Poster

Polymorphism of ribavirin at high pressure

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Exhaustive characterisation of polymorphism and phase transitions in active pharmaceutical ingredients is crucial in the development of solid forms in patient therapy. Polymorphs may differ in physicochemical properties, such as solubility and compressibility, which affect the bioavailability or tabletability of a drug [1]. High pressure offers an attractive method for studying the underlying crystal packing through the minimisation of volume, and without chemical interference [2]. Changes in intermolecular interactions and the thermodynamic environment under high pressure can lead to phase transitions, resulting in new phases that may typically not achievable under normal conditions. These pressures do not necessarily have to be exceedingly high, as research in this field is predominantly conducted below 10 GPa (~100,000 atm).

Ribavirin ($C_8H_{12}N_4O_5$), is a synthetic nucleoside analogue used in the treatment of hepatitis-C, Lassa fever, and respiratory syncytial virus [3]. Only two ambient conditions polymorphs are reported in literature, V1, and V2, which are conformationally different. Both forms were studied to 35 and 10 GPa, respectively, by single crystal X-ray diffraction in a diamond anvil cell (Fig 1a). V1 is remarkably stable to 35 GPa, but V2 undergoes three high-pressure phase transitions, attributed to its unprecedented degree of torsional flexibility in the ribofuranosyl moiety, which is not seen in V1. V2 transforms to a short-lived V3 phase at 5.4 GPa, which manifests as a tripling of the unit cell volume and the b-axis, with three unique conformers in the asymmetric unit ($P2_12_12_1$, Z = 12, Z' = 3). V3 further transitions into V4 ($P2_12_12_1$, Z = 4, Z' = 1) at 6.0 GPa with similar cell parameters to V2 but the ribofuranosyl moiety changes from an envelope to a twist conformation. Finally, V5 ($P2_12_12_1$, Z = 4, Z' = 1) which is conformationally similar to V4, forms at 7.2 GPa and manifests as a further rotation about the hydroxymethyl group (Fig 1b.).

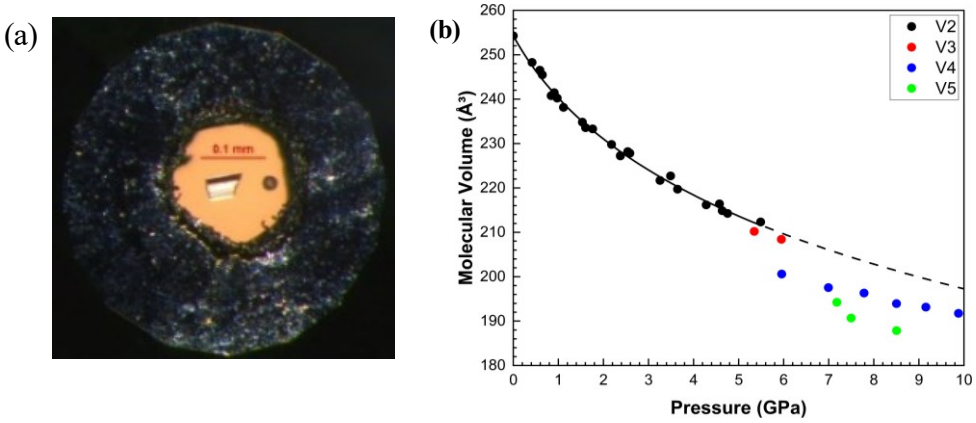

Figure 1 (a) a single crystal of the V2 form of ribavirin loaded in a diamond anvil cell at 1.8 GPa **(b)** molecular volume of ribavirin as a function of pressure.

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