Creation of an Atomistic Force Field for Lipid Simulation

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A number of force fields have been developed and are utilized for the study of peptides, proteins, RNA and DNA. However, there are a limited number of force fields available for modeling lipids, and none that are easily usable with the AMBER program. A carbohydrate force field called Glycam06[1] has been recently developed, and contains some of the necessary parameters for modeling lipids using AMBER. Extension of this force field to lipids will allow for the investigation of an array of biological systems, including the modeling events that occur on a cell's surface. For instance, the lipid force field will be a tool that can be used to study the interaction of amyloid plaques with a cell membrane, a phenomenon that has been linked to an array of conditions known as amyloidoses diseases. This extension is the first continuation step towards the development of a single force field that can be applied to all types of biological systems, which was how Glycam06 was designed. Such a force field will provide the tools necessary to understand all of these systems on a level that surpasses the bounds of experimental analysis.

Here we will focus on the creation of a force field for lipids. The parameters that are missing from the Glycam06 force field are those that correspond to carbon-carbon double bonds that may be found in the tails of lipids. These values are generated through the creation of a small training set of simple alkenes such as ethene, tetramethylethylene, and isobutene. Relevant potential energy surfaces are computed at the B3LYP/6-31++G(2d,2p)//HF/6-31G(d) theory level. Systems involving van der Waals forces known to be insufficiently described by density function theories will therefore be calculated at the MP2/aug-cc-pVDZ level of theory. The OPLS-AA parameter set contains all of the non-bonded van der Waals parameters required to model lipids, and will therefore be added to this force field as well. An example of torsion values generated from the parameterization of ethene is shown below in Figure 1.

In addition to the lipid force field, we would like to develop prep files that correspond to different lipid components. There are estimated to be over 100 different kinds of lipids. Generally, each lipid molecule is a composition of three different chemical components, illustrated in Figure 2. Creating an individual prep file for each class of lipids will result in an easily accessible database of residues that can be used to model a wide variety of lipid molecules.

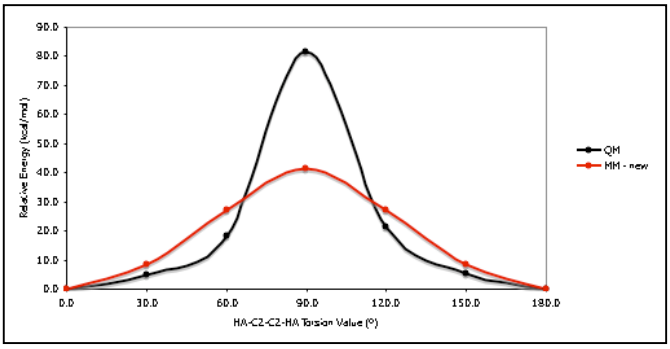

Figure 1. To the right is a graphical representation of the relative energy for the H-C-C-H torsion geometries of ethene. The black line indicates the values that were obtained from quantum mechanics calculations using Gaussian. The red line represents the values obtained using the new parameters with AMBER9. This energy transition state was experimentally determined to be 65 kcal/mol at a temperature between 425 and 525 K.

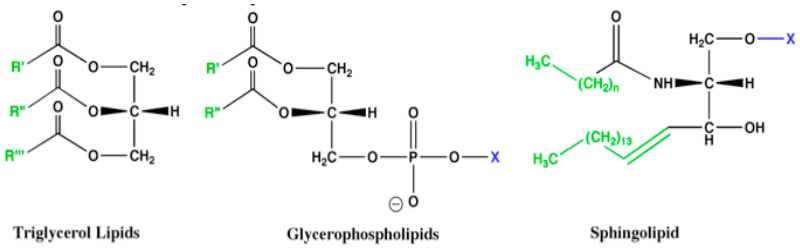

Figure 2. Chemical components of lipids represented for three different classes of lipids. The fatty-acid component is shown in green, the glycerol-based residue is shown in black, and the head group is shown in blue.

[1] Kirschner, K.N., Yongye, A.B., Tschampel, S.M. et al., GLYCAM06: A Generalizable Biomolecular Force Field. Carbohydrates. *J. Comp. Chem.*, accepted, July 2007.
[2] Nevins, N., Chen, K., Allinger, N.L., Molecular Mechanics (MM4) Calculations on Alkenes. *J. Comp. Chem.*, accepted, September 1995.