# Preparative-Scale Separation of Enantiomers Using Intercalated α-Zirconium Phosphate

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New lamellar compounds that have potential utility in preparative-scale enantiomeric separations were developed by combining principles from solid-state and molecular host–guest chemistry. Intercalation of α-zirconium phosphate (α-ZrP) by a cationic chiral π-acceptor produces a solid that selectively binds one enantiomer of a π-donor analyte from a racemic solution. Both crystalline and semicrystalline α-ZrP were investigated in order to determine whether crystallinity and particle size have an effect on this process. Under favorable conditions, preparative-scale separations can be achieved in a batchwise process by means of multiple passes through the intercalated solid. Even if scaled up for single-pass enantioseparation, these solids provide over 30 times the separation capacity per gram relative to brush-type chiral selectors immobilized on chromatographic silica. The intercalated solids were characterized by UV-visible and FT-IR spectroscopies and by powder X-ray diffraction. A dramatic concentration effect is seen in the enantioselective binding; at low concentration of the enantiomer which forms a complex with the intercalated chiral selector there is essentially no binding, while above 150 mM the intercalated chiral host–guest complex is formed almost quantitatively. The structural nature of this concentration dependence is discussed.

## Introduction

The preparative-scale separation of organic molecules from mixtures continues to be a pressing problem in chemistry today. The problem of separation becomes amplified when the analytes are chemically very similar, such as an enantiomeric pair in which the two molecules possess chemically identical functionality.[1] The separation of chiral molecules has become increasingly important in the pharmaceutical field, thanks to a growing appreciation that two enantiomers of a drug often have different activity in the human body, the extreme case being where one enantiomer has the desired pharmaceutical effect while the other is toxic. Other methods of producing enantiomerically pure compounds such as direct stereospecific synthesis and enzymatic amplification of stereochemistry are also being explored, but in many cases the avenues prove to be difficult and time-consuming. Resolution of a mixture of stereoisomers is often the only method available to obtain a pure enantiomer. Many chiral separation systems have been studied and even developed commercially to date;[2] however, almost all of these techniques operate on an analytical scale. Some examples include chiral amino acid derivatives,[3] cyclodextrins,[4] macrocyclic antibiotics,[5] and cellulose esters,[6] all of which are immobilized on conventional supports such as chromatographic silica. Some of these systems have even been expanded to preparative scale; these provide useful separations in specific cases.[7] However, even with the success of these systems, a viable, general method of large-scale chiral separation has yet to be achieved.

The development of microporous solids for both separations and catalysis continues to be another extremely active area of research. The selectivity of small-molecule intercalation into these solids on the basis of size, shape, charge, and chemical functionality has been widely investigated, especially in the case of zeolitic solids. Separation of enantiomers by chiral inorganic solids such as zeolite β[8] has been attempted, but the success of this approach has so far been limited. Intercalation reactions with inherently chiral lamellar solids have also been attempted and can affect limited enantioseparation.[9] These inorganic systems in general perform poorly in organic separations because they lack the multipoint noncovalent interactions that are responsible for the high degree of specificity found in molecular host–guest complexes. The approach to this problem described in this paper is to combine the specificity of a molecular host–guest system with the high capacity and chemical selectivity of inorganic

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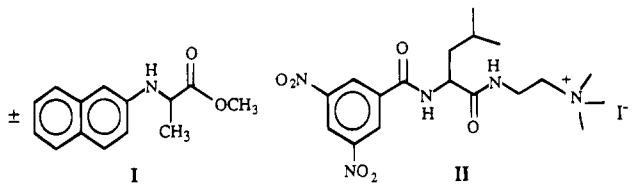
intercalation compounds.

A well-studied case of enantioselective host–guest chemistry involves $\pi$-acceptor (or $\pi$-acid) chiral selectors, which can bind $\pi$-donor ($\pi$-base) analytes enantioselectivity. When the selector is immobilized on a solid support, the differential bind of the two enantiomers of the $\pi$-donor can be used to effect enantioseparation. Pirkle and coworkers have shown that when a silane derivative of *N*-(3,5-dinitrobenzoyl)-L-leucine is covalently bound to chromatographic silica, racemic mixtures of the analyte **I** can be separated into their enantiomeric



**I** **II**

forms by HPLC.[10] If the selector is instead functionalized with a cationic quaternary ammonium group as shown for **II**, it can be ion-exchanged into the solid host $\alpha$-$Zr(HPO_4)_2 \cdot H_2O$ by reaction of the latter with tetrabutylammonium hydroxide, followed by an ion-exchange with the iodide salt of **II**.

Intercalating the host solid with the selector molecule has some advantages over chemically bonding the two together, most notably being the ease and mild conditions required for intercalation. The mild conditions used to prepare the chiral solid also limit the chance for racemization of the enantiomerically pure selector. Intercalation of chiral molecules such as amino acids[11] and cyclodextrins[12] into metal phosphates has been studied previously, but to date there have been no reports of enantioselective binding of molecular analytes in these materials.

The **I**–**II** analyte/selector combination was chosen for the present study because of the documented enantioselective complexation of its solution-phase and silica-bound analogues.[10,13] In a previous communication we reported preliminary data for enantioselective formation of this complex in $\alpha$-ZrP.[14] In this paper we describe the use of this complexation/intercalation reaction to effect the batchwise preparative separation of enantiomers of **I** and structural studies of the complexed and uncomplexed form of intercalation compounds containing **II**.

The use of this particular host–guest complex also allows for a standard test of new intercalated solids under conditions where one expects that there should be chiral complexation. In solution, the S–S complex is formed almost quantitatively over the S–R. The S–S complex has a binding constant of about 100 $M^{-1}$, and under comparable conditions, the S–R complex is not observed due to the fact that S–S complexation and even dimerization are more highly favored.[13] To select the host solid, we had several requirements, most importantly, good ion-exchange capacity and high internal surface area. In addition, the solid should be robust and reasonably inert to side reactions with solvents and organic analytes. Several layered host solids were investigated, including $\alpha$-$Zr(HPO_4)_2 \cdot H_2O$, titanium phosphate ($\alpha$-$Ti(HPO_4)_2 \cdot H_2O$),[15] and antimony phosphate ($SbH(PO_4)_2 \cdot H_2$).[16] Also, the mesoporous solids MCM-41[17] and kanemite ($NaHSi_2O_5$)[18] were studied as possible host materials. $\alpha$-ZrP was found to be the only one among these that was suitable for preparative-scale enantioseparations. This is due to the satisfactory ion-exchange capacity of $\alpha$-ZrP with the chiral selector **II** and its stability under the conditions required for exchange and enantiomeric separation. This behavior is not surprising when one examines the wealth of information on the intercalation chemistry of $\alpha$-ZrP found in the literature,[19] it has been shown to be extremely versatile as a host solid in many applications.[20] The other host solids investigated performed poorly, because difficulties associated with intercalation of the cationic selector **II**.

## Experimental Section

All materials were of reagent grade quality and were used as received. Solvents for high-performance liquid chromatography (HPLC) experiments were of HPLC grade and were degassed with He for 20 min before use. Analytical HPLC experiments were performed on a Waters 600E system with a Waters 991 photodiode array detector using Pirkle phase columns obtained from Regis Chemical Co. $^1$H NMR was carried out on either a Bruker AM300 or ACE200 instrument. FT-IR was performed on a Nicolet 730 spectrometer with a liquid nitrogen cooled MCT-A detector. UV–vis was carried out on a Hewlett-Packard 8452A diode array spectrophotometer for solution samples and on a Varian DMS 300 fitted with a diffuse reflectance attachment for the solid samples. Powder X-ray diffraction was performed on a Philips diffractometer using monochromatized Cu K$\alpha$ radiation. Elemental analyses (CHN) were performed by Atlantic Microlabs, Norcross, GA.

**Crystalline $\alpha$-Zirconium Phosphate $\alpha$-$Zr(HPO_4)_2 \cdot H_2O$.** Zirconyl chloride octahydrate ($ZrOCl_2 \cdot 8H_2O$, 10 g) was dissolved in 100 mL of deionized water in a plastic or Teflon container. Approximately 12 mL of phosphoric acid (85%) was added, resulting in the formation of a thick gelatinous product.[21] The gel was fluidized by addition of 50–100 mL more water, and the reaction vessel was placed into an oil bath. Hydrofluoric acid (48%) was added to the gel while stirring until a clear solution was obtained. This mixture was heated at 60 °C and bubbled with air using plastic tubing. Heating

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was continued for 7–10 days, and water was added periodically to make up for lost volume. The product precipitated as a white, powdery solid.[22] After precipitation was complete, the remaining liquid was decanted and the solid was filtered on a glass frit filter and washed with water; yield 80%. The solids were ground to a fine powder in a mortar and pestle and characterized by powder X-ray diffraction. The solids so obtained showed no marked differences in comparison with previously published powder XRD data.

**Semicrystalline α-Zirconium Phosphate α-Zr-$(HPO_4)_2 \cdot H_2O$.**[23] A 1 M solution of $ZrOCl_2 \cdot 8H_2O$ (310 mL) and 2 M phosphoric acid (345 mL) were added dropwise and simultaneously to 50 mL of distilled water in a 2 L beaker with vigorous stirring. Stirring was continued for 1 h after completion of the addition, and the thick gel was allowed to stand overnight. The product was filtered and washed copiously with water (1 L) and then dried at 50 °C. The dried gel was ground to a fine powder and refluxed in 700 mL of 2.5 M phosphoric acid for 48 h. The solid was collected by centrifugation and washed with water to a pH of 3–3.5. The product was again dried at 50 °C and ground to a fine powder; yield approximately 75%.

**(*R,S*)-(±)-Methyl *N*-(2-Naphthyl)alaninate (I).** The product was prepared by a modified version of Bischoff's method.[24] To 1 g (7 mmol) of 2-naphthylamine (*Caution*: potent carcinogen!) dissolved in 50 mL of DMF was added 2.33 g (1.56 mL, 14 mmol) of methyl (±)2-bromopropionate. $K_2HCO_3$ (3 g) was added, and the mixture was heated under inert atmosphere to 70 °C for 24 h. After this was cooled to room temperature, 20–30 mL of $H_2O$ was added and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed extensively with $H_2O$ (4–5 × 50 mL) to remove residual DMF. The extracts were dried over $MgSO_4$ and concentrated on a rotary evaporator, producing a brown oil. The oily product was redissolved in hot hexane and placed in the freezer, where white-brown crystals slowly formed. The yield of product was 0.67 g (42%). $^1H$ NMR ($CD_3CN$) δ 1.5 (d, 3H), δ 3.65 (s, 3H), δ 4.25 (q, 1H), δ 4.95 (d, 1H), δ 6.72 (d, 1H), δ 6.98 (dd, 1H), δ 7.17 (t, 1H), δ 7.35 (t, 1H), δ 7.05–7.25 (m, 3H).

**(*S*)-(+)-*N*-(3,5-Dinitrobenzoyl)leucine *N*-Ethyltrimethylammonium Iodide (II).** Dinitrobenzoyl chloride (6.45 g, 34.76 mmol) was dissolved in 500 mL of dry tetrahydrofuran (THF), and 4.56 g (34.76 mmol) of L-leucine was added in one portion. Propylene oxide (2.21 g, 38.24 mmol) was added dropwise with a syringe over 15 min. The mixture was stirred overnight in a tightly closed flask after which most of the leucine had dissolved. The remaining leucine was filtered off, and the tetrahydrofuran was removed on a rotary evaporator. Vacuum drying of the yellow oil afforded a crude yellow solid which was recrystallized from $H_2O$/2-propanol to give a white crystalline product, *N*-(3,5-dinitrobenzoyl)leucine; yield 80–87%.[25]

A solution of 6.5 g (20.05 mmol) of *N*-(3,5-dinitrobenzoyl)-leucine in 100 mL of dry THF was cooled to −10 °C with an ice–NaCl bath. This solution was neutralized with 2.40 mL of *N*-methylmorpholine (20.05 mmol). Isobutyl chloroformate (2.64 mL, 20.05 mmol) was added, followed 60–90 s later by *N,N*-dimethylethylenediamine. The reaction mixture was allowed to warm to room temperature and was concentrated by rotary evaporation to about 20 mL. About 300 mL of water was added, and the mixture was cooled to 2 °C for 4–12 h. A purplish oily precipitate formed. Most of the water was decanted from the product and it was washed once with 0.5 M $KHCO_3$. The aqueous washes were cooled to 2 °C to afford a small amount of clean product (precipitated as yellow-brown crystals) after 10–24 h. The remaining product (oily solid) was redissolved in $CH_3CN$ (20 mL). To this solution, 300 mL of $H_2O$/0.5 M $KHCO_3$ was added, and the entire mixture was cooled again to 2 °C to afford 2.98 g (38%) of product (combined) after filtration, $H_2O$ washing, and vacuum drying.[26]

The crystals were dissolved in 50 mL of $CH_3CN$ and treated with $CH_3I$ (10-fold excess) to quaternize the tertiary amine. This solution was stirred overnight, and then a large excess of diethyl ether was added. The mixture was cooled overnight to −20 °C, and the final product precipitated as a bright orange solid. It was collected by filtration, washed with ether, and vacuum dried. The yield of product was 3.14 g (78%).

Enantiomeric purity was checked by polarimetry and measured quantitatively by chiral HPLC on a Pirkle covalent naphthylalanate column. Products were all 95–99% enantiomerically pure. $^1H$ NMR ($CD_3CN$) δ 0.95 (dd, 6H), δ 1.6–1.8 (m, 3H), δ 3.1 (s, 9H), δ 3.42 (t, 2H), δ 3.6 (m, 2H), δ 4.5 (m, 1H), δ 7.6 (t, 1H), δ 8.05 (d, 1H), δ 9.0 (s, 2H), δ 9.05 (s, 1H). Anal. Calcd for $C_{18}H_{28}N_5O_6I$: C, 40.20; H, 5.21; N, 13.03. Found: C, 39.80; H, 5.38; N, 12.70.

**Synthesis of Tetrabutylammonium α-Zirconium Phosphate Intercalates.** In a typical experiment, 2–3 g of α-ZrP was suspended in water (75–100 mL) and titrated to pH 8 with a standardized solution of tetrabutylammonium hydroxide (ca. 0.5 M). The titration takes at least 14–20 h to complete with the microcrystalline materials (precipitated from HF solution[21]) because the pH rises rapidly and then slowly falls as the tetrabutylammonium ($TBA^+$) cations diffuse into the solid. Since the particle size is much smaller in the semicrystalline materials, the titration of these solids takes only 2–4 h. After the pH had stabilized at 8, the solid was separated by centrifugation and was washed with water 2–3 times to remove excess $TBA^+$ salts. After air drying either at room temperature or at 50 °C, the samples were ground to a fine powder in a mortar and pestle and characterized by powder X-ray diffraction and CHN analysis.

**Synthesis of Chiral Selector α-Zirconium Phosphate Intercalates.** The TBA-intercalated α-ZrP (1–2 g) was resuspended in a solution of chiral selector (**II**). The solution was prepared in a 60/40 water/ethanol mixture and contained an equimolar amount of selector for $TBA^+$ at a concentration of approximately 0.05 M. The solid was allowed to stir in this solution for 24 h and was then separated by filtration on a glass frit. The solid was washed with an equal portion of 60/40 $H_2O$/ethanol and air dried. The dried solid was suspended in 100 mL of $CH_3CN$ and stirred for 4–10 h to remove any free selector. It was filtered and washed on the frit with $CH_3CN$ and dried at 50 °C. The light yellow solid (color due to the presence of the dinitro moiety of the selector molecule) was characterized by powder X-ray diffraction and CHN analysis.

## Results and Discussion

**Stepwise Ion-Exchange in Zirconium Phosphate and Chiral Analyte Separation.** The procedure for exchanging the cationic chiral selector **II** into α-ZrP and other lamellar host solids was performed in two stages. Since the inner-layer hydroxyl groups of α-ZrP, α-Ti-$(HPO_4)_2 \cdot H_2O$, $SbH(PO_4)_2 \cdot H_2O$, and kanemite ($NaHSi_2O_5$) contain acidic, ion-exchangeable protons, it is possible to perform an acid–base reaction of these groups using strong aqueous base. This is done with a bulky cation ($TBA^+$) in order to "prop open" the inner layers. After the solid is neutralized and exfoliated in this way, a simple ion-exchange reaction can be used to incorporate the alkylammonium selector **II**.

In the case of α-ZrP, the amount of $TBA^+$ exchange was found from CHN analysis to be between 19–25% of the available proton sites. The semicrystalline materials, in which solid-state diffusion of intercalated ions proceeds over smaller dimensions, gave $TBA^+$ exchange in the higher regions of this range. The extent of ion-exchange of selector (**I**) for TBA was again

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determined by CHN analysis. The amount of selector exchange for $TBA^+$ was 85–100%. This corresponds to a selector concentration of approximately 0.7–0.9 mmol/g.

For α-ZrP, the solid was easily collected at each stage of the intercalation. However the titanium and antimony phosphates were difficult to isolate from colloidal suspensions following intercalation with $TBA^+$. Due to this problem, their effective ion-exchange capacity was less than α-ZrP, i.e., less $TBA^+$ could be reacted. The ion-exchange capacity of MCM-41 was found to be significantly inferior to that of any of the layered phosphates owing to lack of reactive $SiO^-$ sites, which are lost during pyrolysis of the cationic micellar template. On the other hand, exfoliated kanemite, while having a relatively high ion-exchange capacity, was unstable in aqueous suspensions at pH ≤ 9, because of interlayer condensation of Si–OH groups. At pH ≥ 9 the cationic selector can be ion-exchanged at relatively high loading, but the chiral molecule racemizes at high pH.

Enantiomeric separation experiments with α-ZrP were done in a batchwise method. For most samples, a ratio of 4:1 analyte **I** to selector **II** was maintained for ease in analysis. A known amount of the loaded α-ZrP was placed in a vial, and the appropriate amount of racemic analyte solution (and extra solvent if necessary) was added. The concentration of analyte in these solutions was varied in the binding study experiments and was kept constant in experiments involving large-scale separations. Acetonitrile was used as the solvent for all of the chiral separation experiments because it adequately solubilized the analyte while also swelling the layers of α-ZrP to facilitate intercalation. It should be noted that the complexation can be visually observed in these solids. The α-ZrP containing only selector is light yellow in color; when exposed to a solution of the analyte, it turns a deep orange due to the formation of a charge-transfer complex (vide infra).

The enantioselectivity of complexation between intercalated **I** and **II** could be quantified as enantiomeric excess (EE), defined as

$$\mathrm{EE} = \frac{|[\mathrm{R}] - [\mathrm{S}]|}{[\mathrm{R}] + [\mathrm{S}]}$$

To determine the EE of a solution (either the supernatant in a binding experiment, or the solution extract of a complexed solid), it was separated from the solid by centrifugation with a ultramicrocentrifuge and/or filtered on a glass frit. A small portion of this solution was diluted to approximately 10 mM and directly analyzed by chiral HPLC with a Pirkle covalent phenylglycine column. For solid samples, the analyte could be extracted in the following way. After the supernatant was removed, the solid was washed with hexane to remove analyte molecules physisorbed on the external surface. Bound **I** was then liberated from the solid by washing with fresh acetonitrile. This filtrate was collected and suitably diluted for HPLC analysis.

The binding isotherm for racemic **I** with selector-modified α-ZrP shows non-Langmuirian behavior (Figure 1). Analysis of the supernatant solution shows that very little analyte is intercalated at low concentrations, but as the concentration increases the fractional coverage (i.e., number of intercalated analyte molecules per molecule of selector) approaches unity. This implies

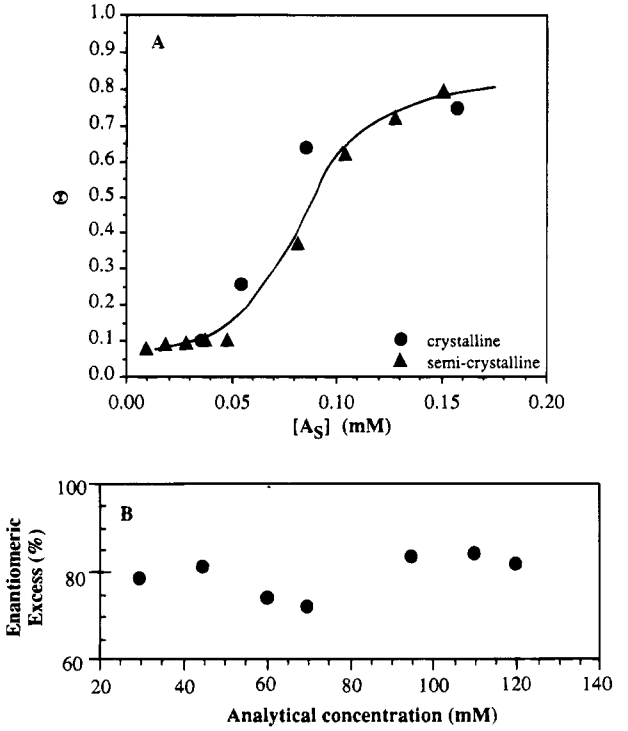


**Figure 1.** (A) Binding isotherm of the loaded solid. Graph shows fractional coverage (Θ) vs equilibrium concentration of the S enantiomer of the analyte ($[A_S]$). (B) Enantiomeric excess (EE) vs analytical concentration ($R + S$ enantiomer of analyte) for analyte **I** extracted from complexed solids.

that a certain concentration threshold must be reached in order to drive the intercalation and subsequent complexation. The EE for the analyte extracted from the solid shows the expected high concentration of the other enantiomer. These EE's should be close to 100% if the intercalation reaction is as enantioselective as is host–guest complexation of the solution-phase analogues.[13] The deviations seen are due to surface-bound analyte molecules that are not thoroughly removed in the hexane washing step. The upper graph in Figure 1 shows data for both semicrystalline and crystalline α-ZrP. The performance of the two solids is essentially the same; however, due to higher initial loading of $TBA^+$, the loading of selector is slightly higher in the semicrystalline materials.

Figure 2 shows typical chromatograms for these experiments. The supernatant solution shows 23.5% enantiomeric excess for a 4:1 system (expected value 33%). Analyte extracted from the solid shows a high EE (84.5%) of the other enantiomer which is indicative of enantioselective binding in the solid by the intercalated selector.

If this system is used under conditions that maximize the chiral complexation (i.e., high concentration of **I** in solution), large-scale enantioseparations can be achieved. Figure 3 shows an example of a preparative scale separation with intercalated α-ZrP. This experiment was done by isolating **I** from the supernatant after each pass and then adjusting the concentration to approximately 0.2 M. This solution was analyzed by chiral HPLC and then reexposed to the original solid, which had been washed with fresh acetonitrile to remove bound analyte. Of course, the solid proves to be reusable with little loss in performance. The significantly higher loading in the α-ZrP system allows for separation of large amounts of analyte with relatively small

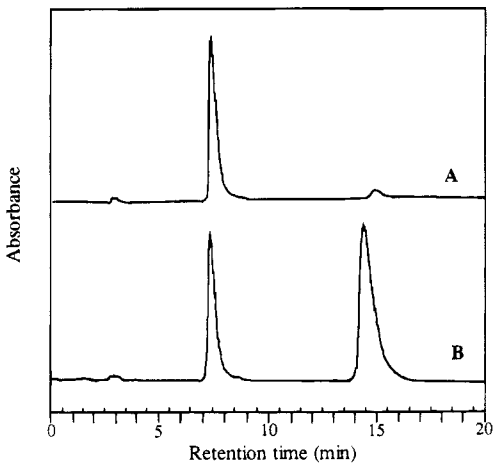


**Figure 2.** Chromatograms showing typical EE's for extracted (A) and supernatant (B) HPLC experiments. (A) EE = 84.50%; (B) EE = 23.45%.

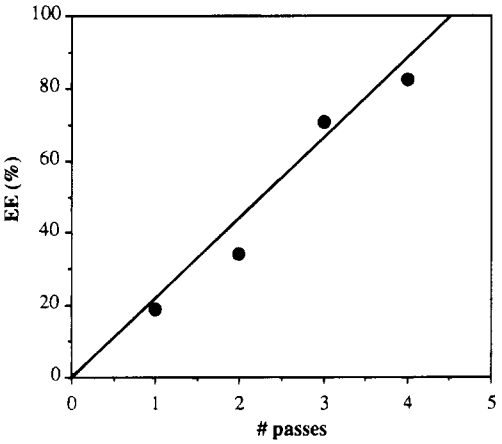


**Figure 3.** Preparative-scale batchwise racemic analyte separation. Amount of selector-loaded solid, 570 mg; starting amount analyte, 310 mg of racemate; collected amount of analyte, 90 mg (58% of theoretical); EE after four passes, 82%.

amounts of solid. This shows the advantage in scale of using a layered, high surface area solid as a support material. For comparison, in order to separate 1 g of a derivative of analyte **I** in one pass on an HPLC column, 250 g of selector-modified silica was needed.[27] Chemically similar analytes have been separated on preparative scale with a 2 in. × 30 in. column containing about 1 kg of stationary phase.[7] Using such a column, 14 g of a racemic alcohol was separated in four passes.

**Characterization of Modified α-Zirconium Phosphates.** Figure 4 shows FT-IR spectra of modified α-ZrP at each stage of the intercalation/complexation process. In the spectra of native α-ZrP, two sharp bands are seen around 3500 and 3700 $cm^{-1}$. These are due to the intralayer PO−H stretch and the H−O−H stretch from water contained in the crystal lattice. The sharp band at 1620 $cm^{-1}$ is the scissors deformation mode of lattice water. The P−OH vibration at 1250 $cm^{-1}$ in α-ZrP shifts during the intercalation reaction due to coupling between the phosphate group and intercalated water. A C−H stretching vibration in the 2900 $cm^{-1}$ range is evident for the samples exchanged with organic cations. C=O stretches (1640 $cm^{-1}$) from the amide moiety are also evident in both the selector-exchanged and the complex-containing solids. The α-ZrP sample

(27) Pirkle, W. H.; Pochapsky, T. C. *J. Org. Chem.* **1986**, *51*, 102.

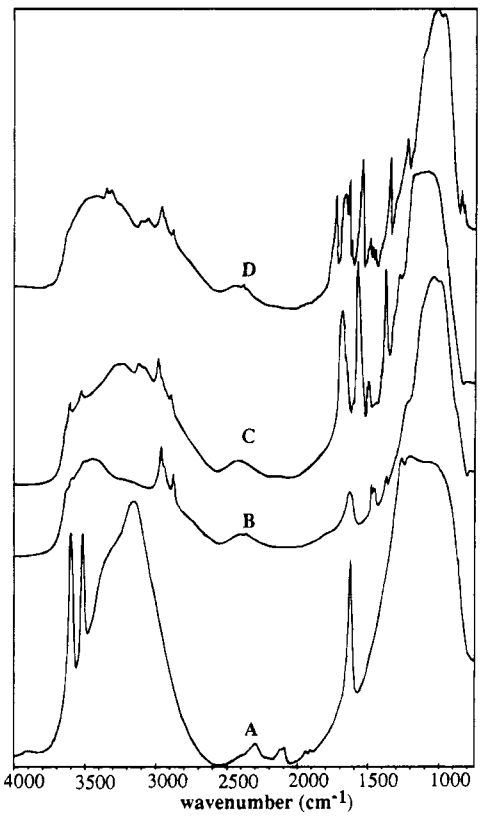


**Figure 4.** FTIR spectra of native and loaded α-ZrP samples (crystalline). (A) Native α-ZrP. (B) $TBA^+$-exchanged α-ZrP. (C) Selector-exchanged α-ZrP. (D) α-ZrP containing the chiral I−II complex. All spectra were taken as KBr pellets.

containing the complex shows an extra band at 1750 $cm^{-1}$ due to the presence of the ester C=O group of **I**.

Clearer evidence of host−guest complexation is seen in the solution and solid-state UV−visible spectra.[28] Figure 5 shows solution and solid phase spectra of **II**- and complex-loaded α-ZrP. The UV−visible behavior of the selector is much the same in solution and when intercalated into α-ZrP. A charge-transfer (CT) band at 475 nm is seen in the solid containing the complex. The dependence of this CT band on concentration of **I** in the solution phase (equilibrated with the solid) is shown in the lower graph.

Powder X-ray diffraction (XRD) patterns of the modified α-ZrP give some clues to the origin of the concentration dependence of the host−guest complexation reaction. The layer spacing progressively increases from 7.5 Å (α-ZrP), to 14.4 Å, and then to 21.1 Å as first the $TBA^+$ ion and then the larger selector molecule **II** is intercalated. The layer spacing finally increases to ca. 30 Å upon complexation of the analyte. The increase in volume that attends this last reversible complexation step forces this dramatic increase in interlayer spacing. Complexation can only be achieved when the analyte concentration is high enough to overcome the work involved in this process.

Figure 6 shows XRD patterns of α-ZrP intercalated by **II** and equilibrated with different concentrations of **I**. In addition to the small α-ZrP impurity found in all samples (including the TBA-exchanged precursor), two

(28) The diffuse reflectance and absorption are taken to be roughly equivalent in this qualitative comparison. The relationship between reflectance and adsorption is $2\alpha vp/S = (1 - R)^2/2R$, where $\alpha$ = absorption coefficient, $R$ = diffuse reflectance, and $S$ = scattering coefficient.

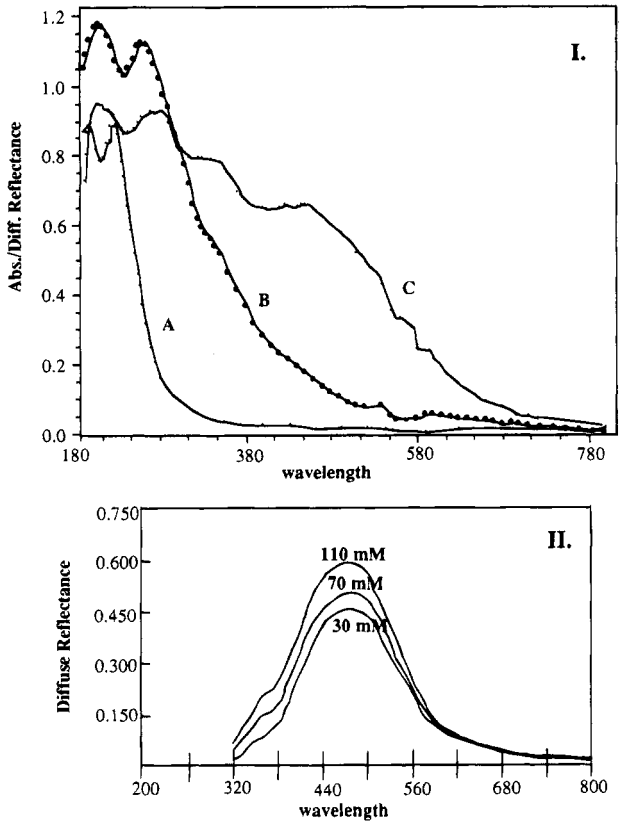


**Figure 5.** Solution and solid UV–visible spectra. I. Spectra for selector in solution (A) and solid (B) as compared to the solid containing the I–II complex (C). Note charge-transfer band at 475 mm. II. Increase of the charge-transfer absorbance at 475 nm with increasing complex concentration. Spectra were background-corrected using selector-exchanged α-ZrP as a reference.

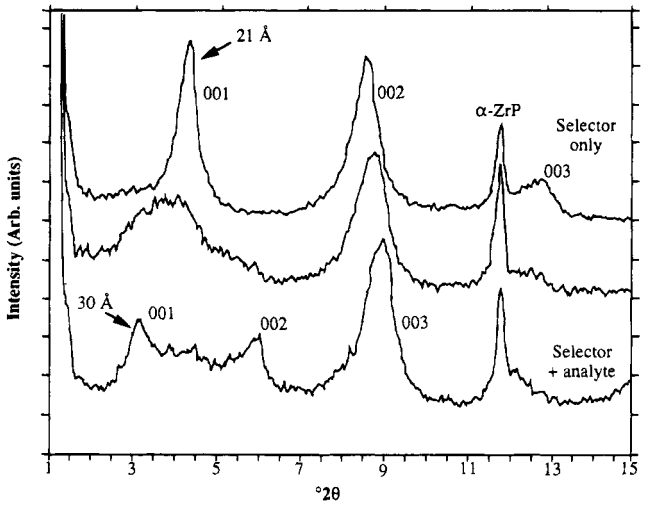


**Figure 6.** Powder X-ray diffraction patterns of selector-intercalated α-ZnP containing the chiral analyte **I** at zero, intermediate, and saturation loading. Note that the solid undergoes a phase transition (see text) from a 21 to a 30 Å phase.

phases can be identified by their 00*l* diffraction peaks. The compound intercalated with **II** only (top pattern) has a layer spacing of 21 Å, whereas the compound intercalated with **I** and **II** at high loading can be indexed to a pure 30 Å phase. Interestingly, the intermediate composition shows these two phases together, rather than a solid solution. As the amount of complex increases, the α-ZrP goes through an apparent first-order phase transition, changing abruptly from the 21 Å phase to the 30 Å phase. This transition is in contrast to certain other mixed intercalation systems, which follow solid solution behavior and show a gradual progression from one intercalated phase to the next. Pinnavaia et al. have studied substrate rigidity effects in intercalated clays and have shown that layer stiffness plays a major role in determining whether two-phase or solid solution behavior will be observed.[29] In those systems, the intercalates are chemically and sterically similar and the XRD patterns show true solid solution mixing as expected. However, it has been noted that in the upper limit of his model (infinitely rigid layers) one should expect "phase transition like" behavior. We note finally that this analysis points the way for future modification of this system, for if the solid can be "preorganized" into a more open form prior to analyte intercalation, then the phase transition should not occur and the binding isotherm should revert to a more Langmuirian form.

## Conclusions

We have shown that zirconium phosphate (both crystalline and semicrystalline) can be modified by stepwise ion-exchange to contain an enantiomerically pure chiral selector molecule. Performance is similar in the case of crystalline and semicrystalline solids with the semicrystalline material intercalating more rapidly and having slightly higher loading. Resolution of racemic analyte was achieved in both of these intercalated layered compounds. EE values up to 85% were found for the intercalated host–guest complex. The solids are reusable and preparative scale separations are readily achieved. The binding isotherm for this system is non-Langmuirian, and the abrupt onset of enantioselective binding at high analyte concentration is a consequence of the work needed to accommodate the volume of the guest in the solid. The phase transition that attends this intercalation reaction is apparent in powder XRD patterns.

These composite materials show promise for efficient, preparative-scale enantiomer separation via reversible host-guest complexation in the solid state. The ion-exchange procedure developed here should be quite generally applicable to the intercalation into α-ZrP of many different chiral selector molecules. Modification of the chiral selector to address the problems of selectivity and solid-state host preorganization are currently underway.

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