

Title : "Polymorphism" and Hydration of Zopiclone : How to Give the Marketed Drug a real identity card !

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Polymorphism is concerned with crystalline chemically-identical solids in different crystalline packings which form the same liquid and the same vapour when they melt or sublime. Inappropriate denomination of "pseudo-polymorphs"¹ is often given to hydrates or solvates, i.e. crystalline binary compounds including water or organic-solvent molecules, which are also frequently found in the molecular organic solid-state. Solids made of chiral molecules are also concerned with these phenomena. Since chemistry may provide pure (optically active) enantiomers or racemic (optically inactive) modifications, as far as "asymmetric" atoms are concerned, stereochemistry complexifies the solid-state features of those compounds which contain such atoms.

In this study, three states of Zopiclone, a chiral molecule with a hypnotic activity, are investigated. Although Terblanche *et al.*² studied Zopiclone in the solid-state using X-ray diffraction and/or thermal analysis, the phase relationships between phases made of Zopiclone were still to be determined. Racemic Zopiclone crystallises in anhydrous media as a conglomerate (Phase or state A), i.e. the 50/50 mixture of enantiomer crystals which exhibit an orthorhombic lattice³. In the presence of water, Racemic Zopiclone crystallizes as a dihydrate (DH), which dehydrates into an anhydrous phase (phase or state B). Structural information on these two phases (DH and B) were gained by two groups^{4,5}. It came out that DH is a dihydrated racemate, frequently forming single crystals, and that the loss of water leads to an anhydrous polycrystalline pseudomorph racemate anhydrous (phase B). The structure of phase B is very similar to that of DH: the DH lattice contracts by 7% following water molecules departure. An isotherm of water activity confirmed that DH and B easily revert into each other. A Zopiclone-Water phase diagram was inferred from thermal analyses using DSC with open and sealed pans at various heating rates. Assuming spontaneous enantiomerization occurring on heating, it is also possible to draw a hypothetical binary phase diagram between the two enantiomers (R,S) by incorporating calorimetric data in the Schröder equation. The melting temperature predicted⁶ from this equation is close to that observed for a pure enantiomer. A p, T phase diagram for the phase-relationships between states A (conglomerate) and B (anhydrous racemate) has been constructed⁷ from crystallographic and thermodynamic data. It was assumed that the topological method used should apply because states A and B share the same liquid phase and the same vapour one at composition $x=0.5$ and because the eutectic (50/50) mixture of enantiomers melts like a pure single phase. Indeed, although this p-T diagram is not concerned with dimorphism *stricto sensu* since state A consists of an equimolar mixture of two mirror-related phases, it unambiguously indicates that state B is metastable with respect to state A whichever the temperature and the pressure. Thus an overall monotropic behaviour (i.e. as a function of p and T) may be inferred for state B.

¹ The term "pseudo-polymorph" is inappropriate since the composition of polymorphs differs from that of the corresponding solvates.

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