# QUANTIFYING WEAK PACKING INTERACTIONS IN HYDRATED AND ANHYDROUS FORMS OF THE ANTIBIOTIC CIPROFLOXACIN: A COMBINED SOLID-STATE NMR, X-RAY DIFFRACTION AND COMPUTER SIMULATION STUDY

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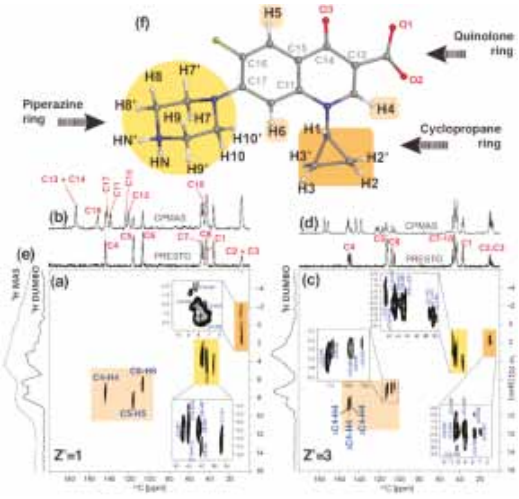


Understanding how molecular systems self-assemble in the solid-state continues to be a challenge. In this regard, Hbonding and van der Waals interactions are considered to play major roles as structure-driving entities in the construction of supramolecular arrangements. This is of particular relevance in pharmaceutical sciences, as multiple crystal forms of the same active pharmaceutical ingredient (API) occur frequently, posing diverse problems in the pharmacokinetics, stability, and formulation of drugs.

In an attempt to better understand how drug hydrates self-assemble in the solid-state and reorganizes to produce its anhydrous form, we present a detailed experimental NMR, X-ray diffraction (XRD), and computational study of packing interactions of different types such as weak/strong H-bonds and π···π interactions that constitute the supramolecular assemblies of two crystalline forms of the antibiotic ciprofloxacin (CIP) [Figure 1f]:1 one anhydrate (form I) and one hydrate (form II) forming water wormholes, emphasizing the effect of nonconventional hydrogen bonds and water on NMR chemical shifts. The complete resonance assignment of up to 51 and 54 distinct 13C and 1H resonances for the hydrate is reported, using a toolbox of advanced high-resolution 2D 1H CRAMPS-based NMR experiments and high magnetic fields (Figure 1a-e) combined with GIPAW calculations of 1H/13C chemical shifts. The effect of crystal packing on the 1H and 13C NMR chemical shifts including weak interionic hydrogen bonds and π···π interactions, is quantified through in silico structure dismantlement of I and II (Figure 2). For example, 1H chemical shift changes up to ~ –3.5 ppm for CH···π contacts and ~ +2 ppm (CH···O(–)); ~+4.7 ppm ((+)NH···O(–)) were estimated for hydrogen bonds.1 Water intake induces chemical shift changes up to 2 and 5 ppm for 1H and 13C nuclei, respectively. We show that such chemical shifts are found to be sensitive detectors of hydration/dehydration in the highly insoluble CIP hydrates.

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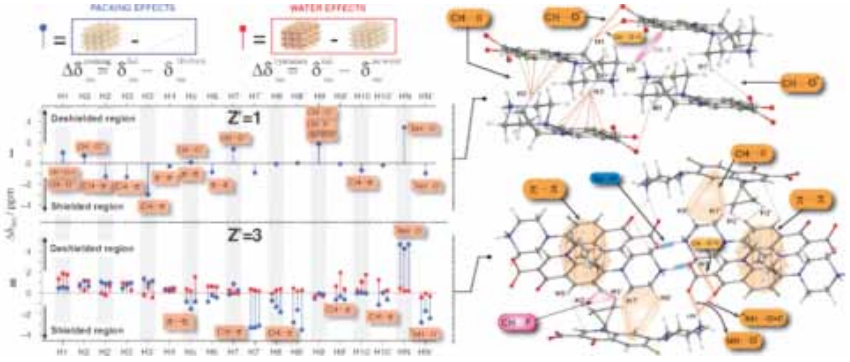


**FIGURE 1**

2D 1H–13C PRESTO-HETCOR of CIP forms (a) I and (c) II recorded at 800 MHz. (b, d) 13C CPMAS spectra recorded at 400 MHz. (e) 1H MAS and wDUMBO spectra of I are shown for comparison with the F1 projection of (a). (f) Labeling scheme adopted for CIP. The capability of PRESTO transfer to select only the directly bonded C– H is manifested by comparison with the 13C CPMAS spectra [i.e., (a, c) vs (b, d)].

**FIGURE 2**

(Left) Stem plots showing the contribution of the crystal packing (blue stems) and water molecules (red stems) to the calculated 1H chemical shifts (positive Δδ values indicate low-field shifts) of the ciprofloxacin forms I and II. In II, each of the three stems per nuclei corresponds to the crystallographically distinct CIP molecules 1, 2, and 3 (from left to right); (right) detailed view of intermolecular interactions in packings of I and II.