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Polymorphism and hydration of zopiclone: Determination of crystal structures, and thermodynamic studies as a function of temperature and water vapor pressure

J. Giovannini[1,2], R. Céolin[3], M.-A. Perrin[1], S. Toscani[3], D. Louër[2] and F. Leveiller[1]

[1] *AVENTIS PHARMA, Global Pharmaceutical Development, Pharmaceutical Sciences, Material and Drug Delivery Design, CRV1, 13 quai Jules Guesde, BP. 14, 94403 Vitry-sur-Seine cedex, France*
[2] *Institut de Chimie, Laboratoire de Chimie du Solide et Inorganique Moléculaire, UMR 6511 du CNRS, Cristallographie des Poudres et Réactivité des Solides, Université de Rennes I, avenue du Général Leclerc, 35042 Rennes cedex, France*
[3] *Faculté des Sciences Pharmaceutiques et Biologiques, Laboratoire de Chimie Physique, Université Paris V, 4 avenue de l'Observatoire, 75270 Paris cedex 06, France*

Abstract. Racemic Zopiclone crystallises as a dihydrate (DH) or as a conglomerate (A). Upon heating, DH dehydrates to an anhydrous racemate (B) which transforms into the 1:1 mixture of enantiomers (A). It can be inferred from crystallographic and thermodynamic data that the anhydrous racemate is metastable with respect to the 1:1 mixture of enantiomers (A) whatever the water vapour pressure and the temperature. Thus, the B → A transition appears to occur monotropically.

1. INTRODUCTION

Zopiclone (Fig. 1) is an organic compound with hypnotic activity. The molecule possesses 4 torsion angles (T1, T2, T3, T4) and a chiral center. In an anhydrous media, each enantiomer systematically crystallises in an orthorhombic lattice (phase A) whose crystal structure was solved [1] using single crystal data. In the presence of water, a dihydrated racemate (DH) forms. Dehydration of DH (under heat, vacuum, or decreased residual water pressure) results in an anhydrous racemic phase (phase B).

Structural and thermodynamic studies of the polymorphism and hydration of zopiclone were undertaken for characterisation purposes. Preliminary results, which clarify a previous study by Terblanche [2], are presented here.

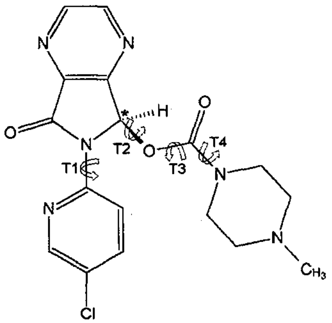


Figure 1. Zopiclone molecule

2. EXPERIMENTAL DATA

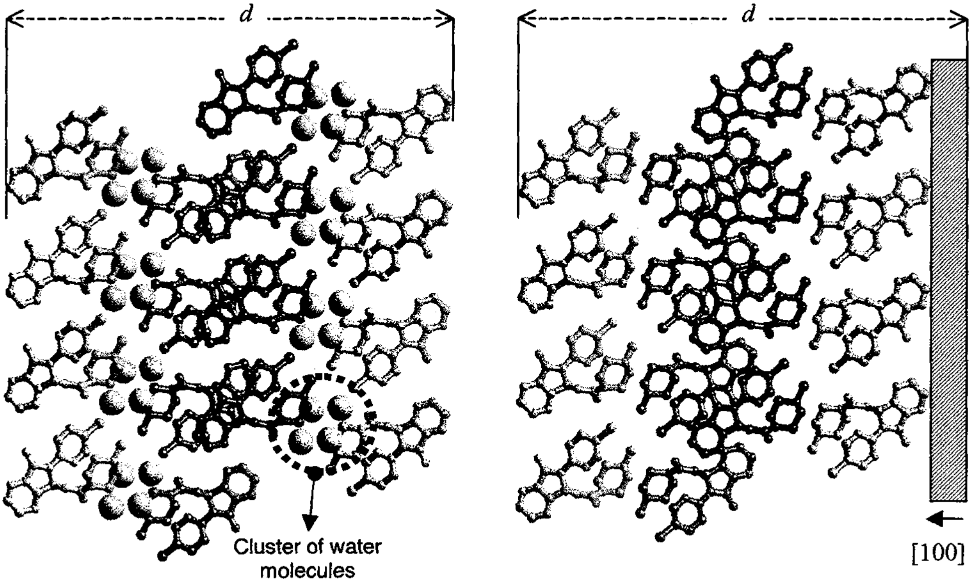
2.1 Structural analyses

The structures of hydrate DH and phase B were solved : the former using a single crystal, i.e conventionally and the latter using powder according to a procedure described elsewhere [3]. The release of water molecules from a single crystal of the DH results in a polycrystalline pseudomorph of phase B. As single crystals of phase B could not be obtained, high resolution X-ray powder diffraction was used to solve the structure. To minimise preferred orientation effects, a transmission diagram was recorded using a rotating capillary. Based on the molecular structure, unit cell indexing and space group determination, the solution in direct space has been determined using a Monte

Carlo Simulated Annealing (MCSA) algorithm (*PowderSolve* programme [4]). The solution was refined by the Rietveld method using a rigid body approach. Table 1 summarises the crystallographic data for the three forms. The molecular packings of the two forms (DH and B) are shown in Fig. 2. The structure of phase B is very similar to that of DH. The lattice contracts by 7% following water molecules departure. The difference between the equivalent volumes $[(V/Z(DH) - V/Z(B))/n_{water} = 20.6\ Å^3]$ is very close to the volume attributed to the water molecule in hydrates [5] (24.5 $Å^3$). In phase DH, the water molecules that bridge zopiclone molecules are assembled four by four inside cavities. In contrast with the DH and A forms, the anhydrous B form does not exhibit strong intermolecular hydrogen bonds that could contribute to its thermodynamic stability.

	Dihydrate racemate	**Anhydrous B racemate**	**Anhydrous A enantiomer**
Empirical formula	$C_{17}H_{17}ClN_6O_3, 2H_2O$	$C_{17}H_{17}ClN_6O_3$	$C_{17}H_{17}ClN_6O_3$
Cell setting	monoclinic	monoclinic	orthorhombic
a (Å)	16.489(2)	15.185(3)	35.650(3)
b (Å)	7.150(1)	7.112(1)	8.845(1)
c (Å)	17.408(2)	17.559(2)	5.572(1)
β (°)	109.85(1)	111.43(2)	90
V ($Å^3$)	1930.6(4)	1765.4(3)	1757.2(3)
Space Group	$P2_1/c$	$P2_1/c$	$P2_12_12_1$
Z	4	4	4
D_{calc}	1.4617	1.4629	1.4697
M_{20}	39	41	57
F_{30}	113(0.0055,48)	102(0.0068,29)	83(0.0071,51)
R_{wp}	0.142	0.112	—
R_1	0.057	—	0.060

Table 1. Crystallographic data of the zopiclone system



(*a*) (*b*)

Figure 2. Crystal structures (*a*) of dihydrate DH (showing water molecules assembled four by four), (*b*) of the anhydrous B form illustrating the contraction which is essentially along the direction [100]. Strong structural similarities are observed.

2.2 Thermal behaviour of the dihydrate (DH)

As shown on the DSC curve (Fig. 3) and confirmed by temperature-dependent X-ray powder diffraction, phase B, arising from dehydration of DH, melts at 420 K ; then phase A crystallises and melts at 446 K.

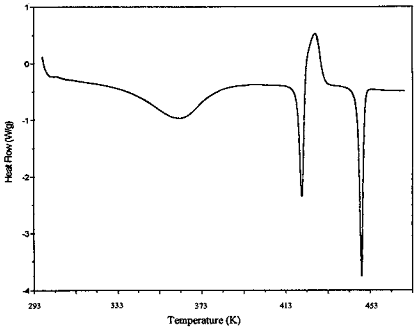


Figure 3. DSC profile (5 K/min), (exo up).

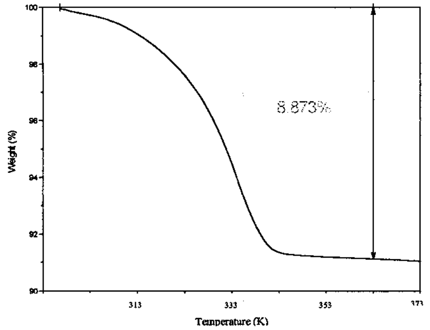


Figure 4. TGA profile (5 K/min)

On heating, phase DH loses its crystallisation water (Fig. 4, weight losses as observed by thermogravimetric analysis (TGA) : 8.4 - 8.8%, theoretical : 8.5%). Differential scanning calorimetry (DSC) showed that dehydration absorbs 240 - 280 Joules per gram of DH in the 313 and 393 K range (Fig. 3). When the heating rate was increased, an endothermic peak ($T_{onset} \approx 393$ K) appeared in the final part of the dehydration peak (Fig. 5). This could indicate the existence of a peritectic invariant onsetting at about 393 K in the water-zopiclone system, which remains to be investigated. This was corroborated by the endotherm at 390 K (onset) recorded when DH was heated in a sealed pan (Fig. 7).

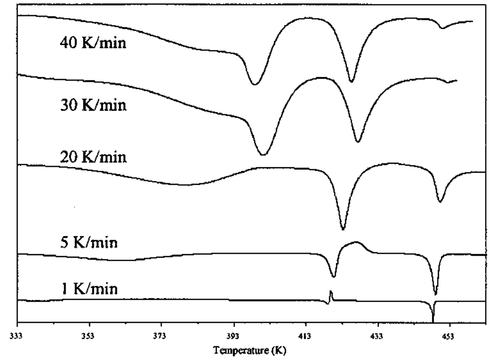


Figure 5. DSC profile under various heating rate (exo up)

2.3 Effect of water vapour

The anhydrous B phase obtained by dehydrating the DH phase at room temperature was exposed to increasing then decreasing water vapour pressure at 298 K. It hydrated when the relative humidity reached 30% [$p(H_2O) = 10^3$ Pa] (Fig. 6). On lowering the water vapour content, dehydration was observed at a relative humidity of about 7% [$p(H_2O) = 230$ Pa].

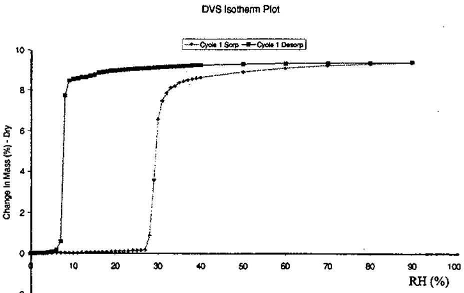


Figure 6. Isotherm of water activity

X-ray powder diffraction (T = 298 K, RH = 30 to 50%) showed that phase B was rapidly transformed into DH whereas phase A remained unchanged after 19 days under the same conditions. The anhydrous A form could only be transformed at room temperature into the dihydrate under very high relative humidity (>90% RH).

2.4 Zopiclone 'dimorphism'

Application of the first law of thermodynamics to the determination of melting and transition enthalpies yields $\Delta_m H(A) = 94$ J/g, $\Delta_m H(B) = 82$ J/g and $\Delta_t H(A \rightarrow B) = +12$ J/g. Taking melting points Si-l as triple points Si-l-v, a hypothetical transition A-B at low temperature would correspond to triple point A-B-*v* at the origin of the A-B equilibrium curve separating the B domain (stable at low temperature) from the A domain (stable at high temperature). This implies that the A-B equilibrium endothermally shifts on heating (Le Châtelier's principle). As this hypothesis is ruled out because $\Delta_t H(A \rightarrow B) > 0$, that of a stable B domain under pressure remains. However, this is ruled out by comparing (Le Châtelier's principle) the densities of the two phases [$V(A) < V(B)$]. Therefore, phase B appears to be metastable with respect to phase A, whatever the temperature or the pressure. Consequently, the transition from phase B to phase A appears to be an intrinsically monotropic process.

3. DISCUSSION

The zopiclone molecule is chiral. The crystal structure attributed to phase A (space group $P2_12_12_1$) is that of one of two enantiomers whereas that of phase B ($P2_1/c$) corresponds to a racemate [6].

In other words, immediately after melting of racemate B, conglomerate A (mixture of two enantiomers in equal proportions) forms then melts at a higher temperature than B. Thus the 'enantiomerisation', on heating, of a racemate (dehydrated dihydrate) prepared through nonstereospecific synthesis cannot be related to dimorphism.

In addition, when DH was heated (at 5 K/min, Fig. 7) in a sealed pan, an endothermic peak was observed (probably the peritexy of DH), followed by an exotherm and by a final endotherm peaking at 414 K. The exotherm may correspond to the transition from the metastable equilibrium 'phase B + liquid' to the stable equilibrium 'enantiomers + liquid'. If it is also assumed that $T_m(A)$ is the temperature of a eutexy forming between enantiomers, the melting point of each enantiomer can be

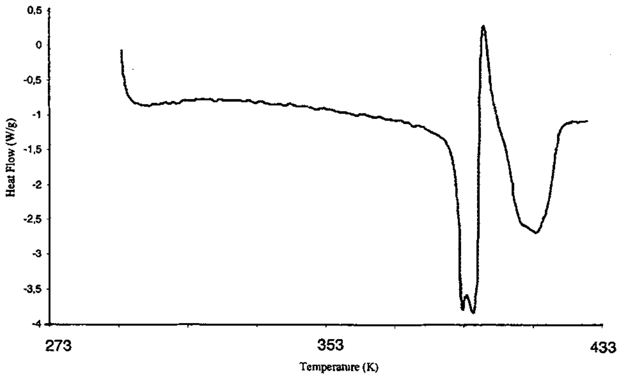


Figure 7. DSC curve of DH heated in a sealed pan (exo up).

calculated (Schröder equation) to be about 480 K. This implies that the dimorphism of each enantiomer is likely. Assuming that the melting of racemate B (420 K) is congruent, this indicates, in a T-x representation (Fig. 8), the existence of two metastable eutectic equilibria that are symmetric with respect to x = 0.5 and thus two liquidus curves from the melting points $T'_m(A)$ of the two enantiomers may exist, so that $T'_m(A) < T_m(A)$.

Lastly, all the DSC results obtained can be understood by taking into account the ternary system formed between water and the zopiclone enantiomers, which remains to be investigated.

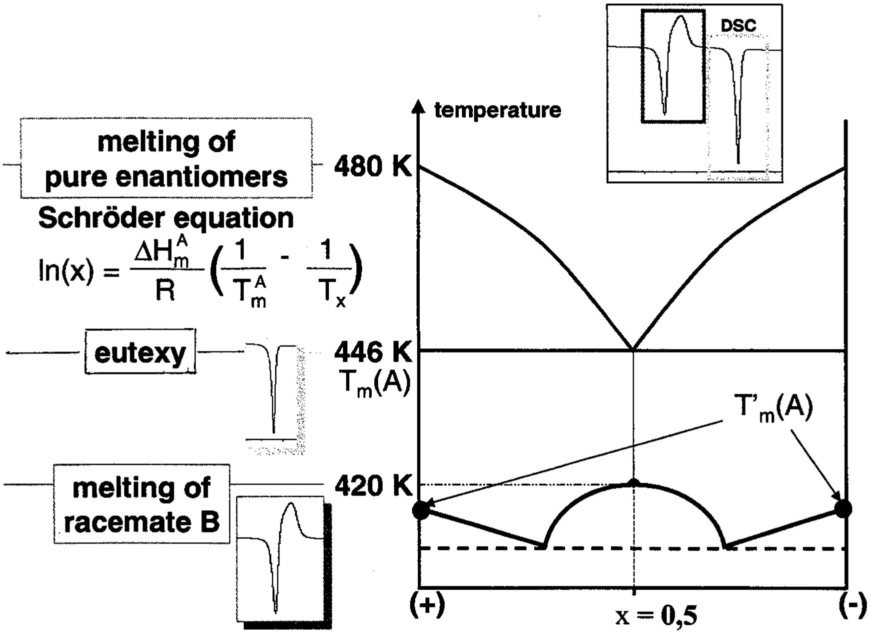


Figure 8. Hypothetical T-x binary phase diagram for (+) and (-) zopiclone system.

4. REFERENCES

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