Project Title:

Estimation of Chemical Shift Anisotropic Tensor Components by Quantum Chemical Calculations.

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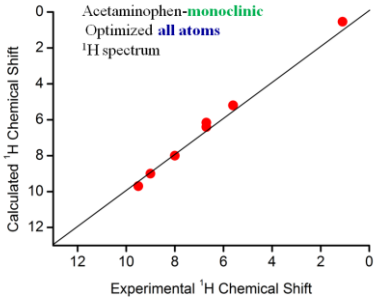
Solid-state NMR has been considered as a valuable technique for the study of structure and dynamics of different kind of molecules at atomic scale. It has been successfully applied to understand the intermolecular interactions, crystal packing and polymorphism of the molecules. Polymorphism is one area of research where molecules can exists in more than one form and also has different crystal symmetry and packing. The study of polymorphism in pharmaceutical molecules becomes more interesting, since their physical and chemical properties are varied based on their molecular forms. Polymorphism has been extensively studied based on diffraction techniques. However, the position of the protons obtained from the diffraction techniques are not accurate due to low scattering cross section of proton nuclei. The position of the proton nuclei is more useful for the study of the molecules, since they are located on the surface of the molecule and are directly involved in hydrogen-bonding, aromatic π-π interactions and molecular packing. Due to the limitation in getting precise proton position from diffraction techniques, Solid-state NMR in combination with quantum chemical calculations on optimized geometry could be a good complimentary approach to the diffraction methods for the determination of precise proton position. In ssNMR, proton has become an interesting nucleus to probe the structure due to its inherent high sensitivity and high natural isotopic abundance. However, due to the dense network of strong homonuclear dipolar couplings among protons in solids lead to very broad and feature less resonances. In recent times, advancement in probe technology as well as sophisticated methods development leads the accessibility of proton chemical shifts. Here, we have studied acetaminophen pharmaceutical molecule and it has been exist in different polymorphic forms; among them we could choose two stable polymorphic forms they are orthorhombic and monoclinic forms.

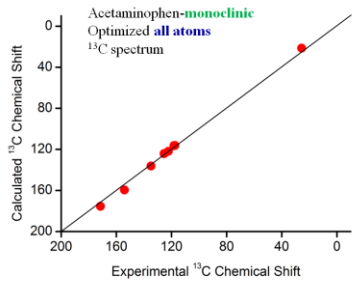
In ssNMR, the understanding of the crystal polymorphs has been done based on isotropic proton and carbon chemical shifts and proton-proton dipolar couplings. Here, we have chosen proton anisotropic chemical shift tensor components to understand the polymorphism. Due to difference in crystal packing the isotropic and anisotropic chemical shielding of protons would vary. Experimentally, we have applied R-symmetry based chemical shift anisotropy recoupling (CSA) approach for extracting the CSA tensor components of both the polymorphs and the assignment of the resonances have been done based on the proton-detected HETCOR at ultra-fast MAS. The experimental approaches were clearly shown that the deviation in their isotropic and anisotropic proton chemical shifts (not given here). This is mainly due to the independent crystal packing of the two polymorphs. In that monoclinic has π-π stacking of the molecule due to that proton chemical shielding tensors have different shielding than the orthorhomobic where it does not have π-π stacking. Due to these independent packing of the molecule we could see the clear difference in proton isotropic and anisotropic chemical shielding tensors.

These experimentally obtained results have been confirmed by using quantum chemical calculations. Here we have used plane wave based DFT (density Functional Theory) approach to compute the NMR isotropic and anisotropic carbon and proton chemical shifts to validate the experimental results. Here GIPAW module incorporated in Quantum ESPRESSO code has been

used for the computation of NMR shielding tensors. For the geometry optimization of the molecules, we have taken initial crystal coordinates from Cambridge Crystal Database (CCD), the calculations were performed on the PBE exchange correlation functional. The optimization of the protons and all atoms position was conducted with the cutoff energy of 90 Ryd for the plane waves. Then we performed GIPAW calculations on the optimized geometry for the chemical shielding tensor components. The computed proton and carbon isotropic chemical shifts of monoclinic form are given in the Figure 1a and 1b and found that they are very good in agreement with the experimentally obtained results. Similarly the orthorhombic form proton and carbon chemical shifts were computed and are given in the Figure 1c and 1d, also found that they are in good agreement with the experimental results.



(1a)



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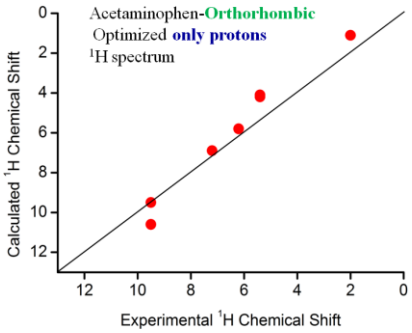
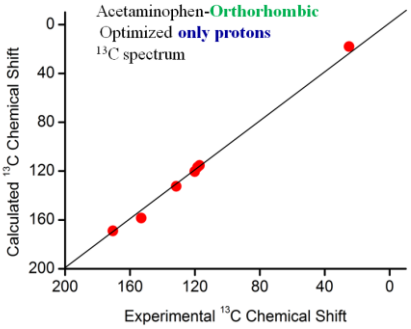


(1c)



(1d)

Figure 1: Experimental versus calculated chemical shifts of Actaminophen monoclinic (a) proton (b) carbon and orthorhombic (c) proton (d) carbon.

From both the results extracted from ssNMR and computational (GIPAW) approach, we could see the significant deviation in the isotropic and anisotropic proton chemical shifts and carbon isotropic chemical shifts. From this we concluded that the deviation observed from both the results is mainly due to their independent crystal packing and their aromatic π-π interactions.

The method, in combination of ssNMR experimental and quantum chemical calculations, adopted here will help to understand the crystal polymorphism and crystal packing of drug molecules at their isotopic abundance.