Calculations of pKa and Free Energies of Complexes

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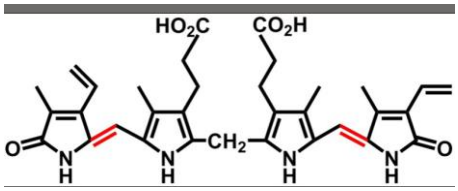
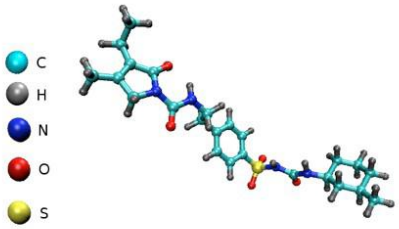
At the design of novel drugs it very important to understand and to know how they will reach their target, because on their way to there, there are many “boarders” (membranes) they have to cross. If the transport through the certain membrane is understood, it is much easier to design a new medicine. With molecular simulation some insights and directions to ease this work can be given, so the lab process is planed much more easier, efficiently, and at the end its results are much more reliable.

In our study we decided [1], we will critically evaluate and calculate pK_a values with quantum mechanical methods and solvation models (Langevin Dipoles (LD) model [2-4] and Solvent Reaction Field (SCRF) of Tomasi and co-workers [5]) to calculate free energies of solvation. At first we ran the calculations for few carboxylic acids, and then for molecule of bilirubin, which is one of the end products of heme group metabolism of hemoglobin. In sloutin bilirubin co-exists in equilibrium of three forms: diacid form, monoanionic and dianionic form. Bilitranslocase as an organic anion transporter (3D structure is not known) participates in the transport of bilirubin through the hepatocytic cell membrane. Though mechanism of hepatic uptake is not yet completely understood. Therefore with calculations of pK_a values we contribute some new insights in understanding the protonation states of bilirubin that are most probably chenged during the transport process, as our calculations implied reasonable agreement with the experimental value of 8.1, for the first protonation step (5.5 (HF/6-31G(d)) and 6.5 (B3LYP/6-31*G(d,p)) in conjunction with LD solvation model that peformed better than SCRF, while there were severe disagreements with the experimental value of 8.4 in the case of the second protonation step. The reason for later could be in fact we have to compensate the bond energy of almost 400 kcal mol^{-1}. From the results it was also evident they very much depend on the flexibility of the basis set. This study is preliminary to all atom simulation of bilirubin transport by bilitranslocase, where protonation states are most probably changed.





By knowing how to critically evaluate and calculate pK_a values with quantum mechanical methods and solvation models we determined the depronation site of glimepiride (oral antidiabetic drug, poorly soluble in water), because up to now it has just been assumed where it could be. It turned out that the NH of sulphonylurea group of glimepiride gets deprotonated, as the results of our calculations were in very good agreement with the experimental values of Grbič et al. [6]. This gave us some insight in how to design complexes between glimepirid and hyperbranched polymers, i.e. dendrimers, which should increase solubility of glimepiride in water. Hence we calculated free energies of interactions for complexes glimepiride-dendrimer. Vibrational analysis was also included. It turned out that the semiempirical method PM3 is insufficient here, as there was a H-bond formation between certain part of glimperide and dendrimers (intermolecular H-bond), and also among specific type of terminal functional groups of certain type of dendrimers (intramolecular H-bond). Nevertheless we were also limited with the syze of the system and geometrical parameters that are very »sensitive«, when forming this kind of complexes. The calculations were in quite good agreement with the experimental data from IR and NMR spectra.

This calculations represent first step toward understanding the nature of the glimepiride complexation with poly(esteramide) hyperbranched polymers on the atomic level using QM calculations in conjunction with proper solvation models. Understanding glimepiride complexation and binding on the atomic level is a promising pathway for yielding new insights to design dendrimers with improved properties and oral antidiabetics of the next generation.

1. Borštnar, R., et al., *Calculation of pKa values of carboxylic acids: Application to bilirubin.* Journal of Molecular Structure: THEOCHEM, 2010. **947**(1-3): p. 76-82.
2. Florian, J. and A. Warshel, *Calculations of hydration entropies of hydrophobic, polar, and ionic solutes in the framework of the Langevin dipoles solvation model.* Journal of Physical Chemistry B, 1999. **103**(46): p. 10282-10288.
3. Florian, J. and A. Warshel, *Langevin dipoles model for ab initio calculations of chemical processes in solution: Parametrization and application to hydration free energies of neutral and ionic solutes and conformational analysis in aqueous solution.* Journal of Physical Chemistry B, 1997. **101**(28): p. 5583-5595.
4. Florian, J. and A. Warshel, *Langevin dipoles model for ab initio calculations of chemical processes in solution: Parametrization and application to phosphate ester hydrolysis and conformational analysis in aqueous solution.* Abstracts of Papers of the American Chemical Society, 1997. **214**: p. 85-PHYS.
5. Tomasi, J., *Thirty years of continuum solvation chemistry: a review, and prospects for the near future.* Theoretical Chemistry Accounts, 2004. **112**(4): p. 184-203.
6. Grbic, S., et al., *A Contribution to the Glimepiride Dissociation Constant Determination.* Journal of Chemical and Engineering Data, 2010. **55**(3): p. 1368-1371.