THEORETICAL AND SPECTROSCOPIC STUDY OF CARBAMAZEPINE POLYMORPHS

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Abstract: This study reports on the use of the computational method DFT B3LYP/6-31G(d) to predict vibrational spectra of the pharmaceutical drug, carbamazepine. The calculated modes are then used to explain the vibrational spectral variations due to polymorphism in this drug.

The polymorphic behaviour of drugs may have considerable formulation, therapeutic, legal and commercial implications. It is crucial to be able to adequately identify and characterise different polymorphic forms of drugs as early as possible in the drug discovery and development process. At an early stage only very small amounts of drug are available, making the development of vibrational spectroscopic techniques for identification and characterisation of polymorphs desirable. Ab initio calculations on the target molecules offer a more incisive view of the vibrational spectroscopic data collected. Ab initio modelling of pharmaceutical drugs has not been widely investigated. Ranitidine HCl has been studied in relation to crystallographic data [1], but we are unaware of any other studies involving drug polymorphism involving prediction of vibrational spectra in combination with drug polymorphism.

The carbamazepine (CBZ) structure is an attractive system to model using ab initio methods because the most common polymorphs (form I and III) have a rigid structure [2]. The rigidity of the molecule makes it easier to locate a minimum energy geometry from which the frequencies of vibration may be calculated.

The vibrational frequencies and their IR and Raman intensities for the CBZ molecule were calculated using DFT calculations; B3LYP functional with the 6-31G(d) basis set (Gaussian 98W [3]). The frequencies were scaled by 0.9692, obtained by taking the least-squares difference between theoretical and experimental frequencies in the 1000 to 1750 cm⁻¹ region.

The predicted geometry of the single molecule calculation was compared to the crystallographic data on each of the polymorphs (CBZ forms I [2] and III [4]). From the predicted geometry it was possible to calculate the IR and Raman spectra (Figure 2). These predictions compare favorably to the observed spectra of both polymorphs of CBZ for most of the bands.

The spectral differences between the polymorphs are more striking in the IR than the Raman spectra, with strong IR bands at 1688 and 1396 cm⁻¹ in the spectrum of form I shifting to 1678 and 1388 cm⁻¹ for form III.
Figure 2. Calculated and experimental IR (left) and Raman (right) spectra of CBZ. Calculated spectrum monomer, trace a; dimer, trace b; experimental spectrum form III, trace c; form I, trace d.

The experimental spectra of CBZ reveal that for this drug IR is more polymorph sensitive than Raman spectroscopy. Analysis of the potential energy distributions for the calculated normal modes reveal that the vibrations are localized on different ring systems of the carbamazepine molecule and the polymorph-sensitive modes in the IR spectra are localised to the pendant CONH$_2$ group; it is these modes that show the greatest disparity from the calculated spectra, and it is this group that is perturbed in the polymorph crystal structures.

In both crystal forms the molecules associate into dimers with hydrogen bonding between the CONH$_2$ groups, and so the calculations were repeated on the dimer. The calculated dimer structure is similar to that of the single molecule however the polymorph-sensitive IR modes are significantly better predicted by the dimer calculation.

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References: