The Influence of Solvent, Stereochemistry and the Carbon Ring Backbone on the Conformation of Sulfated Neurosteroids

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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. In order to understand more about the flexibility of small molecules that bind to and modulate iGluR proteins, we conducted a conformational search of the neurosteroids pregnenolone sulfate (PS) and 3α-hydroxy-5β-pregnan-20-one sulfate (PregaS). These steroids are of interest because of their diverse impact on the iGluR despite the similarity in structure, except for the double bond between C5 and C6 and the chirality of the C3. By using a variety of algorithms and starting each search from a different point on the potential energy surface, we were more likely to achieve an exhaustive search of available conformational space.

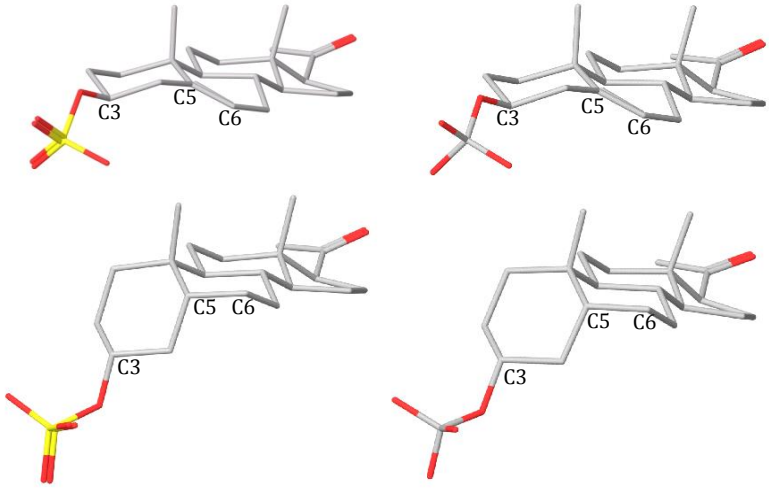

Figure 1. The lowest energy conformations of PregaS, PS and their analogue structures. From top left: PS, PS analogue, PregaS, PregaS analogue

Also, because the location of the binding site is currently unknown, each conformational search was conducted using the water, chloroform and octanol solvents to model hydrophobic, hydrophilic and ampiphilic environments. The chloroform and octanol Generalized Born – Surface Area (GB-SA) continuum solvent models were not parameterized for the sulfur atom in the sulfonate group bonded to C3 (See Figure 1); therefore an analogous non-sulfonated structure was created.

Results will be presented that indicate that PS and PregaS are relatively rigid molecules with limited conformational flexibility, with little variation nor dependence on the method and solvent used. To determine the impact of the ring system in the final shape of the neurosteroids, the conformations of cyclohexane, dicyclohexane, tricyclohexane, and tricyclohexane cyclopentane were also determined. The structural importance of the double bond in PS was also examined using desaturated ring analogues, with a double bond in the same position as the steroid. The stereoisomers of both the sulfated and analogous structures were examined via the same method and solvent combinations and exhibited similar trends to the original nerosteroids.