Theoretical Hydration Energies of Biologically Relevant α-Keto Amides

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α-Keto amides are used in the pharmaceutical industry. Two drug molecules which contain α-keto amide functionality are Varespladib, a drug used for treating acute coronary syndrome, and Boceprevir, a drug used for treating hepatitis C. Our goal is to use hydration propensity as a lens through which we can predict what form of the α-keto amides is more active, i.e., the ketone or the ketone hydrate. All hydration energies were calculated using the B3LYP method and 6-31+G(d,p) basis set using the Gaussian 03 suite.

In this investigation, we calculated the energies of hydration of numerous α-keto amides in vacuum. Next, these α-keto amides were optimized using water and chloroform as implicit solvents using the CPCM solvent model. These solvent calculations employed the same method and basis set as above. Both UAKS and UA0 radii were investigated for all solvent calculations. Their energies of hydration were determined in both solvents. Thus far, analysis of the hydration reaction in vacuum suggests that the ketone form is favored for all α-keto amides. Aside from a few fluorine-containing compounds, this trend holds in water and chloroform using UAKS radii. However, when using UA0 radii many compounds both in water and in chloroform favored the hydrate.

Ultimately, our goal is to use hydration energy to investigate what form of these compounds is most active in the human body and hence what form (ketone or hydrate) should be expected in α-keto amide-containing pharmaceuticals.