Understanding hydrogen bonding structure of molecular crystals by electron- and NMR-nanocrystallography

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Hydrogen bonding plays an important role in formation of molecular crystals. It is crucial to locate the hydrogen at the right position and to understand the hydrogen bonding network in the crystal structure. However, if only micro- to nano-sized crystals are available, the limited scattering power hamper the application of X-ray diffraction (XRD). While electron diffraction (ED) solves the structure even from single nano-sized crystals, ED poorly locates the hydrogen position and fails to distinguish atoms with similar atomic numbers such as carbons, nitrogens, and oxygens in organic molecules. On the other hand, solid-state nuclear magnetic resonance (SSNMR) provides complementary information as SSNMR can directly observe hydrogen (^{1}H), carbon (^{13}C), and nitrogen (^{14}N/^{15}N) atoms. Here, we propose the combined method of ED and SSNMR with the first principle quantum calculation to fully understand the structure of organic crystals. Rotational ED patterns were obtained from submicrometer-sized crystals and determined the atomic positions except for hydrogens. SSNMR complemented the proton position and the carbon/nitrogen/oxygen assignments with the assistance of the quantum computation which provides the calculated NMR parameters from the structures. The approach described here successfully revealed the 3D crystal structures and the hydrogen bonding network of a known L-histidine and a pharmaceutical compound, cimetidine form B whose structure had been unknown. The determined structure well described the relationship between the hydrogen positions and the formation of hydrogen bonding network, or the stabilization of the molecular structure.