Hydration and Dehydration of the Pure Enantiomer and the Racemic of Phencyphos

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Abstract

This study is devoted to the understanding of phencyphos hydration/dehydration behaviour. Phencyphos is a resolving agent used in the so-called Dutch resolution. Batches of phencyphos contain various amounts of water (from 0 to 1 equivalent of water) evolving over time, inducing wrong dosages.

Phase diagrams between phencyphos, water and methanol or ethanol were determined. Then, solid phases were characterized and compared with the means of X-ray Powder Diffraction, InfraRed spectroscopy, Differential Scanning Calorimetry and Dynamic Vapour Sorption. All these experiments have led to reliable conversion methods and storage conditions.

Keywords:

Phencyphos, Hydration, Dehydration, Phase diagrams

1 INTRODUCTION

Phencyphos, or 2-hydroxy-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane (Figure 1), is a resolving agent belonging to the phenylcyclophosphoric acid family. This family is one of the resolving agent family used in Dutch resolution [1].

Enantiopure phencyphos is used in chiral purification, and asymmetric induction, inhibition or synthesis.

The amount of water in batches of phencyphos (racemic from suppliers or home-made enantiopure) is variable (from 0 to 7% in mass, consistent with 0 to 1 equivalent of water) and is evolving over time. This can induce wrong dosages and unwanted introduction of water when using phencyphos (PP hereafter). This study is devoted to the understanding of its hydration/dehydration behaviour, in order to develop robust conversions and stable storage methods.

2 PHASE DIAGRAMS

2.1 (R)-phencyphos/(S)-phencyphos/solvent system

In a previous study [2] performed at Syncom BV. It has been highlighted that anhydrous racemic phencyphos crystallizes as a racemic compound ((RS)-PP hereafter) (Figure 2) while its monohydrate crystallizes as a conglomerate (equimolar mixture of (R)-PP.H_2O and (S)-PP.H_2O phases) (Figure 3).
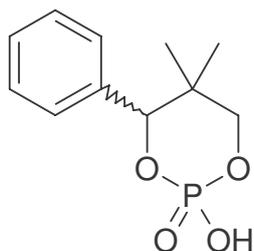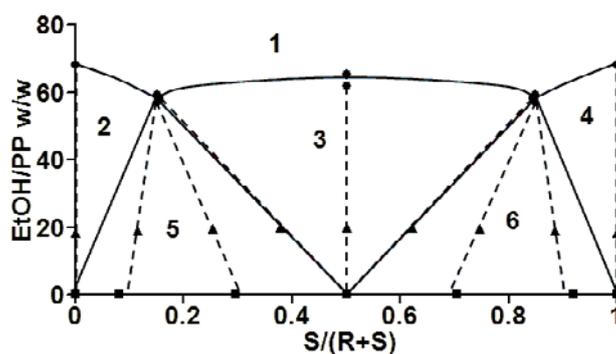

Figure 2: Jänecke representation of the phase diagram of phencyphos in ethanol (EtOH) at 25 °C. Domains are delimited by solid lines: 1: liquid, 2: <(R)-PP>+liq., 3: <(RS)-PP>+liq., 4: <(S)-PP>+liq., 5: <(R)-PP>+<(RS)-PP>+liq., 6: <(S)-PP>+<(RS)-PP>+liq. Dashed lines show experimental determination
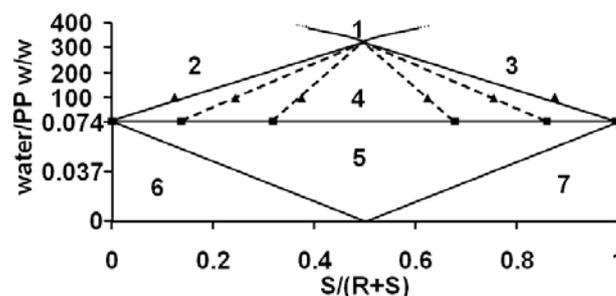

Figure 3: Jänecke representation of the phase diagram of phencyphos in water at 25 °C. Domains are delimited by solid lines: 1: liquid, 2: <(R)-PP.H_2O>+liq., 3: <(S)-PP.H_2O>+liq., 4: <(R)-PP.H_2O>+<(S)-PP.H_2O>+liq., 5: <(R)-PP.H_2O>+<(S)-PP.H_2O>+<(RS)-PP>, 6: <(R)-PP.H_2O>+<(R)-PP>+<(RS)-PP>, 7: <(S)-PP.H_2O>+<(S)-PP>+<(RS)-PP>. Scale has been discontinued to make domains 5, 6 and 7 visible. Dashed lines show experimental determination

Figure 1: Phencyphos, $C_{11}H_{15}PO_4$, MW = 242.21g.mol^{-1}

2.2 (R)-phencyphos/(S)-phencyphos/solvent/water system

In order to find conditions to prepare anhydrous or hydrated samples, the quaternary system (R)-phencyphos/(S)-phencyphos/water/solvent system has to be studied. Phencyphos monohydrate is quite insoluble in water while anhydrous phencyphos has poor solubilities in almost all usual solvents. Methanol (MeOH hereafter) was chosen as cosolvent because of its acceptable solubilisation of PP and its volatility. The racemic section of the quaternary diagram phencyphos/water/methanol has been determined (figure 4). As enantiopure and racemic phencyphos have quite the same solubility in methanol (cf; fig.2) and as its monohydrate is quite insoluble whatever the enantiomeric excess, the ternary border of the studied quaternary system (i.e. enantiopure phencyphos/water/ methanol) should be similar to the racemic section.
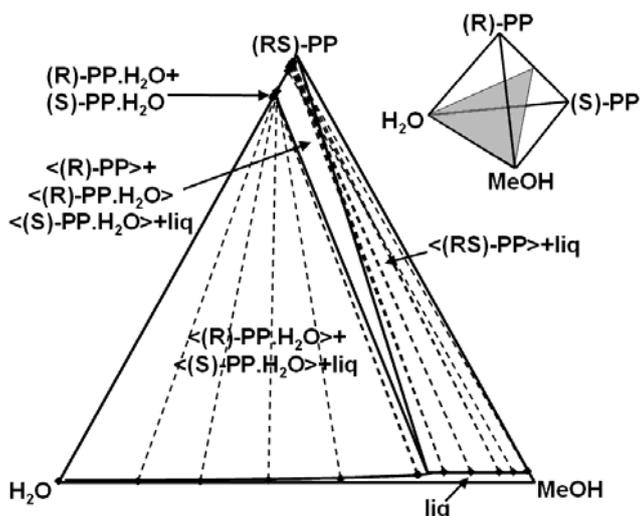
Figure 4: experimental racemic section of the phencyphos/water/methanol phase diagram in mass fraction at 25 °C. This section is extracted from the quaternary diagram on the top right corner. Dashed lines show experimental determination

From this diagram, preparation protocols have been developed:

- PP suspended in dry methanol will give the anhydrous form,
- PP suspended in wet methanol will give the monohydrate form (a minimal fraction of 20% in mass of water is required in racemic conditions, less for the enantiopure).

2.3 Phase characterization

Four solids have been prepared:

- Anhydrous enantiopure phencyphos, noted (R)-PP
- Anhydrous racemic compound, noted (RS)-PP
- Enantiopure phencyphos monohydrate, noted (R)-PP.H_2O
- Phencyphos monohydrate conglomerate, noted PP.H_2Ocongl (i.e. equimolar mixture of phases (R)-PP.H_2O and (S)-PP.H_2O)

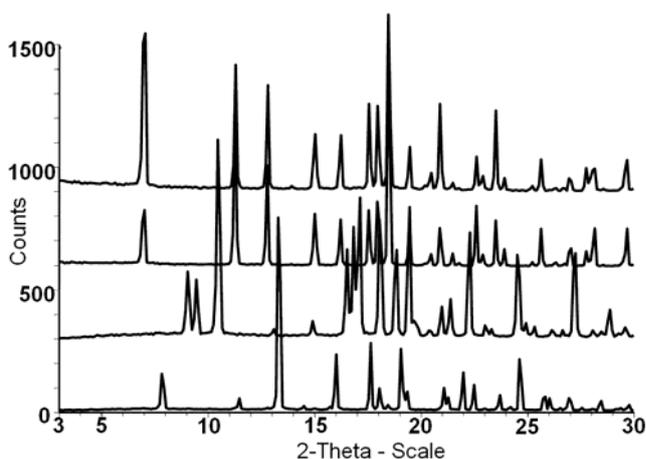These solids were characterized by IR spectroscopy and XRPD (Figure 5)

Figure 5: Experimental X-ray powder diffraction patterns of the 4 solids prepared in suspension. From bottom to top: (R)-PP, (RS)-PP, (R)-PP.H_2O and PP.H_2Ocongl

3 PHASE BEHAVIOUR

3.1 Dessicating, heating, rehydration

Different treatments have been applied to samples:

- storage under 100%RH to induce hydration,
- storage under 0%RH or heating at 80 °C under vacuum to cause dehydration.

The mass and the nature of samples have been monitored during these treatments.

(RS)-PP did not respond to hydration treatment (even after 40 days of storage at 100%RH).

Conversely, (R)-PP can be hydrated and dehydrated reversibly within a day.

PP.H_2Ocongl can also be dehydrated are rehydrated reversibly. However, after dehydration, a metastable anhydrous conglomerate (PPcongl) is obtained instead of (RS)-PP.

3.2 Differential scanning calorimetry

The thermal behaviour of solids has been studied by DSC. Analyses were performed several times and interrupted just after thermal phenomena to immediately check the phases by Infrared Spectroscopy or XRPD.

(RS)-PP and (R)-PP

Only one phenomenon occurs: an endotherm immediately followed by an exotherm at circa 200-230 °C. This phenomenon corresponds to a thermally activated chemical degradation of the phencyphos (Figure 6). This phenomenon cannot be used to identify phases as a melting can.

(R)- PP.H_2O (from suspension and from 100%RH)

Although chemically (same mass loss on dehydration) and structurally (XRPD, IR) identical, (R)-PP.H_2O prepared in suspension and (R)-PP.H_2O formed in a 100%RH atmosphere differ on their dehydration endotherm (Figure 7) starting at about 60 °C. It is wider for the former (end around 150 °C @10K/min) than for the latter (end around 135 °C @10K/min) and presents two steps.
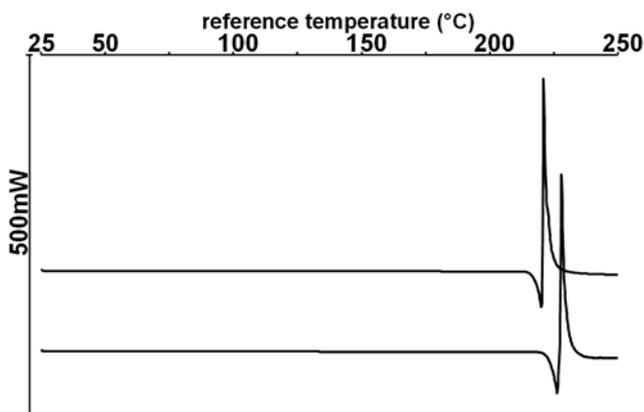
Figure 6: Thermograms of (RS)-PP (top) and (R)-PP (bottom). The heating rate was 10K/min
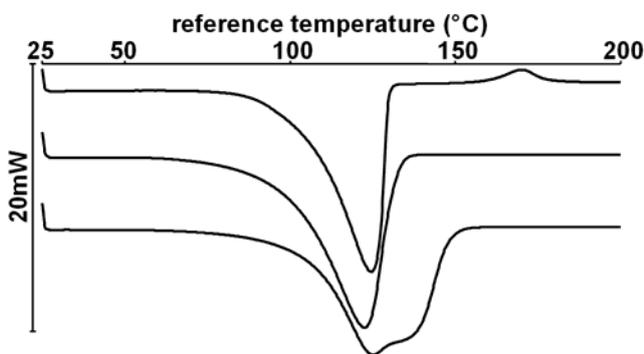

Figure 7: Detail of thermograms at 10K/min of hydrated phases. From bottom to top: (R)-PP.H_2O (from suspension), (R)-PP.H_2O (from 100%RH), and PP.H_2Ocongl

As already seen in lactose hydrate by Garnier et al. [3], this dehydration in two steps can be explained by the existence of several dehydration mechanisms for a same crystalline phase. Crystallinity, defects, crystal size, adsorbed impurities, amorphous coating, etc, can make easier some mechanisms than others. More investigations are needed to support this hypothesis.

Both thermograms end by the same degradation as anhydrous phases.

PP.H_2Ocongl

The thermogram of PP.H_2Ocongl starts with a wide dehydration endotherm from 75°C to 130°C (similar to (R)-PP.H_2O). A small exotherm follows, spread from 140° to 190°. It corresponds to the irreversible transition from metastable PPcongl (obtained after dehydration) to (RS)-PP. The thermogram ends by the thermal degradation like the other solid phases of the system.

3.3 Dynamic vapour sorption

In order to confirm the results obtained by static storages at 0%RH or 100%RH, a DVS study at 20°C has been carried out

Monohydrated phases

Samples of (R)-PP.H_2O and PP.H_2Ocongl were studied by DVS. A 90-0-90-0%RH program was used (Figure 8). Both show quite the same behaviour.

During the desorption steps (90%RH to 0%RH), no mass loss was recorded until 0%RH was reached. During this drying stage, the dehydration starts after a short incubation time (20 minutes for the first dehydration, only 2 minutes for the second one), it accelerates then slows down before stabilization (sigmoid evolution of the mass).

The mass loss of 6.9% is consistent with the theoretical value (6.92%)
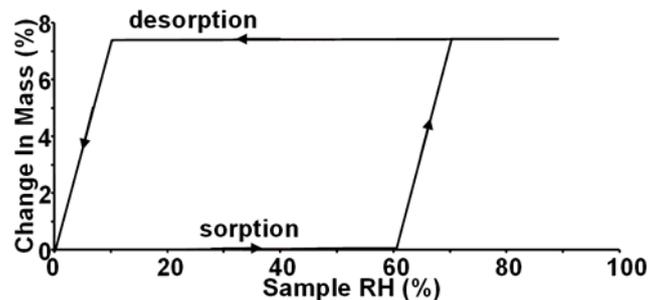

Figure 8: mass change of phencyphos monohydrate during desorption/sorption cycles

During sorption steps, no mass uptake was recorded below 70%RH. The mass uptake was consistent with the theoretical value and it has the same kind of sigmoid evolution.

This sigmoid evolution of the mass is characteristic of a nucleation/growth process: the original phase stands in a metastable state until nuclei of the new phase appear and start to grow (releasing or absorbing water).

The RH thresholds of the dehydration and the hydration are much apart, which is characteristic of dehydration/ hydration mechanisms involving high activation energies.

(RS)-PP

This phase remained unchanged regardless RH variation. These results confirm that racemic phencyphos is refractory to hydration via moisture.

Thus, contrary to the enantiopure anhydrate, hydration of the racemic compound seems very difficult if not mediated by a solvent.

3.4 Discussion

We can sum up all the results obtained in the two following charts (Figure 9 & Figure 10).

This study has shown that a total reversibility of the hydration/dehydration is observed for enantiopure solids. Concerning the set of racemic solids ((RS)-PP, PPcongl and PP.H_2Ocongl), this reversibility exist only in suspension. Indeed, hydration of the racemic compound cannot be solvent-free, while solvent-free dehydration of the monohydrate conglomerate (PP.H_2O congl) never leads to the racemic compound (unless a 140°C is reached). Moreover PPcongl may be difficult to obtain in a solvent (metastable).
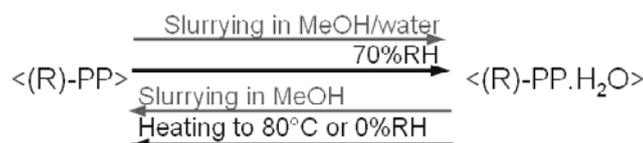

Figure 9: Phase transformation chart for enantiopure phencyphos. Solvent mediated conversions are represented in grey and solvent-free conversions in black
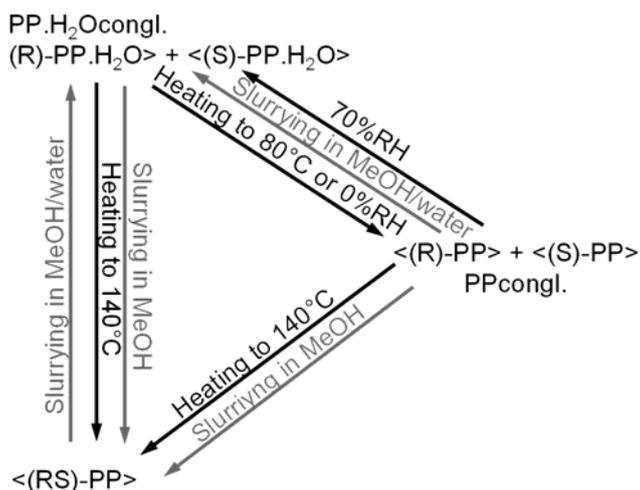
Figure 10: Phase transformation chart for racemic phencyphos. Solvent mediated conversions are represented in grey and solvent-free conversions in black

The stability of the anhydrate racemic compound in a solvent-free medium even under high RH could find some explanation.

Indeed, a water layer exists on every surface exposed to moisture. This layer should dissolve a tiny amount of material that could recrystallize as the monohydrate, but it appeared that nothing happened. Two possible and complementary hypotheses can be formulated:

- The kinetic of hydration is very low and on short time-scale, the hydration is not detectable
- The hydration of the surface creates a waterproof layer, making further hydration very slow if not impossible

4 CONCLUSION

The degree of hydration of phencyphos has been studied. Behaviours difference have been shown between racemic and enantiopure material. Indeed, enantiopure anhydrate is hygroscopic and the racemic compound is not.

Fully hydrated phencyphos and anhydrous racemic compound can be stored in ambient conditions, while enantiopure anhydrate and metastable anhydrate conglomerate should be kept in dry conditions. Apart from the racemic compound, hydration and dehydration can be carried out reversibly by storage at a suitable RH.

Some investigations should be carried out to complete the present work:

- Structural determination (in progress) and molecular modelling as well as hot-stage and RH controlled microscopy to understand the hydration/dehydration mechanism.
- Influences of crystal size distribution, mechanical stress (miling, grinding) or other treatment (ageing, preheating) to understand the presence of the two-step dehydration peaks in the thermogram of some samples.

5 EXPERIMENTAL PART

5.1 Chemicals used

Phencyphos was supplied by Syncom BV. Two batches were used. (±)PPbatch, a racemic batch that contains 6% in mass of water, and (−)PPbatch, a 98%ee batch that contains 5% in mass of water.

Methanol (J.T. Baker) was used without further purification (99.8%)

Water was produced using an "ELGA Purelab Option" water purifier.

5.2 Characterization techniques

Almost all X-ray powder diffraction patterns were measured at IMM (Nijmegen) on a D8 diffractometer from Bruker (Cu Kα, λ=1.5418Å), with a 2-theta/theta locked setup. Acquisition was done from 1.000° to 50.074° with a step size of 0.101° and a step time of 4 seconds. Other were measured in SMS laboratory (Rouen) on a D5000Matic from Bruker (Cu Kα, λ=1.5418Å), with a 2-theta/theta locked setup and acquisition from 3° to 30° with a step size of 0.04° and a step time of 1 second. Powder diffraction experiments were done at room temperature

DSC experiments were carried out using a DSC822e from Mettler Toledo. 40µL aluminium crucibles sealed with a perforated aluminium lid were used. The heating rate was 10K/min.

DVS studies were done in SMS laboratory (Rouen), using DVS-1 instrument (Surface Measurement Systems, London UK). Measurements were done at 20°C, with steps of 10%RH, using a threshold of 0.0005%in mass per minute and a waiting delay of 2000 min (a step cannot last more than 2000 minutes and it ends when the mass variation is less than 0.0005% per minutes).

5.3 Solid phase preparation

Starting materials were suspended in a suitable solvent and stirred at room temperature for 2 days. The suspensions were then filtered under vacuum and the collected solids were dried (12hrs at 80°C under vacuum for anhydrous phases, 3 days in ambient conditions for the monohydrate). Details are given in the following Table 1

Solid prepared	Starting material	Solvent used	Solid/solvent ratio w/w	yield
(R)-PP	(−) PPbatch	MeOH	0.15	75%
(RS)-PP	(±) PPbatch	MeOH	0.15	80%
(R)-PP.H₂O	(−) PPbatch	MeOH:H₂O 1:1 w:w	0.15	70%
PP.H₂O congl.	(±) PPbatch	MeOH:H₂O 1:1 w:w	0.2	94%

Table 1: experimental details for each solid prepared in suspension

6 REFERENCES

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7 ACKNOWLEDGEMENT