

Exploring the effect of the methods to assign partial atomic charges for drug-like molecules

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The bound conformation (bioactive) of a drug to a target protein does not have to be the preferred conformational for that compound in solution (solution conformation). If those conformations were different, then there would be a penalty to move from the ensemble of solution conformations to the bioactive one, which would have to be recouped by the binding energy for the ligand to the target. We are focusing in this presentation on the effect that the choice of structure used perform charge calculations will have on the issue described above. We have parameterized a data set of 90 drug-like molecules and about 1500 of their conformers using the General Amber Force Field (GAFF). We have compared the locally minimized energies for the conformers in solution to the energy of the bound structure for the ligands (bioactive conformation). The average energy difference between the bioactive state and the global minimum conformations is about 5 kcal mol⁻¹. We further studied the effect of the charge methods on the energetic properties of these molecules and conformers. One can now discuss how to assign the charges for each conformer. One could, if available, parametrize the bioactive conformation and reuse that charge set for all conformers. One could also use the charge set for the lowest energy solution conformer, and reuse it for all others. Possibly, one could create a charge set for each individual conformer without reusing it. We show that the energy changes caused by changing the charge sets are widely distributed, suggesting that force field methods may not be expected to yield accurate conformational energies of the drug-like molecules. The energetic ranks of the conformers in their conformational space, on the other hand, show consistent results through the three charge sets. Therefore, the force field methods should be able to serve as acceptable, qualitative approaches to facilitate current drug discovery efforts.