Team 11: Quantum Mechanical pKa Predictions of Drug-like Molecules

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One of Pfizer Inc.'s goals is to improve their ability to predict molecular and solid state properties in order to aid drug design and delivery. A molecule's degree of dissociation in solution is a vital characteristic that determines a number of key properties such as, formulation, stability, bioavailability, absorption, and salt formation. The pKa defines a molecule's extent of ionization in solution and in the pre-formulation stage the pKa value assists in deciding which salts are viable targets for drug design. Empirical methods for pKa determination are fast but potentially produce large errors. In these situations *ab initio* quantum mechanical investigations may present a more accurate alternative for pKa determination for drug-like molecules because these calculations do not depend on training sets or experimental information. Although using quantum mechanical computations to predict the pKa value leads to marginal increases in the cost of research, it is advantageous to use when faster and less accurate approaches produce inconsistent pKa results or crucial design decisions are being made and more certainty is needed.

A variety of *ab initio* quantum mechanical calculations and statistical analysis of the obtained results were preformed to establish the accuracy of currently used conventions for pKa predictions in drug-like molecules. An understanding of the advantages and disadvantages of each method was obtained. To conduct this investigation, computational research was done using the Gaussian code. This program was used to predict energetics, structure, and thermodynamic properties of molecules in the gas and solution phases. These energies were then used to calculate the molecule's pKa, which was then compared with the corresponding experimental data.

The thermodynamic cycle shown in the figure below is a strategy that was employed to calculate the pKa value of a molecule of interest (propionic acid in the example). It was concluded that the choice of reference base (Ref- in the figure) plays a critical role for achieving high accuracy. However, further research is being conducted to discover a reliable way of identifying these references.