Sa1: The Low Temperature Crystalline Polymorphic Phase Transition of the Valpromide

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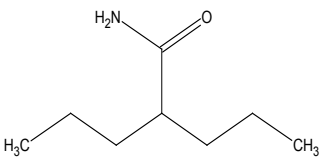
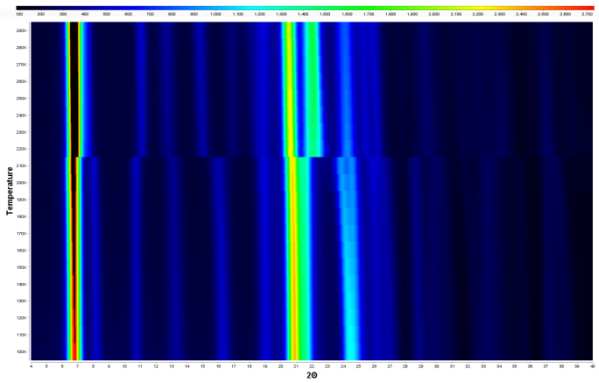
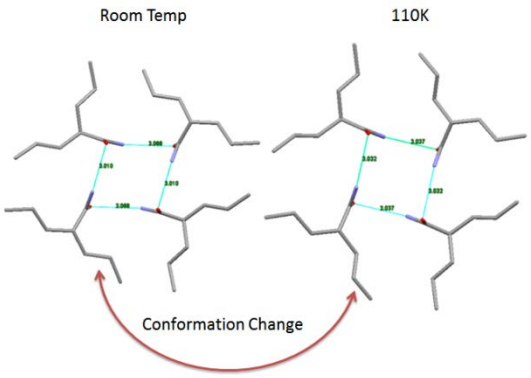


Valpromide (2-Propylpentanamide) is a carboxamide derivative of valproic acid used in the treatment of epilepsy and is available in Europe under the trade name Depamide. The solid form of valpromide undergoes a reversible polymorphic change at about 215K as determined by variable temperature powder diffraction (heat plot). The polymorphic change, between 216K and 214K, is characterized by a 1.4% change in the unit cell volume. Also the structures for Valpromide have been determined at room temperature and 110K. The conformation of the carboxamide differs between the room temperature structure and the 110K structure. For the room temperature structure the carboxamide fragment is *anti* to the methyl group in one of the two independent Valpromide molecules and *gauche* to the methyl group at 110K. Valpromide is an example of an active pharmaceutical ingredient (API) that undergoes a reversible polymorph change at reduced temperature (215K, -58C). Storage of Valpromide in dry ice will transform the room temperature polymorph to the low temperature polymorph. For Valpromide this polymorph transition is reversible however this may not be the case for other APIs, which in turn demonstrates a need to search for polymorphic transitions for APIs at temperatures below ambient conditions.





Crystal data for room temperature structure of Valpromide $C_8H_{17}NO$ (M =143.22 g/mol): monoclinic, space group C2 (no. 5), a = 28.560(3) Å, b = 4.8935(5) Å, c = 16.2596(14) Å, β = 121.968(6)°, V = 1927.8(3) Å^3, Z = 8, T = 295 K, μ(CuKα) = 0.501 mm^{-1}, *Dcalc* = 0.987 g/cm^3, 21795 reflections measured (6.408° ≤ 2Θ ≤ 128.378°), 3138 unique (R_{int} = 0.0918, R_{sigma} = 0.0597) which were used in all calculations. The final R_1 was 0.0739 (I > 2σ(I)) and wR_2 was 0.1947 (all data). Crystal Data for low temperature (110K) Valpromide: monoclinic, space group C2 (no. 5), a = 27.091(2) Å, b = 4.8613(4) Å, c = 16.6992(14) Å, β = 125.415(4)°, V = 1792.3(3) Å^3, Z = 8, T = 110 K, μ(CuKα) = 0.539 mm^{-1}, *Dcalc* = 1.062 g/cm^3, 14787 reflections measured (8.008° ≤ 2Θ ≤ 128.482°), 2820 unique (R_{int} = 0.0762, R_{sigma} = 0.0548) which were used in all calculations. The final R_1 was 0.0518 (I > 2σ(I)) and wR_2 was 0.1394 (all data).