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# The Resolution of 2-Hydroxy-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinan 2-Oxide (Phencyphos) by Preferential Crystallization

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**Abstract:**

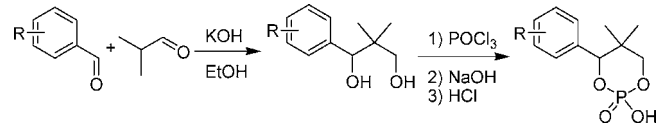
**An inexpensive, reliable resolution method for the resolving agent, 2-hydroxy-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinan 2-oxide (phencyphos) was required. Anhydrous phencyphos is a racemic compound, but the hydrate is known to be a conglomerate. After examination of various solvent mixtures a preferential crystallization process in methanol/water solvent mixtures was chosen to deliver the pure enantiomers in good yields. The preferential crystallization process can be repeated up to 50 times without significant loss of efficiency.**

## 1. Introduction

Classical resolution by means of diastereomeric salt formation is a frequently used method to separate racemates capable of salt formation.[1] In 1985 ten Hoeve and Wynberg[2] introduced a new class of highly acidic resolving agents, cyclic phosphoric acids, prepared as shown in Scheme 1. The IUPAC names for these compounds are unwieldy, which led to the introduction of the trivial names phencyphos (R = H), chlocyphos (R = 2-Cl) and anicyphos (R = 2-OMe) for the most frequently used members. Over the years, these acids have proven time and again to be effective resolving agents.[3] These cyclic phosphoric acids were also the first "family" to be investigated in the new resolution technique now known as Dutch Resolution.[4]

Asymmetric syntheses of these materials have not been developed, and therefore, enantiomerically pure material must be obtained by resolution. The most frequently used phosphoric acid is phencyphos itself. Phencyphos can be resolved with (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol (APPD, structure not given), the unwanted enantiomer in the production process of the antibiotic chloramphenicol.[5,6] A change in the production process led to both scarcity and high prices for APPD. As a result, the large-scale resolution of phencyphos with APPD is no longer attractive, and cheaper alternatives are necessary.

***Scheme 1.*** **General synthesis of cyclic phosphoric acids**




An attractive method to resolve racemates is by preferential crystallization (entrainment), for which a resolving agent is not necessary.[7] A major restriction is that this method is restricted to conglomerates. They must be solids at normal operating temperatures. They must not exhibit epitaxial behavior. These and other complications make many conglomerates unsuitable for a resolution by preferential crystallization. And finally only 5−10% of chiral organic compounds exhibit conglomerate behavior.[7,8] The principle of preferential crystallization is shown schematically in Scheme 2. The racemate of the conglomerate crystals is added to, for example, a (+)-biased system and heated to dissolution to produce situation 1. The solution is then cooled to supersaturation. Because the (+)-enantiomer is more supersaturated than the (−)-enantiomer, it will preferably crystallize within a kinetic window (optionally by the help of seeding). It is collected by filtration before the supersaturated (−)-enantiomer begins to crystallize. Note that the amount of (+)-enantiomer obtained is the same as the amount of racemate added in order to obtain the reciprocal mother liquor. To continue the process, racemate is again added to this mother liquor, now enriched in the (−)-enantiomer, and the mixture is heated to dissolution (3). This solution is then cooled, and now the (−)-enantiomer can be collected and the procedure repeated from the beginning with the mother liquor (**4**).

In the original publication on the synthesis and resolution of phencyphos[2] it is mentioned in the Experimental Section that the hydrate of phencyphos (isolated from an aqueous mixture) was suspected to be a conglomerate. Recent work has shown that this supposition is correct.[9] This triggered us to investigate the resolution of phencyphos hydrate by preferential crystallization.

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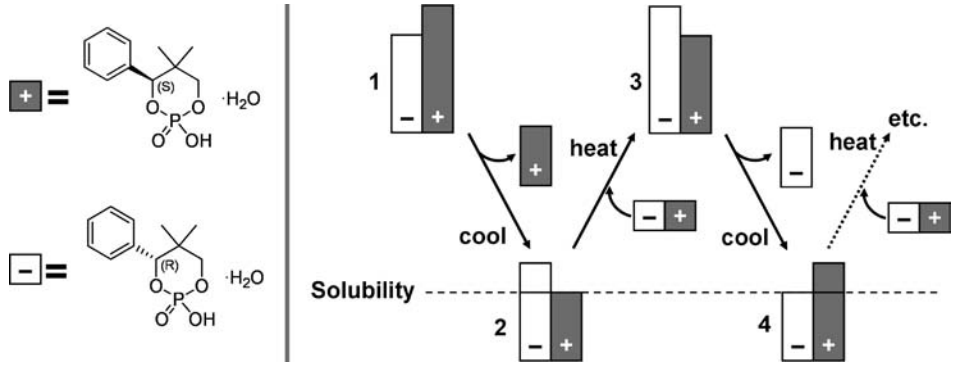
***Scheme 2.*** **Schematic representation of a resolution by preferential crystallization**




## 2. Results and Discussion

First we investigated whether anhydrous phencyphos is also a conglomerate. A ternary phase diagram with ethanol as solvent was constructed, which showed that anhydrous phencyphos (PP) is not a conglomerate but rather a racemic compound with eutectic values at 70% ee (**A** and **A′**) as shown in Figure 1.

Ethanol is not incorporated in the crystal lattice.[10] On the other hand, the hydrate obtained by crystallization from water is, in principle, suited for preferential crystallization. Unfortunately, the solubility of phencyphos hydrate in water is only 3.2 mg·mL$^{-1}$ at 20 °C. Mixtures of water and another solvent were investigated to see whether phencyphos would still form a hydrate but of higher solubility. To this end, the solubility of racemic phencyphos in several solvents has been investigated. These experiments showed that (anhydrous) racemic phencyphos dissolved best in DMSO, DMF and MeOH with solubilities of 142, 81, and 17 mg·mL$^{-1}$, respectively, at 20 °C.

**2.1. DMSO/$H_2O$ Mixtures.** A phase diagram was constructed for racemic phencyphos in mixtures of DMSO and water. The phase diagram is depicted in Figure 2. Since DMSO is notoriously difficult to remove without dehydration of hydrates or destruction of solvates, XRPD spectra were measured of the wet residues after filtration. The solids, isolated from solution mixtures containing more than ~25% wt water, gave phencyphos hydrate (PP·$H_2O$). With less water, anhydrous phencyphos was isolated. Region A represents the phase separation zone in which phencyphos hydrate may be found. The solubility in the solvent mixture where phencyphos hydrate is found is not very high (~13 mg·mL$^{-1}$ for solvent mixture 36 wt % of $H_2O$ in DMSO). Furthermore, the crystallization of the hydrate was slow.

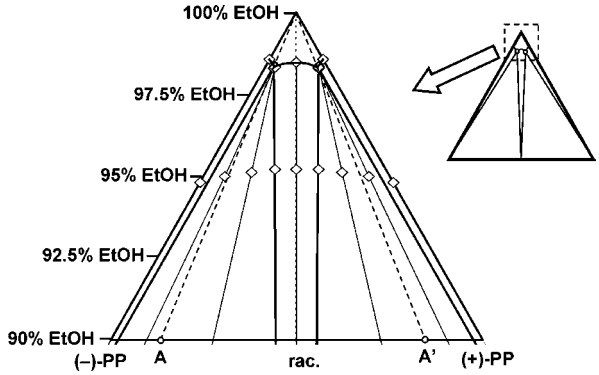



***Figure 1.*** **Solubility diagram of PP, in EtOH at 20 °C in weight fractions. Open dots are measured points.**

**2.2. DMF/$H_2O$ Mixtures.** In a similar fashion, the phase diagram for DMF/water mixtures has been determined. Again we were unable to determine whether the solid phase consisted of PP·$H_2O$ without dehydrating the solid phase during the removal of residual DMF. An assumption was made from the shape of the solubility line. The phase diagram is depicted in Figure 3, which shows that at least 13% wt water in DMF is needed to form the hydrate

Starting with 17 wt % of $H_2O$ in DMF as solvent and solid PP·$H_2O$, which was enriched in the (−)-enantiomer (15% ee), cooling crystallization gave high ee's in the first crystals. However, before enrichment in the mother liquor could take place also the (+)-enantiomer began to crystallize leaving a racemic mother liquor and crystals with only 55% ee. Apparently, either crystal growth of PP·$H_2O$ in this water/DMF mixture is slow or a small metastable zone width makes this system unsuitable for a resolution by preferential crystallization.

**2.3. MeOH/$H_2O$ Mixtures.** The phase diagram of (±)-phencyphos, water and MeOH has been constructed in the same manner as for the previous phase diagrams. However, since MeOH is volatile, most of the MeOH evaporated on exposure to air overnight and after further drying at 100 °C *in vacuo*, the water (hydrate) content could be determined. The phase diagram in Figure 4 shows that at least 22% wt water in MeOH is needed for the formation of PP·$H_2O$. To make sure the process is reproducible even when the water content fluctuates

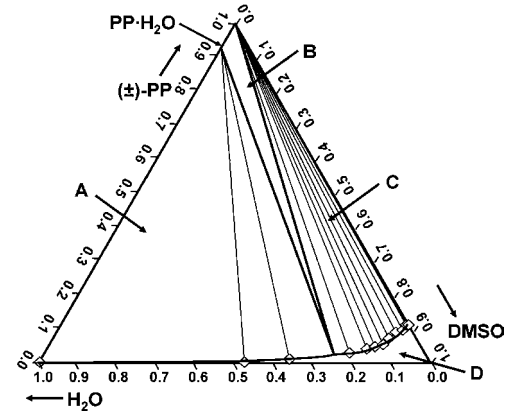



***Figure 2.*** **Solubility diagram of (±)-phencyphos [(±)-PP], water and DMSO at 20 °C in weight fractions. Region A: Solid PP·$H_2O$ and solution. Region B: mixtures of anhydrous PP (racemic compound), PP·$H_2O$ (conglomerate) and solution. Region C: Solid anhydrous PP and solution. Region D: undersaturated solution. Open dots are measured points.**

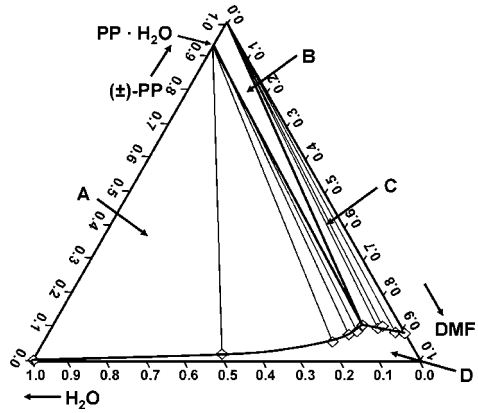



***Figure 3.*** **Solubility diagram of (±)-PP, water and DMF at 20 °C in weight fractions. Region A: Solid PP·$H_2O$ and solution. Region B: mixtures of anhydrous PP, PP·$H_2O$ and solution. Region C: Solid anhydrous PP and solution. Region D: undersaturated solution. Open dots are measured points.**

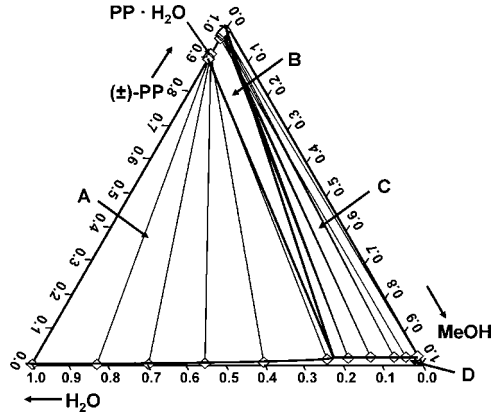



***Figure 4.*** **Solubility diagram of (±)-PP, water and MeOH at 20 °C in weight fractions. Region A: Solid PP·$H_2O$ and solution. Region B: mixtures of anhydrous PP, PP·$H_2O$ and solution. Region C: Solid anhydrous PP and solution. Region D: undersaturated solution. Open dots are measured points.**

and at higher temperatures, 30 wt % of water in MeOH (solubility of racemic phencyphos hydrate: ~11 mg·$mL^{-1}$ at 20 °C) was used in the preferential crystallization process.

Preferential crystallization experiments starting with 30 wt % of water in MeOH were performed on different scales and with different concentrations of phencyphos. Starting on small scale, 2.36 g (±)-PP·$H_2O$ was taken up in 100 mL of 30 wt % water in MeOH at 54.0 °C. The solution was cooled with a thermostatted water bath to 28.9 °C in 35 min (maximum cooling power), and primary nucleation started 90 min after the start of the cooling.[11] When this mixture was reheated to 54.0 °C and enriched by addition of 385 mg (−)-PP·$H_2O$ prior to the cooling, primary nucleation started at 31 °C so there was no need to seed the mixture with optically pure phencyphos hydrate. The suspension was left to age for another 30 min, and then the suspension was filtered which yielded ~0.77 g of PP·$H_2O$. The ee of the mother liquor was as high as 20% which is one of the highest recorded mother liquor ee's in a resolution by preferential crystallization. Then, 0.77 g (±)-PP·$H_2O$ was added to the mother liquor, the mixture was heated to 54.0 °C (dissolution), and the cooling cycle was repeated to obtain 0.77 g (+)-PP·$H_2O$. The isolated filter cakes were only sucked dry but not washed to prevent the dilution of the mother liquor. In practice, the whole resolution process gave 50% of the crude crystals of each enantiomer (ca. 93% ee) and in 41% (>99% ee) after recrystallization from a mixture of 30% wt $H_2O$ in MeOH. Failure to obtain >99% ee in the crude crystals is due to a remainder mother liquor and premature primary nucleation of the unwanted enantiomer.

In this manner, the resolution of phencyphos has been scaled up from 100 mL to 2 L and 35 L scale, respectively. On 35 L scale, in each run 270 g of (−)-phencyphos hydrate or (+)-phencyphos hydrate were isolated in alternating turns. With a temperature-programmed reactor, five batches were performed each day. In order to minimize the risk of crystallization of the unwanted enantiomer, the temperature program of the reactor should be controlled precisely so as not to overshoot during cooling, which results in premature crystallization of the unwanted enantiomer. Furthermore, care should be taken that the crystals are collected before (large amounts of) the unwanted enantiomer crystallizes.

## 3. Conclusions

Because phencyphos hydrate crystallizes as a conglomerate, resolution by preferential crystallization can be performed and has been scaled up to 35 L. This process, although quite laborious, has a yield of 41% for each enantiomer. In total 30 kg of each enantiomer of phencyphos hydrate have been prepared. Almost no waste is produced since after each run the mother liquor can be recycled up to 50 runs, depending on the purity of the racemate. Furthermore, no expensive resolving agent has to be used (and recycled).

## Acknowledgment

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**Note Added after ASAP:** In the version published on the Web on August 19, 2009, one of the co-authors is missing. This has been corrected in the version published on the Web August 27, 2009.

## Supporting Information Available

Procedures and materials required for the preferential crystallization separation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The IR spectra of (±)-phencyphos crystallized from methanol, ethanol, or 2-propanol were the same which indicates that the crystals are the same and neither solvent forms a solvate with phencyphos. The IR spectrum of (±)-phencyphos hydrate was different from that of (±)-phencyphos crystallized from either of the above alcohols. The IR spectra are available in Methods in Supporting Information.

(11) Note that the ternary phase diagram in Figure 4 was constructed at 20 °C and is thus somewhat different at 28.9 °C.