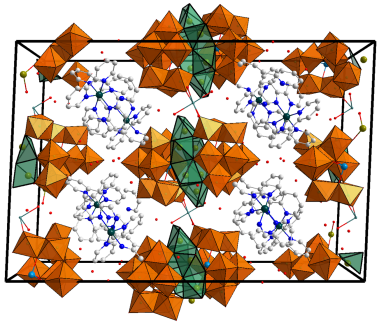

Figure 1. Packing diagram of the POM-PS-complex $[Ru(bpy)_3]_4[Mn_3(H_2O)_3\{As_2W_{18}O_{66}\}]$: WO_6 octahedra (orange), Mn (green), Ru (black).

Keywords: Polyoxometalates, Catalysts, Self-Assembling, Multidimensional Structures, Polymorphism

MS32-P21 Towards understanding solvent-mediated conformational polymorphism

Anikó Udvarhelyi[1], Grahame Woollam[1]

1. Novartis Pharma, Basel, Switzerland

email: aniko.udvarhelyi@novartis.com

Polymorphism, the existence of different crystalline forms of the same molecule, represents a major challenge to the pharmaceutical industry. Different polymorphic forms of the same drug substance may significantly impact solubility, dissolution rate, bioavailability, chemical potential and physical/chemical stability. Differences in these properties may be especially pronounced in the case of conformational polymorphs where different molecular conformations of the same chemical species are arranged in the polymorphic lattices. Our aim is to uncover the molecular mechanisms that govern conformational polymorphism of pharmaceutical molecules in order to highlight the risk of polymorphism during drug development and to guide the solvent selection in experimental crystallisation screens.

Here we focus on the conformational changes of the molecule going from the gas to solution phase and ultimately to the crystal phase. The questions of interest to us include what conformational energy penalties are compensated by crystal forces? How is the gas-phase conformational population distribution altered when entering the solution phase? And how is the minimum-energy conformer in a given crystallisation solvent related to the crystal structure?

To tackle these questions we use quantum-chemistry tools and the continuum solvation model COSMO and its extension for real solvents. In COSMO-RS, the pairwise interaction energy between the ideally screened surface patches of contacting molecules is computed within a statistical thermodynamics framework. This framework allows the population prediction of relevant molecule conformations in solvents of interest. We present for the first time a conformation generation and filtering workflow to identify the relevant conformers to be used in the COSMO-RS calculations with an extraordinary example of polymorphism, ritonavir. The weighted conformers in selected solvents are compared to the respective ritonavir polymorphs and its gas-phase conformers.

Keywords: molecular conformations, polymorphism, COSMO-RS, solvent effects, computational models