THEORETICAL STUDY OF THE FORMATION OF CAFFEINE AND CREATINE CO-CRYSTALS

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Introduction

The number of physical activity practitioners has grown in recent decades. According to the Brazilian Ministry of Health this number increased 28.7% from 2009 to 2019.[1] In this scenario, the food supplement industry is also developing itself, targeting amateur practitioners and professional sportsmen who want to improve their performance. Caffeine and creatine are quite popular dietary supplements among physical activity practitioners due to their ergogenic qualities. Caffeine belongs to the group of xanthines acting in the organism as a potent stimulant of the central nervous and respiratory systems. [2]. Caffeine acts quickly in the body increasing awareness, wakefulness, attenuating fatigue and enhancing muscle contraction.[2,3] Creatine, unlike caffeine, is a non-essential amino acid, produced by the liver, kidneys and pancreas. Its phosphorylated form is a quick source of phosphate groups and energy for ATP production, during intense physical activity. Creatine phosphate also acts as a pH controller in muscle cells, delaying fatigue caused by lactic acid production.[4] In order to improve caffeine and creatine ergogenic features by increasing the bioavailability of these substances, this work investigates the formation of caffeine and creatine co-crystals by evaluating possible interactions between both substances in gas and water phase using ab initio, DFT approach (M062X and B3LYP) and Polarizable Continuum model. All optimized geometric parameters were compared with data found in reference articles, when possible. In order to predict and design solid-state forms, as well as, to investigate and justify their physical-chemical properties, computational molecular modeling has often been used to study several systems in good agreement with experimental data. predicted The crystalline structure of anhydrous creatine was predicted for the first time using ab initio method in 2011.[5] In 2013, Sivastava and Singh studied the structure and vibrational spectra of anhydrous caffeine using Ab Initio and DFT methods.[6] Gunajyoti Das (2014) wrote about the conformational aspects of the non-ionic creatine using modeling methods,[7] and Soumyajit Ghosh and co-workers also used computational methods to explain some distinct mechanical behavior of two co-crystal polymorphs of caffeine:4-chloro-3-nitrobenzoic acid which have close structural similarity.[8] In another contest, Marlena Gryl und co-workers used ab initio calculations to study the charge density in melamine-barbital co-crystal and isolated molecules.[9] The study revealed competition between atoms to form hydrogen bond and a mesomeric form of the isolated molecule. In addition, in other studies, computational methods are widely used to design solid state-forms already discovered and to produce simulated graphs to compare with experimental ones found.

Method

The structure of the compounds were built and full-optimized using Gaussview 6.0 software package. The ground state molecular structure of caffeine and creatine were obtained using second order Møller-Plesset (MP2) perturbation theory and density functional theory employing B3LYP and M062X exchange correlation functions. The formation of the caffeine and creatine co-crystal has been simulated in the gas and condensed phases. The interaction points between both substances have been evaluated using Fukui function and NPA.

Results / Discussion

From the fully optimized structures of caffeine and creatine, single point calculations were performed to obtain the Natural Bond Orbital (NBO). NBO associates the localized Natural Lewis Structure (NLS) with the wave function of the molecule to have a better description of molecular charge distribution. That is a good starting point for building co-crystal structures and to evaluate the strength of interactions after structure optimization and energy decomposition. The structures of individual substances fully optimized can be visualized in figures 1 and 2.

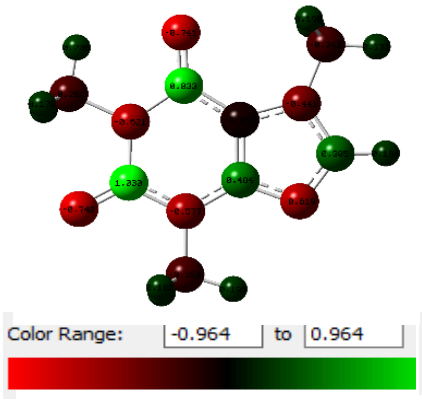

Figure 2: NPA charge for caffeine.

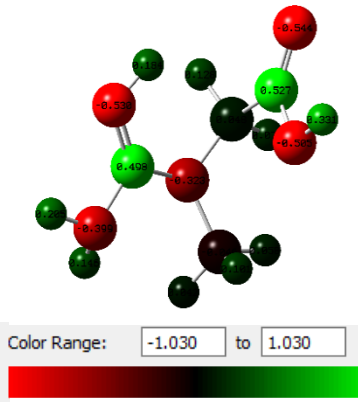

Figure 1: NPA charge of creatine.

The NPA negative charges on the oxygens in the caffeine pyrimidine ring and in the nitrogen of the creatine amine groups show that these points are excellent nucleophilic regions and hence anchor points (Figures 1 and 2). In contrast, the hydrogens of methyl groups have NPA positive charges showing that they are good eletrophilic regions. That is why we believe that these regions of both molecules interact with each other to form a caffeine and creatine co-crystal. Figure 3 shows the fully optimized theoretical structure of the co-crystal.

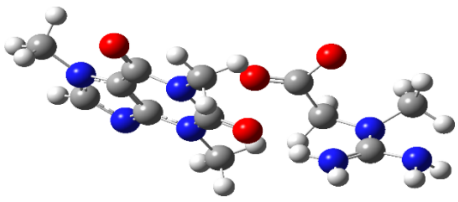

Figura 3 Caffeine and creatine co-crystal

As seen in figure 3, methyl hydrogens from one methyl group of caffeine interact with the oxygen of the carboxyl group of creatine, while the oxygen of caffeine interacts with the hidrogens of the creatine amine group. These points of interactions are in good agreement with Debraj Gangopadhyay and co-workers [10] that showed points of the interaction in creatine dimers.

Conclusion

It's possible to predict structures of caffeine and creatine co-crystals, based on the preliminary results we also obtained structures similar to those found by other authors.

Acknowledgments

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