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## Influence of solid/vapour equilibria on the stability of organic solids.

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### Abstract

The influence of water (in its gaseous state) on the stability of crystallized organic compounds was investigated. Through two examples of solid/vapour equilibria, several behaviours were highlighted (stoichiometric or non stoichiometric hydrates, hydration/dehydration mechanisms, stability domains of multi-hydrates as a function of relative humidity). Phase diagrams (as a function of partial water pressure) and stability diagrams have been proposed for each example. This study illustrates that solid/vapour equilibrium knowledge is a crucial step during the complete characterization of solid organic compounds.

### Keywords:

solid/vapour equilibrium, pharmaceutical compounds, hydration-dehydration

## 1 INTRODUCTION

In materials science, the study of interactions between water molecules and solid compounds is of prime importance. Indeed, these interactions impact on the behaviour of materials during many steps of their development (e.g. formation of a new phase during crystallization or storage, degradation by corrosion in drastic humidity conditions, caking, etc.).

In the field of organic solids, water/solid interaction play a great role as water is often used as a crystallization (co-) solvent or is present in ambient atmosphere facilitating the appearance of hydrated nuclei. Moreover, among the solvated crystalline phases, the specific class of hydrates is the most represented, in particular in pharmaceutical products [1]. As a consequence, the water (vapour) pressure could affect the behaviour of hydrated or anhydrous solid such as: the hydration level [2], the hydration-dehydration mechanism [3], the domain of deliquescence [4]; the presence of efflorescent hydrates; the formation of stoichiometric or non-stoichiometric hydrates [5], [6], the decrease of the glass transition temperature for amorphous solids (water = plasticizer) [7], [8].

Many experimental techniques permit to characterize these influences [9]. Among them, the association of techniques controlling the Relative Humidity (hereafter RH), like the Dynamic Vapour Sorption (hereafter DVS), with the static vapour sorption [10], the Infrared Spectroscopy [11] [12] [13] or classical analyses as X-Ray Powder Diffraction (XRPD hereafter), Thermogravimetric analyses associated to Differential Scanning Calorimetry (TG-DSC hereafter) [13], [14] are very helpful to understand solid-vapour equilibria.

The present study aims at describing these equilibria through some examples treated in our laboratory. It intends also to prove that phase equilibria determination can be helpful during the industrial development of an organic solid. In particular, the use of DVS combined with other characterization techniques (XRPD at different relative humidity) permitted us to draw theoretical phase diagrams between water and drugs, and illustrated the importance of the storage atmosphere.

## 2 MATERIALS AND METHODS

### 2.1 X-Ray Powder Diffraction (XRPD)

XRPD analyses (at ambient temperature and under ambient humidity) were performed on a D5000 matic diffractometer (Bruker) and those at variable temperature or humidity on a D5005 diffractometer (Bruker). Variable relative humidity was controlled inside the diffraction chamber by imposing a nitrogen flow conditioned at a specific relative humidity.

### 2.2 Karl Fischer water titration

Karl Fisher (KF) water titration was made using a KF 684 coulometer (Métrohm), coupled to a KF 688 oven (Métrohm).

### 2.3 Dynamic Vapour Sorption

Water vapour sorption and desorption were carried out with an accurate humidity and temperature controlled microbalance system (Dynamic Vapour Sorption DVS-1 type, Surface Measurement System, UK). Relative humidity was controlled by continuous gas flow containing pure nitrogen and water vapour in adequate proportions. Temperature and RH were measured with a precision of 0.1°C and 0.5% respectively. Mass variations were recorded continuously with a precision of 0.1 µg. Isotherms were constructed with 10 consecutive steps of relative humidity between 0% and 90% RH at 20°C (0 to 90% during sorption, 90 to 0% during desorption). The mass measured at a given step was considered constant when relative mass variations  $dm/dt$  remained below 0.001% for 10 min. The maximum stabilization time was adjusted to 2000 minutes.

### 2.4 Thermal analyses (TGA-DSC-MS)

Differential scanning calorimetry (DSC) coupled to Thermogravimetric (TG) analysis was performed on a TG/DSC NETZSCH STA 449 C or 409PC instrument. Samples were put in a 30 µl aluminium crucible and heated at a rate 5°C/min. He purging gas was used. The chemical nature of escaping gases during heating was identified by using a Netzsch QMS 403 C mass spectrometer coupled with the 449C TG/DSC apparatus.

### 2.5 Single Crystal X-Ray diffraction

Single crystals were stuck on glass fibers and mounted on the full three circles goniometer of a Bruker SMART APEX diffractometer (MoK $\alpha$ ,  $\lambda = 0.71073$  Å) with a CCD area detector. Three sets of exposures (1800 frames) were recorded, corresponding to three  $\omega$  scans, for three different values of  $\phi$ . The cell parameters and the orientation matrix of the crystal were preliminary determined by using SMART Software. Data integration and global cell refinement were performed with SAINT Software. Intensities were corrected for Lorentz, polarization, decay and absorption effects and reduced to  $F_o^2$ . The program package SHELXTL was used for space group determination, structure solution and refinement. The space group was reliably determined from systematic extinctions and relative  $F_o^2$  of equivalent reflections (XPREP). The structure was solved by direct methods (SHELXS).

## 3 RESULTS AND DISCUSSION

### 3.1 Determination of RH stability domains of successive hydrates

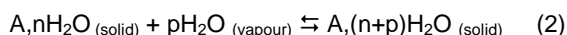
#### 3.1.1. Gibb's phase rule [6]

For a system in equilibrium, the Gibb's phase rule is suitable for thermodynamic interpretations of the hydrate formations. This rule gives the degree of freedom (or variance  $v$ ) as a function of the number of: independent components  $C$ , physical variables  $N$  (temperature, pressure) and phases in presence  $\phi$ :

$$V = C + N - \phi \quad (1)$$

Variance represents the number of independent variables that must be fixed to establish the state of the system. In the following examples, studies were performed at fixed temperature (i.e.  $N=1$ ).

Then, if we consider the formation of a hydrate under a certain RH ( $= (P_{H_2O} / P_{H_2O}^{sat})_{T=const}$ ), the following reaction is observed:



Where  $A, nH_2O_{(solid)}$  and  $A, (n+p)H_2O_{(solid)}$  are two hydrates with  $n$  and  $n+p$  molecules of water per molecule of substrate (i.e.  $n=0$  is the particular case of anhydrous).

In this case, the number of independent components equals 2 (3 components linked by one relation),  $\phi$  correspond to 1 (vapour phase) +  $\phi_s$  (number of differentiable solid phases). Finally:

$$V = 2 + 1 - \phi = 3 - \phi = 2 - \phi_s \quad (3)$$

From equation (3), two cases can be distinguished:

- The presence of two stoichiometric hydrates ( $A, nH_2O_{(solid)}$  and  $A, (n+p)H_2O_{(solid)}$ )  $\phi_s = 2$ , so  $V = 0$ . That is to say that, at a fixed temperature, the water pressure won't change until the complete transformation from  $A, nH_2O_{(solid)}$  to  $A, (n+p)H_2O_{(solid)}$ .
- The presence of a non-stoichiometric hydrate ( $A, nH_2O_{(solid)}$  and  $A, (n+p)H_2O_{(solid)}$  is actually a single phase), with  $\phi_s = 1$ , so  $V = 1$ . So, there is a continuous change of the solid phase composition with reference to the water partial pressure.

#### 3.1.2. Context

The first example chosen to illustrate the influence of RH on stability domains of successive hydrates is a pharmaceutical compound (DNCO hereafter). The solid has been characterized as a nonahydrate (SC-XRD) in water. Nevertheless, others hydrates with lower

stoichiometries were suspected. As presented in figure 1, batch n°1 was composed of nonahydrate phase only. Whereas, batch n°2 presented a lower water content (between 8 and 9 water molecules) and a different X-Ray pattern.

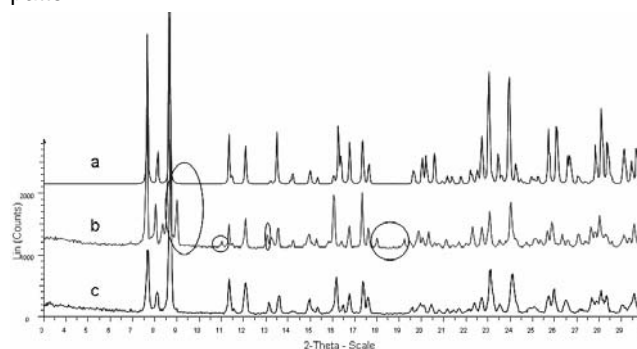


Figure 1: Compared XRPD patterns between DNCO, 9(H<sub>2</sub>O) calculated from the single crystal structure (a), DNCO batch 2 (b) and DNCO batch 1 (c). Ellipses show some differences in batch 2 compared to pure 9H<sub>2</sub>O.

#### 3.1.3. Experiments

Starting from the pure nonahydrate solid phase, X-Ray Powder Diffraction analyses at variable temperature (associated to KF titrations and TGA-DSC) have highlighted 4 hydrates: the nonahydrate, a phase containing at circa 7 H<sub>2</sub>O that seemed to be non stoichiometric, a phase containing 4.5 H<sub>2</sub>O and finally a high temperature phase containing 1.2-1.5 molecules of water which exhibits two polymorphic forms. Based on these determinations, it was proved that batch n°2 was a mixture of hydrates that explains its lower water content compared to the pure nonahydrate.

In order to determine RH stability domains of DNCO hydrates at fixed temperature  $T=20^\circ\text{C}$ , the combination between DVS and XRPD at variable RH was used. The DVS analysis (Figure 2) presents the comparison of isotherms ( $T=20^\circ\text{C}$ ) of sorption-desorption between the two batches (RH versus number of water molecules absorbed by the solid).

Remark: it was proved that the stoichiometry of batch 1 was 1/9 (DNCO/water in mol), so its stoichiometry was imposed to this batch at 50% RH. Moreover, because both batches exhibits the same water content at 0% RH, water stoichiometry of batch n°2 was then adjusted leading to an appropriate comparison between batches.

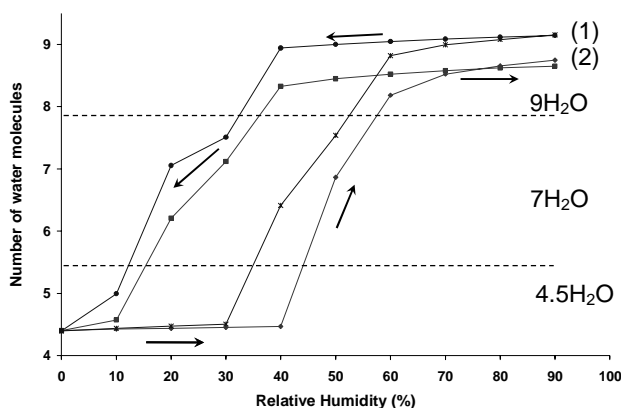


Figure 2: Sorption-desorption Isotherms ( $T=20^\circ\text{C}$ ) of batch 1 (1) and batch 2 (2) of DNCO.

The observation of DVS isotherm shows the presence of three domains of water stoichiometry (figure 2). Indeed, extreme RH (close to 0% and close to 90%) presented well defined stoichiometry (close to 4.5 water molecules and 9 water molecules respectively) and a third one (close to 7 H<sub>2</sub>O) could be present in the middle range of RH. (20 % < RH < 60%)

In order to confirm these hypotheses, X-Ray powder diffraction analyses at variable RH were performed. Thus, batch 1 and 2 were conditioned in the diffractometer under three successive RH: 23%, 0% and 75%. For each of the three RH values, XRPD were performed during 15 hours in order to observe phase transitions. The latest patterns (for each RH) recorded for batch n°1 (as an example) are presented in figure 3.

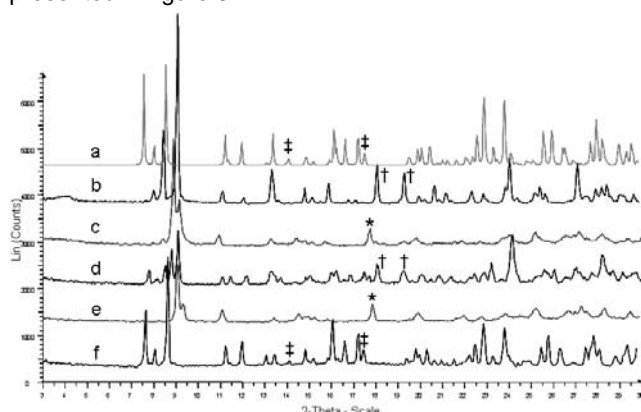


Figure 3: XRPD patterns at variable humidity performed on DNCO batch 1: 9H<sub>2</sub>O calculated (a), 7H<sub>2</sub>O phase (b), 4.5H<sub>2</sub>O phase (c), batch 1 under 23%RH (d), batch 1 under 0% RH (e) and batch 1 under 75% RH (f). Symbols ‡, † and \* highlight specifics peaks of respectively: 9H<sub>2</sub>O phase, 7H<sub>2</sub>O phase and 4.5H<sub>2</sub>O phase.

The results confirmed the domains proposed after DVS analyses. At 23% RH, a mixture between 9H<sub>2</sub>O and 7H<sub>2</sub>O is observed in both batches, but the patterns seemed to evolve toward the 7H<sub>2</sub>O phase over time. This non complete transition could be due to a low kinetic of phase transition in the solid state. At low RH values (close to 0%RH), the two batches collapse into the 4.5H<sub>2</sub>O phase. At high RH values, the batch n°1 was constituted by the nonahydrate, whereas the batch n°2 exhibits still a mixture between the 9H<sub>2</sub>O and the 7H<sub>2</sub>O, confirming the observations by using KF titration and XRPD analyses.

### 3.1.4. Discussion

X-ray diffraction associated with DVS measurements have led to the characterization of several DNCO hydrates. Three domains of hydrates stability were identified at 20°C between 90% and 0% RH: 9H<sub>2</sub>O, 7H<sub>2</sub>O and 4.5H<sub>2</sub>O. These analyses could not permit to conclude on the stoichiometric character of these phases, especially for the 7H<sub>2</sub>O phase. The 1.2-1.5 hydrated phase did not appear accessible at this temperature. Thus, the influence of partial water (vapour) pressure on the DNCO hydrates is summarized in figure 4.

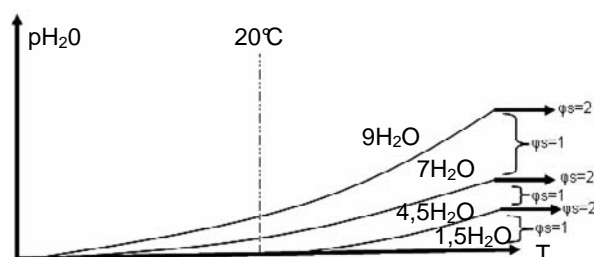


Figure 4: Influence of vapour partial pressure on DNCO.

Moreover, a hypothetical binary diagram (at 20°C and under atmospheric pressure) between DNCO, 4.5H<sub>2</sub>O and water could be proposed (figure 5). According to the collected experimental information, the solid phase 7H<sub>2</sub>O was described as a putative non stoichiometric hydrate.

This study led us to postulate some rationales to explain the differences in water content between batches. The best storage conditions could be also proposed in order to ensure the integrity of crystallized batches.

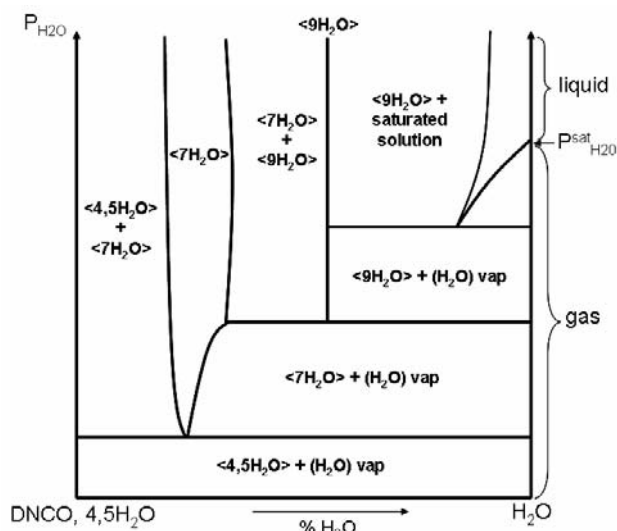


Figure 5: Schematic binary diagram (DNCO hydrates/water) as a function of the partial vapour pressure of water at 20°C.

## 3.2 Mechanism of hydration-dehydration

### 3.2.1 Context

This part aims at the elucidation of the hydration/dehydration mechanism of ciclopirox olamine (2-aminoethanol salt of 6-cyclohexyl-1-hydroxy-4-methylpyridin-2-(1H)-one) (figure 6) [15].

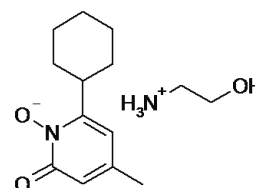


Figure 6: Developed formula of the salt of ciclopirox 2-aminoethanol (1:1)

Remarks:

- The numbers in parenthesis indicate the stoichiometry in ciclopirox and olamine respectively
- This salt exists with two different stoichiometries (the 1:1 and the 2:1). Both of them exhibit a monohydrated form.

### 3.2.2. Experiments

Crystal structures of anhydrous phase and monohydrate of ciclopirox olamine (1:1) were determined by single crystal X-ray diffraction (figure 7). Both crystal structures present some similarities (space group and cell parameters), but no structural filiations were observed between the monohydrate and the anhydrous form. Indeed, a change of ciclopirox molecules orientations appeared during dehydration, inducing a destructive dehydration process. In order to understand the hydration mechanisms of this salt, sorption-desorption isotherms were collected by using DVS measurements at 20°C (figure 8).

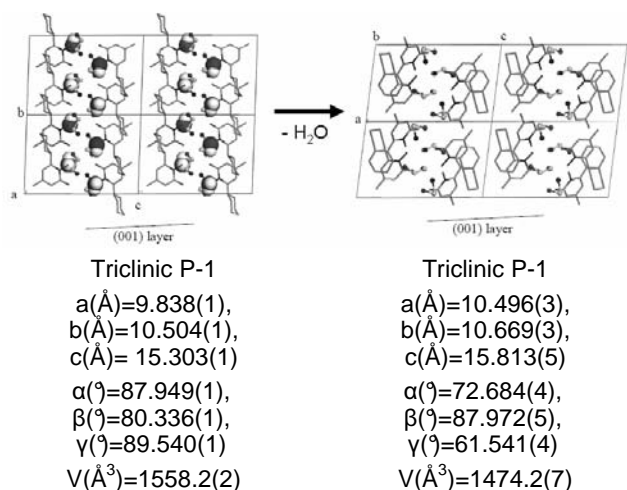


Figure 7: Crystallographic data (single crystal X-ray diffraction) of ciclopirox olamine (1:1) monohydrate(left) and anhydrous(right) salt

During dehydration, a mass loss (7%) which is superior to the theoretical mass (6,2%) is observed. Moreover, the mass uptake related to the hydration of ciclopirox (1:1) under RH>60 to 80% was decreasing during the successive sorption-desorption cycles (figure 8). The non reproducibility of the mass uptake/loss during successive cycles indicates that there was, during the drying step, a simultaneous dehydration/degradation mechanism.

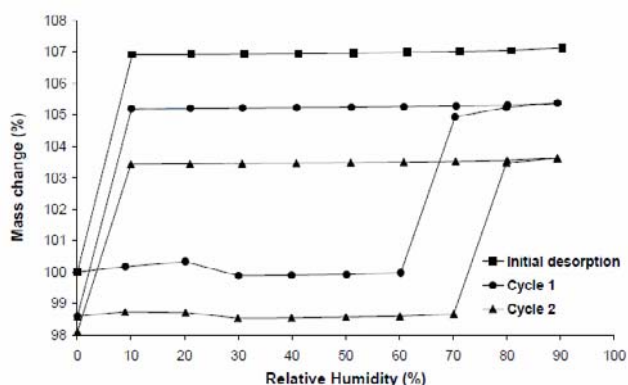


Figure 8: Sorption-desorption isotherms made on ciclopirox olamine (1:1) hydrated salt at 20°C

In parallel, XRPD analyses carried out on product stored under drying condition after three sorption/desorption cycles have confirmed the evolution from the ciclopirox olamine (1:1) towards the (2:1) stoichiometry (figure 9). This irreversible transformation in ambient conditions is due to the departure of a part of ethanolamine molecules (evaporated by the drying nitrogen flux). The kinetic of degradation appeared slow, explaining why a mixture between (1:1) salt and (2:1) salt is obtained (figure 9). A cooperative departure of ethanolamine and water is thus observed during drying, which is likely to be due to a destructive reconstructive mechanism of dehydration.

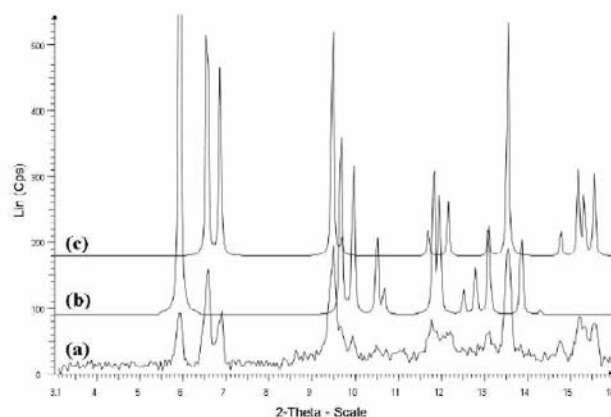


Figure 9: XRPD patterns of (a) ciclopirox olamine (1:1) stored under drying condition in the DVS apparatus after three sorption-desorption cycles compared to (b) ciclopirox olamine (1:1) calculated and (c) ciclopirox olamine (2:1) calculated

### 3.2.3. Discussion

Comparison between the anhydrous and hydrate crystal structures has pointed out a lack of structural filiations. The combination of these results with DVS data (under normal conditions) and XRPD analyses have confirmed the destructive process of the dehydration because of the formation of (2:1) salt resulting from the concomitant departure of water and olamine molecules. According to this line of reasoning the amorphous transient state and the weakness of the ionic bond in ciclopirox olamine (1:1) salt consistent with a  $\Delta pka$  ca. 2.5 are both responsible for the progressive deviation in the 1:1 stoichiometric ratio upon successive cycles of dehydration-rehydration. This degradation can be avoided by working under saturated 2-aminoethanol vapour pressure. Under this specific condition, the dehydration/hydration mechanism of the ciclopirox olamine (1:1) monohydrate becomes reversible. This study have highlighted that without careful precaution during a drying step, the ciclopirox olamine (1:1) evolve irreversibly towards the formation of the (2:1) ciclopirox olamine salt. A diagram of stability of ciclopirox olamine phases can therefore be proposed (figure 10)[15].

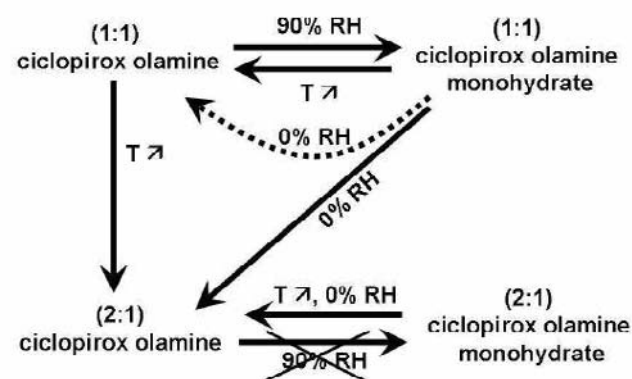


Figure 10: Nature of the ciclopirox olamine salts versus temperature and/or humidity (full line: normal conditions, dotted line: under 2-aminoethanol vapour pressure)

## 4 CONCLUSIONS

The combination of the following techniques XRPD, DVS, single crystal X-ray diffraction applied to the characterization of solid/vapour equilibria lead to a rather clear picture of the nature of the phases in competition.

These data lead to define precise conditions of dehydration – rehydration and storage of hydrates. The two examples treated here also highlight the benefit of a comprehensive knowledge of the rehydration –dehydration mechanism. Indeed it can be necessary to avoid degradation of an active pharmaceutical ingredient.

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