water) and hydrophobic environments that are possible inside the cell membrane. Unfortunately, the chloroform and octanol Generalized Born – Surface Area (GB-SA) continuum solvent models were not parameterized for the sulfur atom in the sulfonate group. In order to counteract this problem the sulfonate moiety was replaced with a carbon-based dihydroxyethanolate group that had a similar tetrahedral geometry and charge distributions. There was only one main conformation identified for each structure; this conformation was not dependent on the solvent used. But a distinct structure was determined for both PregaS and PS. The key difference lies in the conformation of the first ring. Our findings further suggest that PregaS and PS have independent binding sites along the S1 and S2 domains of the ionotropic glutamate receptor. Also, the fact that the analogue steroid structures did not change conformation in different solvents attests to the rigidity of the structure. This suggests that as the steroid passes through different parts of the receptor, the solvent within those elements will not change the steroids' conformation.