

*Using PC Model, answer the questions below. If you have questions/issues working on this Problem Set, do please consider using Piazza to address them.*

1. In the MMFF94 and AMBER force fields, what are the parameters for the harmonic force constants (mdyne/Å) and equilibrium bond lengths (Å) for the bond between an alkyl carbon and an ammonium group as might be found in, say,  $\text{H}_3\text{C}-\text{NH}_3^+$ ? How closely do the two sets of constants agree? Discuss the significance of any difference.

In the MMFF94 force field (as recorded in the mmff94.prm file), an alkyl carbon is atom type 1 and a quaternary nitrogen atom,  $\text{NR}_4^+$ , is atom type 34. In the AMBER force field, an  $\text{sp}^3$  carbon is atom type 1 and an  $\text{sp}^3$  nitrogen is atom type 20. No distinction is made for a neutral vs. a cationic  $\text{sp}^3$  nitrogen in the AMBER force field.

The parameters for the bonds between the above listed atom types are:

MMFF94

bond      1   34   3.8440   1.4800

AMBER

bond      1   20      367.0   1.4710

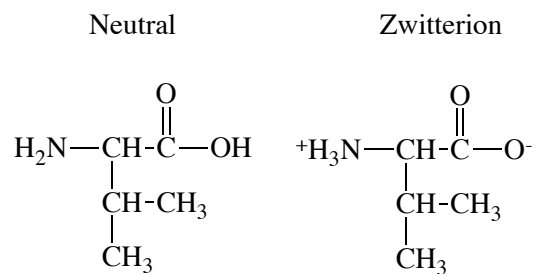
While the equilibrium bond distances are quite close (1.4800 vs. 1.4710), the values for the force constant cannot be directly compared as written above since they do not have the same units. As can be found in the PCModel manual, the units for the MMFF94 force field are in mdyne  $\text{\AA}^{-1}$  while the AMBER force field is in  $\text{kcal mol}^{-1} \text{\AA}^{-2}$ . To convert from mdyne  $\text{\AA}^{-1}$  to  $\text{kcal mol}^{-1} \text{\AA}^{-2}$  one must multiply the MMFF94 constant by a factor of  $143.84 \text{ kcal mdyne}^{-1} \text{ mol}^{-1} \text{\AA}^{-1}$ . This gives us a force constant of  $552.9 \text{ kcal mol}^{-1} \text{\AA}^{-2}$ . However we still cannot directly compare the two force constants. Looking more carefully at the expressions for bond stretching in both parameter files, one finds that in the MMFF94 force field the expression has the usual Hooke's Law form ( $\frac{1}{2}kx^2$ ) while in the AMBER force field the  $\frac{1}{2}$  is absorbed into the value of the parameter k. Therefore, to directly compare the two parameters we should multiply the AMBER force constant by two giving 734

kcal mol<sup>-1</sup> Å<sup>-2</sup>. Now, although we are comparing force constants that have the same energy and the same units, we can see that the two values are quite different (553 vs. 734 kcal mol<sup>-1</sup> Å<sup>-2</sup>).

There are (at least) two reasonable explanations for the observed substantial difference (~30%) in the harmonic force constants. One possibility derives from the two force fields having different functional forms: AMBER is purely harmonic while MMFF94 has higher order polynomial terms. So, for instance, MMFF94 could reduce the steepness of a “too-tight” harmonic (parabola) curve on its dissociative side by including an appropriate cubic term. However, since the MMFF94 force constant is *less* tight than that for AMBER, this cannot be the reason.

Instead, it appears simply to be a question of gaining flexibility from defining additional atom types. If we inspect the MMFF94 parameter file to find the force constant between an alkyl carbon (type 1) and an “amine nitrogen” (type 8), we find a force constant of 5.084 mdyne Å<sup>-1</sup>, which is 731 kcal mol<sup>-1</sup> Å<sup>-2</sup>, which is in near perfect agreement with the AMBER value. Thus, it appears that MMFF94 is likely to give better results for ammonium cations based on using softer bond potentials (assuming that the parameterization was done properly).

2. Optimize all of the torsional conformers of the zwitterionic form of the amino acid valine using the MMFF94 force field. What are the relative energies for the conformers? Now compute the analogous conformers for the neutral form of valine. Discuss your results and include a description of any additional steps you had to take to make this comparison. (Nota bene: pay close attention to your atom types throughout.) Although you are not asked to do it here, to increase confidence in your results, what could you do?



It is very important that you use the correct atom type parameters when performing the MMFF94 calculations. In this case, the following atom types should be used.

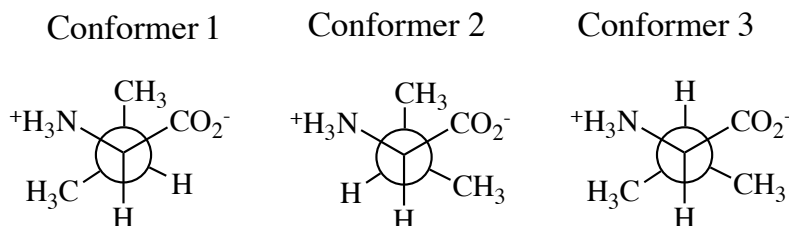
Zwitterion Atom Types:

C (alkyl): 1  
 H (alkyl): 5  
 O (carboxylate): 25  
 N (NR<sub>4</sub><sup>+</sup>): 20  
 H (on nitrogen): 29

Neutral Atom Types:

C (alkyl): 1  
 H (on carbon): 5  
 O (oxo): 7  
 O (alcohol): 6  
 H (on oxygen): 24  
 N: 8  
 H (on nitrogen): 23

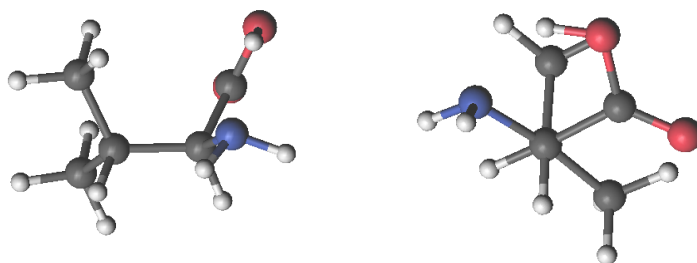
Beginning with the zwitterion, there are three torsional conformers for valine.



Their steric energies with the MMFF94 force field as printed in PCModel are  $-33.4$ ,  $-32.7$ , and  $-31.4$  kcal mol<sup>-1</sup>, respectively. Relative to the lowest energy structure at left, the two other torsional isomers have energies of 0.7 and 2.0 kcal mol<sup>-1</sup>, i.e., they are higher in energy.

In neutral valine, there are a larger number of isomers because of the loss of local symmetry in the ammonium and carboxylate groups. That is, not only do we have to consider rotating the isopropyl group, but we also need to consider the orientation of the NH<sub>2</sub> and CO(OH) groups. I ran a GMMX calculation to find the lowest energy structure and found the following

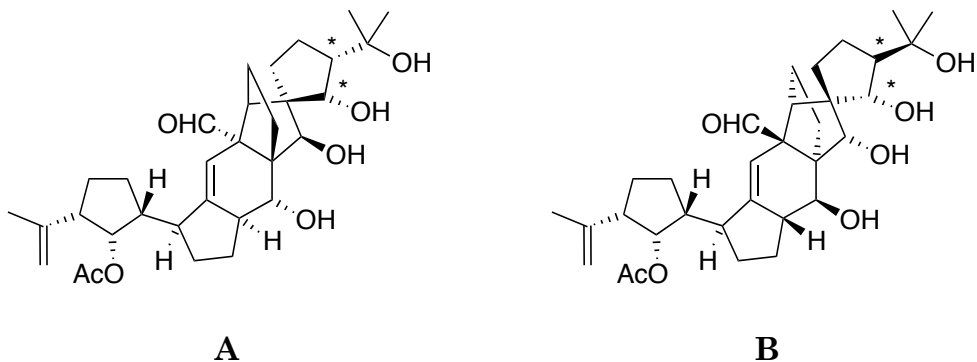
structure to be the lowest with a steric energy of 21.2 kcal/mol. This structure is analogous to conformer 2 in the zwitterion.



From this lowest energy structure, rotating the isopropyl group to form conformers 1 and 3 (and then re-minimizing) gives energies of 23.3 and 22.8 respectively, or relative energies of 2.1, 0.0, and 1.6 kcal mol<sup>-1</sup> for conformers 1, 2, and 3, respectively.

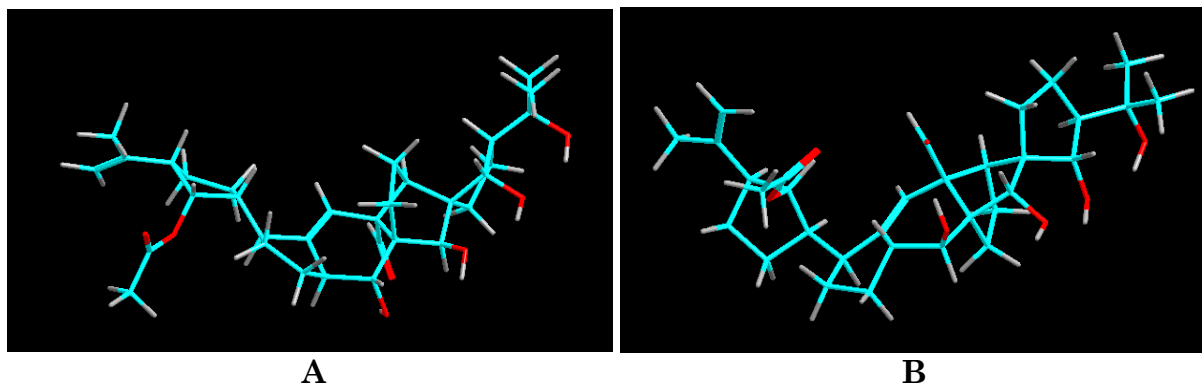
One way to increase confidence in our results would be to repeat these calculations with other (reliable) force fields. Additionally, one could preform this conformational search at a higher level of theory (and maybe we will later in the course...) Finally, since valine is an amino acid, we could also account for the effects of water as solvent in our calculations.

2. One of the two structures below is that originally assigned to a certain natural product. The other is the correct structure, determined later through (extremely costly) total synthesis. Use GMMX and the MM3 force field to find the lowest energy conformations for both structures **A** and **B** (use the default energy window for saving structures). In addition, monitor the coupling constant between the protons on the vicinal centers marked by asterisks. Report the 298 K Boltzmann average coupling constant for both structures. Under what circumstances would you be able to use the computed coupling constant to distinguish between the two possible structures? Note that if you are not confident about interpreting the stereochemistry implied by the drawing for any of the 13 stereogenic centers (or anything else!) please ask.



Send Josh a copy of your \_\_\_\_2.pcm file for each structure by email so that he can verify your structures.

Screenshots of **A** and **B** are shown below. The MM3 energies for **A** and **B** were computed to be 123.6 and 129.6 kcal mol<sup>-1</sup>, respectively. Of course, while the two structures involve the same atom types, they are not interconverting, so it doesn't matter much that **A** is predicted to be lower in energy than **B**. I found for **A** that the lowest energy conformer accounted for 88.6% of the population that included 5 conformers. In the case of **B**, I found more low-energy conformers, with the minimum being 50% of the population comprised of 11.



The coupling constants predicted by the Karplus equation averaged over the populations were 2.9 and 11.0 Hz, respectively. So, if we only had one compound in hand, and it were substantially closer to one value than the other, we'd feel reasonably confident making an assignment (noting, of course, that there are *many* other possible stereoisomers that we are *not* considering).

We'll look more carefully at NMR analysis for these two structures on the next problem set.

3. Find a paper in the chemical literature published since from 2008–2013 that includes a molecular mechanics calculation that you can reproduce in PC Model (you don't have to reproduce it *exactly*, but you should be able to at least follow the same line of inquiry; thus, for instance, the paper might use a force field not found in PC Model, but for a molecule for which *other* force fields in PC Model might be expected to be perfectly fine). Turn in a copy of the original paper and a brief description of what you did and how your calculations compared to those in the paper. Rationalize any differences in results. If you have doubts or concerns along the way, sound off on Piazza or talk to any of the instructors.

There are, of course, many possible answers to this problem. Hopefully you found an interesting case to examine.