Structural characterization of organic salts by combined X-ray Raman Scattering and excited-state DFT calculations

B. Evans[1], L.H. Al-Madhagi[1,2], S.-Y. Chang[1,2], B. Detlefs[3], S. Díaz-Moreno[2], E.A. Willneff[4], B. Mishra[1], H.P. Wheatcroft[5], S.L. M. Schroeder[1,2]

[1]School of Chemical & Process Engineering, University of Leeds, UK; [2]Diamond Light Source, Didcot, UK; [3]European Synchrotron Radiation Facility, Grenoble, France; [4]School of Design, University of Leeds, UK; [5]AstraZeneca Research & Development, Macclesfield, UK; **pmbe@leeds.ac.uk**

Formulating active pharmaceutical ingredients (APIs) as salts can provide favourable biopharmaceutical and physicochemical properties, such as physical and chemical stability, and increased solubility [1]. Predictive modelling of organic salt crystallisation from solution requires knowledge of speciation in solutions, as structural and electronic properties impact on the crystal structure and morphology of the final product. Core level X-ray Absorption Spectroscopy (XAS) has recently been used to probe the properties of organic ions in solution through the Near-Edge X-ray Absorption Fine-Structure (NEXAFS) region, which is highly sensitive to hydrogen bonding and protonation and hence changes in solvation structure [2]. However, currently available vacuum instruments for soft XAS studies of solutions rely on the use of microjets and similar liquid sample dosing technologies, which are prone to nozzle blockage by spontaneous crystallisation of concentrated solutions. Moreover, expansion into vacuum precludes the high degree of temperature control required for nucleation and crystallisation studies.

Detection of the near-edge fine-structure spectra by X-ray Raman Scattering (XRS), which utilizes hard X-rays (photon energy ~10 keV), has allowed us to work around these limitations. We obtained C and N K-edge fine-structure spectra of imidazolium salt solutions (pH 3) at ambient pressure. Comparison with results for neutral imidazole species (pH 10) confirms that the near-edge fine-structure in low momentum transfer XRS agrees well with previously obtained NEXAFS data. The imidazolium cation exhibits N K-edge fine-structure that is fundamentally different from that of imidazole due to equivalence of the nitrogen moieties in the ion. The two π^* resonances of the non-equivalent nitrogen moieties in imidazole result in a single π^* resonance, in agreement with previous observations for the N 1s binding energies by X-ray Photoelectron Spectroscopy (XPS). Time-dependent density functional theory (TD-DFT) calculations were performed for a number of solvation structures, including implicit and explicit solvation models. They reproduce the peak positions and intensities of the K-edge fine-structure features for both neutral imidazole and the cationic imidazolium species. In summary, we have demonstrated that soft K-edge measurement via XRS permits characterization of organic solutes in solution at ambient pressure. TD-DFT calculations model the observed changes successfully and provide an understanding of the effect of solute-solvent interactions.

References

[1] - P.H. Stahl, C.G. Wermuth, Int. Union of Pure & Applied Chem., Handbook of Pharmaceutical Salts: Properties, Selection and Use, VHCA (2011).

[2] - J.S. Stevens, S.J. Byard & S.L.M. Schroeder, Characterization of Proton Transfer in Co-Crystals by X-ray Photoelectron Spectroscopy (XPS). Cryst. Growth Des., 10, 1435–1442 (2010).