

## Communication

# Resolution of a Metastable Racemic Compound of Anhydrous Phencyphos by Hydrate Formation

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**Abstract:** The resolution of 2-hydroxy-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinan 2-oxide (phencyphos) was achieved by dissolution of anhydrous racemic phencyphos, a racemic compound, accompanied by simultaneous secondary nucleation of the dissolved racemate on to enantiopure seeds of phencyphos hydrate, a conglomerate. The seeds were placed in separate compartments and the pure enantiomers could be conveniently collected from these compartments after the dissolution of the anhydrous racemate.

**Keywords:** resolution; phencyphos; pseudo-polymorph; conglomerate; racemic compound



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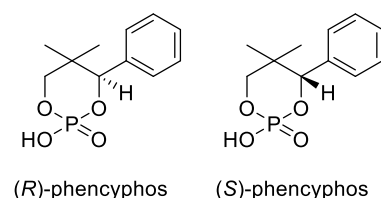
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## 1. Introduction

The cyclic phosphoric acid phencyphos (2-hydroxy-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinan 2-oxide, Figure 1) is an ideal resolving agent for many racemic (weak) bases by diastereomeric salt formation (classical resolution) [1]. Ironically, racemic phencyphos itself is not conveniently resolved into its separate enantiomers by diastereomeric salt formation. With nearly all basic resolving agents, resolution is hampered by gel formation and low diastereomeric excesses in the first formed precipitates. These complications lead to lengthy recrystallizations, low yields, and thus an inefficient resolution.



**Figure 1.** Enantiomers of phencyphos.

Racemic phencyphos, on exposure to water, readily forms a stable monohydrate. The water molecule is hydrogen bonded to the phosphate in the crystal. Three phencyphos molecules and three water molecules form a ten-membered ring [1,2]. The conglomerate hydrate is stable when enough water is present. The hydrate can be dehydrated when exposed to dry air but re-hydrates with moist air [3].

It is also known that the phencyphos hydrate is a conglomerate [2], a crystal form in which the enantiomers crystallize in separate crystals. We have reported previously that resolution via preferential crystallization is possible. Note that the racemate of phencyphos anhydrate forms a racemic compound, in which the crystals contain both enantiomers in equal amounts and in an ordered fashion. This racemic compound has a relatively high eutectic composition of 70% ee in ethanol [4].

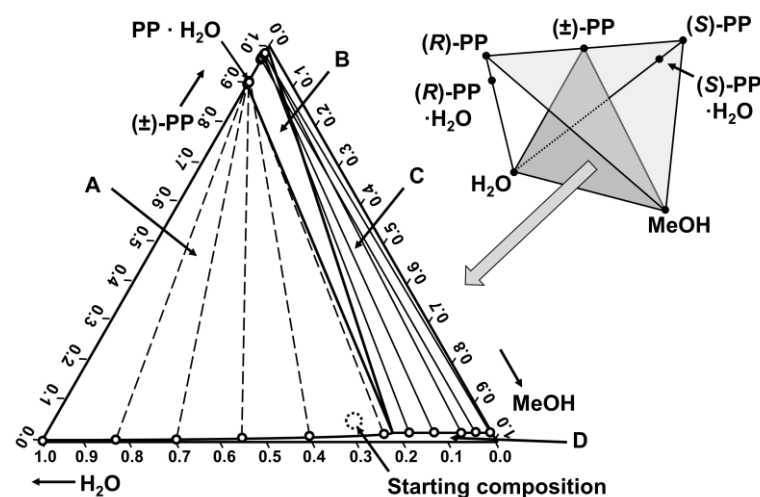
This system of anhydrate/hydrate is therefore a polymorphic relationship in which the transition is accompanied by either addition or loss of a water of solvation [5,6].

Although resolution by preferential crystallization is elegant and scalable, it requires the continuous attention of an operator [4]. We were curious to see if use could be made of the pseudo-polymorphism to carry out a resolution.

There is precedent. For example, 2-chloromandelic acid occurs in two pseudo-polymorphic forms, one a racemic compound and the other a conglomerate. The conglomerate form can be isolated by freeze drying [7]. Also, the deracemization of racemizable compounds by transitions of meta-stable phases into a single enantiomer have been described [8–10]. However, as far as we are aware, polymorphism has not been used to power a resolution of enantiomers of non-racemizable compounds. We considered the possibility of successful use of a polymorphic transition of phencyphos into phencyphos hydrate high and set out to build a device for a simple and hands-off resolution. A proof of principle is provided here.

## 2. Results

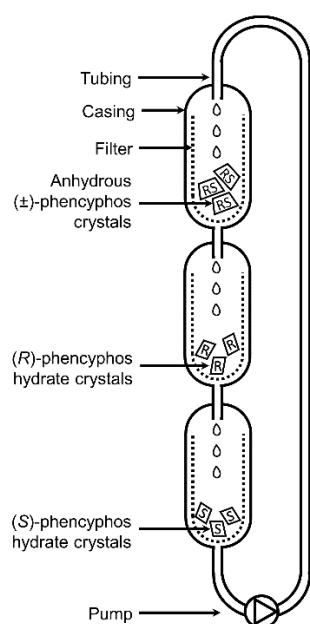
The ternary phase diagram of mixtures of racemic phencyphos in a mixture of methanol and water is shown in Figure 2. At a low water concentration and a sufficiently high concentration of racemic phencyphos (region C), anhydrous phencyphos will crystallize as a racemic compound. However, when sufficient water and phencyphos are present (region A) all material that crystallizes will be phencyphos hydrate, which is a conglomerate. When solid anhydrous phencyphos is introduced to a mixture of water and methanol in such a concentration that the overall composition is in region A, the anhydrous phencyphos will partly dissolve and generate a supersaturated solution of phencyphos hydrate in which, given enough time, primary nucleation of phencyphos hydrate will occur and (via crystal growth) will completely consume the solid anhydrous phencyphos. By the same token, if seeds of both enantiomers of phencyphos hydrate were to be added, these would also consume the anhydrous phencyphos and would lead to overall resolution.



**Figure 2.** Solubility diagram of racemic phencyphos (PP), water and MeOH at 20 °C in weight fractions which is the middle section of the quaternary phase diagram depicted in the top-right corner. Region A: Solid  $\text{PP} \cdot \text{H}_2\text{O}$  (conglomerate) and solution. Note that the tie-lines depicted in this region radiate out of this plane towards the edges of the quaternary phase diagram where  $(R)\text{-PP} \cdot \text{H}_2\text{O}$  and  $(S)\text{-PP} \cdot \text{H}_2\text{O}$  are located, Region B: mixtures of anhydrous PP,  $\text{PP} \cdot \text{H}_2\text{O}$  and solution. Region C: Solid anhydrous PP (racemic compound) and solution. Region D: undersaturated solution. Open dots are measured points.

The experimental setup depicted in Figure 3 was constructed in which the “U” shaped lines represent Soxhlet filters, which are placed inside a plastic casing. The top filter was charged with a suspension of 10 g of anhydrous  $(\pm)$ -phencyphos in 30% wt.  $\text{H}_2\text{O}$  in MeOH (this starting composition has been marked in Figure 2). The middle filter was charged with ~200 mg enantiopure  $(R)$ -phencyphos hydrate seeds and the bottom filter

with ~200 mg enantiopure (*S*)-phencyphos hydrate seeds. The suspension in the top filter is slightly supersaturated in phencyphos hydrate and, after passing through the top filter, the clear solution passes on to the middle filter by gravity. There, the supersaturated (*R*)-enantiomer crystallizes on the seeds of the (*R*)-phencyphos hydrate. The solution which is supersaturated in the (*S*)-enantiomer passes through the filter and crystallizes on the seeds of (*S*)-phencyphos hydrate in the bottom compartment. The filtrate from the bottom filter is then pumped to the top filter dissolving some of the anhydrous phencyphos racemate for another run.



**Figure 3.** Schematic representation of the practical setup.

After three days the filters were inspected. The top filter contained 270 mg of racemic material, the middle filter contained a dense cake of 3.30 g of (*R*)-phencyphos hydrate with 98% ee, and the bottom filter contained a dense cake of 3.70 g of (*S*)-phencyphos hydrate with 99% ee. Since the solution also contained some phencyphos, the sum of all filter contents is not equal to the amount of material put into the top filter. The small difference in yield between the two crops may be caused by small variances in crystal size of the seeds and the flow of the liquid around the crystals. As the two crops had not been washed with fresh solvent, there may be some residual mother liquor in the solids which can explain the slight differences in optical purities between the crops.

### 3. Discussion

The resolution by hydrate formation as described above appears to be an ideal, totally hands-off method to resolve anhydrous racemic phencyphos by a pseudo-polymorphic transition into the hydrate. This technique resembles the technique known as ‘continuous preferential crystallization’ in which two or three stirred reactors are coupled via a system of pumps and filters [11,12]. Other than in our system, supersaturation of the enantiomers is accomplished by a temperature difference between the feed tank (containing the racemate) and the crystallizers (containing seeds of the pure enantiomers). We note that for larger scale application the troublesome clogging of filters needs to be avoided. The process is also relatively slow. Moreover, a lagging supersaturated liquid phase could start primary nucleation and ruin the process, although we do believe that high supersaturation is not achieved as the liquid is only in contact with the crystals for a short period of time and crystal dissolution is not a fast process. We have attempted here only to demonstrate proof of principle and have not attempted to optimize the process for bulk production. This type of resolution might well be useful for the resolution of conglomerates which form

hydrates/solvates. One might even consider using this method for the resolution of a racemate that forms more than one polymorph. A requisite is that the enantiopure seeds form a conglomerate and are more stable than the racemate in the top filter. Furthermore, a polymorphic transition of the racemate in the top filter should not be able to take place through the solid phase.

#### 4. Experimental Section

A setup was built as the one shown in Figure 3. This setup consisted of three Soxhlet filters (41 × 123 mm) each fitted in a PE casing having a funnel type opening in the bottom. The system was fitted with PTFE tubing (ø 8 mm) and a pump (KNF Liquipor). Enantiopure seeds of phencyphos hydrate were prepared by triturating ~95% ee phencyphos hydrate (200 mg) in a hot mixture of water:MeOH (1:3, 0.5 mL) and allowing it to cool to RT. The next day the suspensions were allowed to settle. The wet (R) seeds were placed in the middle filter and the wet (S) seeds were placed in the bottom filter.

Racemic phencyphos mono hydrate (10 g, 38 mmol) was taken up in hot MeOH (170 mL). The resulting solution was given a polish filtration and allowed to cool to RT with stirring. The resulting suspension containing anhydrous racemic phencyphos was treated with water (56 mL, resulting in a mixture of 30% wt water in MeOH) and the suspension was transferred to the top filter. The pump was switched on at such a speed that no air was pumped to the top filter. After three days the rig was disassembled. The solids were isolated from the filter by careful removal with a spatula and dried in vacuo without washing of the solid. The middle filter contained a dense cake of 3.30 g (32% yield) of (R)-phencyphos hydrate with 98% ee and the bottom filter contained a dense cake of 3.70 g (36% yield) of (S)-phencyphos hydrate with 99% ee. The top filter contained 270 mg of racemic material.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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