Visualization of hydrogen-bonding: Electron and NMR nano-crystallography

Product used : Transmission Electron Microscope (TEM), nuclear magnetic resonance (NMR)

Crystalline structure including hydrogen atoms are now available from nano- to micro-crystals of 100 nm to 1 μm using electron and NMR nano-crystallography approach. The overall crystalline structures can be determined by electron diffraction (ED) which is one of the observation mode of transmission electron microscope (TEM). However, the ED based structures have several problems including 1) invisible hydrogen atoms and 2) misassignment of carbon, nitrogen and oxygen atoms. The former brings crucial problems to understand hydrogen bonding networks and the latter results in ambiguous molecular conformation. On the other hand, solid-state NMR can directly observe 1) hydrogen (^{1}H) and 2) carbon (^{13}C) and nitrogen (^{14}N, ^{15}N). Here, we combine ED and solid-state NMR through the first principle quantum computation with the NMR crystallography approach for crystalline structure solution. The method, electron and NMR nano-crystallography, can be applied to nano- to micro-crystals even for mixture samples. First, we have demonstrated the structure solution of L-histidine, whose structure is already known, as a proof of concept. Then, we have solved the crystalline structure of cimetidine form B, whose structure was previously unknown.
The electron and NMR nano-crystallography can be applied to many pharmaceutical samples including pharmaceutical formulation as well as systems, in which only nano- to micro-sized crystals are available, including PCP/MOFs.

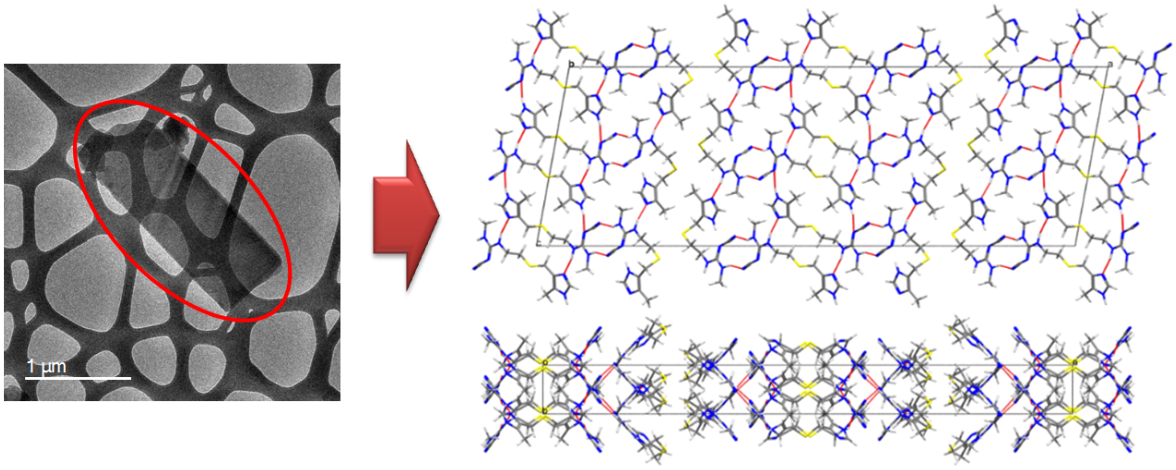

Figure: TEM image of cimetidine form B and crystalline structure solved by electron and NMR nano-crystallography.
The cimetidine form B is needle shape crystals (indicated by red circle on the left figure) and often fails to form a large single crystal for single crystal X-ray diffraction. In addition, the contamination of form C is often observed, hampering the structural solution by powder X-ray diffraction. Here, we solved the crystalline structure of cimetidine form B for the first time.

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