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From photochemical and non-photochemical nucleation induced by LASER to experimental and theoretical interaction energies determination: Carbamazepine III a complete study.

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This paper deals with the nucleation of the carbamazepine (CBZ) molecule by using the Non Photochemical Laser Induced Nucleation (NPLIN). This method is recently demonstrated by Garetz (1) in the crystallization of Glycine (2), urea (3), and L-Histidine (4).

This paper focuses on the CBZ molecule crystallisation. It was observed that on being exposed to the pulsed nanosecond laser (Q-switched Nd: YAG) with wavelength of 532 nm, the CBZ solutions yield an orange coloration. The hypothesis behind the orange coloration is a photochemical reaction that produces iminostilbene from the CBZ. This reaction occurs by breaking the N-CONH₂ bond, the most fragile bond of the molecule and adding hydrogen to the N atom from the surrounding water molecule, present as the solvent or in the moisture. This paper is aimed to verify experimentally the hypothesis. We have imposed proper experimental conditions in order to avert the photochemical reaction resulting in orange coloration and to produce the crystal of CBZ from its solution at the metastable state by NPLIN. The influence of the solvents in the occurrence of the photochemical reaction was also studied in this experiment. Indeed, we used methanol which is a polar protic solvent and Acetonitrile which is a polar aprotic solvent. The effect of polarization of laser beam on the crystal morphology and impact of energy on the crystallization was also studied by using both the linearly and circularly polarized light at different values of energy.

We have for the first time shown that it is possible to obtain carbamazepine crystals using the NPLIN technique, avoiding any photochemical reaction. Moreover, we have obtained in a few days, under stable conditions, large crystals (of type III) high quality (fig 1).

The experimental electron and electrostatic properties of carbamazepine drug molecule (form III) were determined from accurate high resolution X-ray diffraction data collected at 100 K. The results are compared to quantum

mechanics calculations for gas-phase molecule and multimers. The experimental electron density was refined using the Hansen-Coppens multipole formalism and the deformation electron density maps are compared to the theoretical ones. Both experimental and theoretical deformation electron density maps presented here are based on Clementi's promolecule densities used as a reference. The topological analysis of the carbamazepine electron density using Bader's theory has been carried out and the integrated atomic charges are presented and compared to those obtained for molecules with equivalent chemical fragments. The charge values compare qualitatively well with those obtained by theoretical calculations. The electrostatic potential features and the interaction electrostatic energies are also discussed. (5)

This study is a part of an ANR NPLIN-4-drug project (Non Photochemical Light Induced Nucleation for drug). One of the hypothesis of the nucleation mechanism is based on the pre-existence of molecular clusters in the supersaturated solution. For these molecular clusters, the polarisability tensor symmetry would play a crucial role in agreement with a optical Kerr effect. A target molecule actually studied in our group is the CBZ molecule. In that context, an estimate of the binding energies has been carried out in this study. The results show clearly that the first stable dimer formed is that displaying the strongest $\text{NH}\cdots\text{O}$ hydrogen bond ($-64.42 \text{ kJ}\cdot\text{mol}^{-1}$). The second strongest cluster ($-32.37 \text{ kJ}\cdot\text{mol}^{-1}$) binds through the $\text{p}\pi\text{-p}\pi(\text{SH})$ interaction. Considering these first two interactions, the crystal packing could be described as a 1D chain of homosynthons connecting each other through the $\text{p}\pi\text{-p}\pi(\text{SH})$ interaction. When taking into account the third interaction ($-23.10 \text{ kJ}\cdot\text{mol}^{-1}$) a 3D crystal packing is formed. (fig 2).

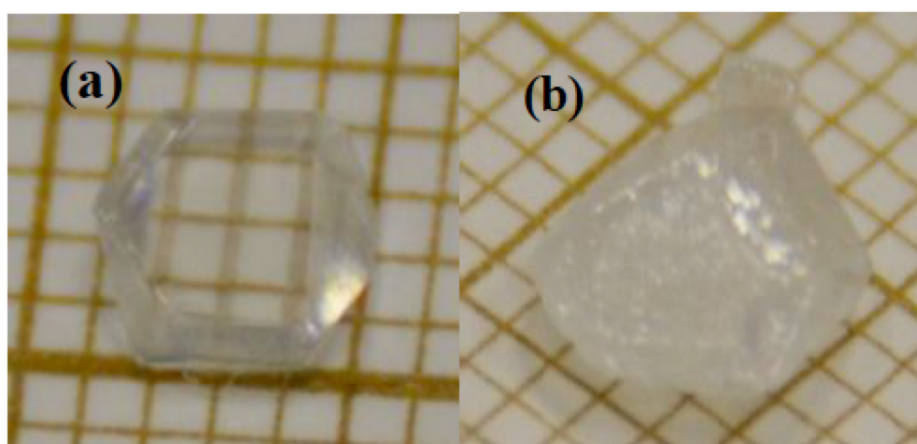


Fig1. CBZ crystals obtained by (a) NPLIN technique (b) Spontaneous crystallization

