

Differences between the electronic structure of paracetamol molecules in the solid state and in polar solutions: N K-edge NEXAFS studies

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Paracetamol (acetaminophen) is a widely studied model system in pharmaceutical science for examining the relationship between solution speciation and the polymorphic outcomes of crystallization from solution. NEXAFS can be used to probe hydrogen bonding and associated conformational changes in organic systems. NEXAFS then becomes powerful in combination with complementary techniques, both experimental (XRD), and computational (DFT).

We have studied the N K NEXAFS of the solid Form I of paracetamol in comparison with the solution state in ethanol and dimethyl sulphoxide (DMSO). The solid-state spectrum was collected from paracetamol powder. The choice of a polar protic solvent, ethanol, vis-a-vis a polar aprotic solvent, DMSO, allows us to examine the influence of hydrogen bonding in the solution. Spectra were interpreted using density functional theory (DFT) modelling, using the ORCA 4.0.0 quantum chemistry package. The spectrum of a single, free paracetamol molecule was determined with the molecular conformation in the crystal structure. The B3LYP functional was used at the TZVP basis level, with an RijCosX approximation applied.

The number and positions of π^* resonances in the NEXAFS were in good agreement with transitions predicted for an isolated molecule by DFT. Analysis of the N-C bond length via the position of the σ^* shape resonance was performed by reference to other compounds with N-C bonds (acetamide, thioacetamide, urea, dimethylurea, aminobenzoic acid).

Relative to the solid state the solution spectra exhibit significant changes in the π^* resonance region, indicating a significant influence of solute-solvent interactions on the electronic structure. Variations in the π^* intensities in the polar aprotic solution are associated with a switch from hydrogen bond acceptance in the ethanolic solution to donation in DMSO. A shape resonances shift to higher energy in solution indicates a change to shorter N-C bond length relative to the solid state.

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