Covalent Bonding of Phosphonates of L-Proline and L-Cysteine to γ-Zirconium Phosphate

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This paper describes the synthesis and characterization of γ-zirconium phosphate-phosphonates based on chiral *N*-phosphonomethyl-L-proline [(–)-$HO_3PCH_2NHC_4H_7CO_2H$; H_3PMP] from L-proline, and *N*-phosphonomethyl-1,3-thiazolidine-4-carboxylic acid [(–)-$HO_3PCH_2NHCH_2SC_2H_3CO_2H$; H_3PMTA] from L-cysteine. Two compounds formulated as [$Zr(PO_4)(H_2PO_4)_{0.53}(H_2PMP)_{0.47}$·$2.0H_2O$] [γ-ZrPMP (**1**)] and [$Zr(PO_4)(H_2PO_4)_{0.50}(H_2PMT)_{0.50}$·$1.6H_2O$] [γ-ZrPMT (**2**)] were obtained by topotactic reaction of H_3PMP and H_3PMTA, respectively, with γ-ZrP in the presence of water/acetone. They possess intercalation capabilities and optical activities.

Introduction

Recently, there has been tremendous interest in the design and synthesis of chiral solids for their important applications in enantioseparation and asymmetric catalysis.[1] The chirality of these compounds mostly results from chiral organic groups,[2] therefore one strategy for obtaining solid materials with optical activity is to incorporate optically active organic moieties into the organic-inorganic hybrid frameworks.[1–3]

Zirconium phosphate (ZrP) derivatives incorporating organic functional groups are very promising materials.[4] The layered structure of ZrP provides a template surface where organic structures of virtually any nature can be chemically deposited in an orderly and predictable manner. Among the different zirconium phosphates, the high rigidity of the lamellae of γ-zirconium phosphate [$Zr(PO_4)(H_2PO_4)$·$2H_2O$] allow the preparation of stable hybrid materials by topotactic exchange of dihydrogenphosphates with mono- or diphosphonic acids.[5] Their replacement may be total or partial, depending on the amount and steric volume of the phosphonate used in the topotactic exchange. Many functional groups, such as biphenylphosphonate,[6] poly(ethylene oxide) chains[7] and C_{60},[8] have been integrated into the frameworks. We therefore aimed to prepare functionalized layered γ-zirconium phosphate-phosphonates anchored with chiral groups.

Proline and its analogs or homologs are very important chiral sources that have wide applications, for instance in stereoselective synthesis,[2,9] enantioseparation[10] and biochemistry.[11] Phosphonic acid derivatives of proline are analogs of amino acids with biological activities.[12] Herein we wish to report the synthesis of functionalized γ-zirconium phosphate-phosphonates based on chiral *N*-phosphonomethyl-L-proline (H_3PMP), formed from L-proline, and *N*-phosphonomethyl-1,3-thiazolidine-4-carboxylic acid (H_3PMTA), formed from L-cysteine. The optical activity and intercalation properties are also discussed.

Results and Discussion

Preparation and Characterization of H_3PMP, H_3PMTA, γ-ZrPMP and γ-ZrPMT

The preparation of these compounds is outlined in Scheme 1. This method, which is based on a literature technique,[13] gave H_3PMP and H_3PMTA from the corresponding amino acids in a Mannich-type reaction in yields of 96% and 85%, respectively. γ-ZrP was prepared according to the reported procedure.[14] The specific rotations $[\alpha]_D$ of H_3PMP and H_3PMTA are −63 and −105, respectively, in aqueous solution 25 °C.

Highly crystalline [$Zr(PO_4)(H_2PO_4)_{0.53}(H_2PMP)_{0.47}$·$2.0H_2O$] [γ-ZrPMP (**1**)] and [$Zr(PO_4)(H_2PO_4)_{0.50}$-$(H_2PMT)_{0.50}$·$1.6H_2O$] [γ-ZrPMT(**2**)] were prepared by treatment of H_3PMP or H_3PMTA with γ-ZrP in water/acetone (1:1, v/v) at 80 °C for 14 d, with a phosphonic acid to γ-ZrP ratio of 1. Their $[\alpha]_D$ values in HF/H_2O solution of are −16 and −21, respectively, at 25 °C.

The X-ray powder diffraction patterns of **1** and **2**, as shown in Figure 1b and c, are characteristic of layered structures[4] with a *d*-spacing of 14.2 Å and 14.1 Å, respectively.

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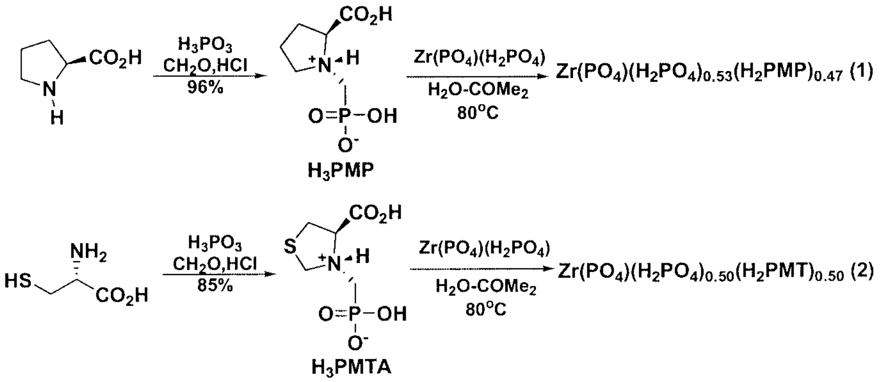

Scheme 1

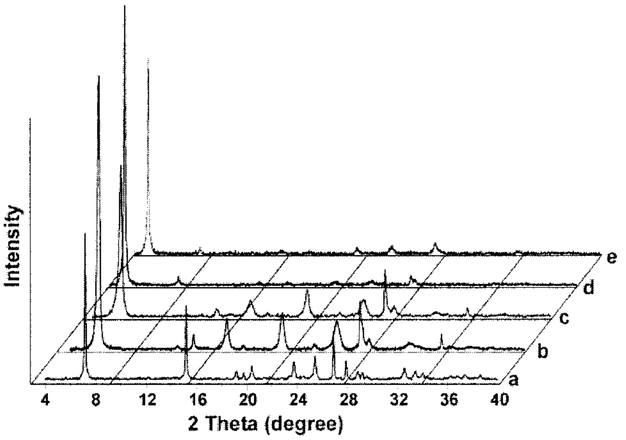

Figure 1. X-ray power diffraction patterns of: (a) γ-ZrP (*d*-spacing 12.2 Å), (b) γ-ZrPMP (**1**) (*d*-spacing 14.2 Å), (c) γ-ZrPMT (**2**) (*d*-spacing 14.1 Å), (d) **3** (*d*-spacing 21.65 Å) and (e) **4** (*d*-spacing 20.94 Å)

As shown in Figure 2, the ^{31}P solid-state MAS NMR spectra of **1** and **2** are similar: each shows three main resonances, one at $\delta = -28.8$ ppm for PO_4^{3-}, one at $\delta = -15.5$ ppm attributed to $H_2PO_4^-$ and one at $\delta = -5.4$ ppm due to the phosphonate phosphorus atom. The ^{31}P MAS NMR spectra of **1** and **2** are similar to that observed for $[Zr(PO_4)(H_2PO_4)_{0.49}(C_6H_5PO_3H)_{0.51}]$.[15] Analyses on the basis of solid-state ^{31}P MAS NMR and high-resolution ^{31}P NMR spectroscopy give $H_2PO_4^-$ to $R\text{-}PO_3H^-$ ratios of 1.13 and 1.01 for **1** and **2**, respectively.

The ^{13}C MAS NMR spectra of **1** and **2** indicate that COOH groups ($\delta = 173$ ppm) exist inside the layers (Figure 3b and d). In the FT-IR spectra of **1** and **2**, the absorption at 1730 cm^{-1} is attributed to COOH (Figure 4d and e). The IR and Raman spectra are in good agreement with the ^{13}C MAS NMR spectra.

On the basis of X-ray diffraction data, inductively coupled plasma (ICP), elemental analysis, TGA data and the ^{31}P NMR spectra, **1** and **2** are formulated as (*S*)-$[Zr(PO_4)(H_2PO_4)_{0.53}(HO_3PCH_2NC_4H_7COOH)_{0.47}\cdot 2.0H_2O]$ (**1**; mol. wt. = 371.39) and (*R*)-$[Zr(PO_4)(H_2PO_4)_{0.50}(HO_3PCH_2NCH_2SC_2H_3COOH)_{0.50}\cdot 1.6H_2O]$ (**2**; mol. wt. = 376.52). The BET surface areas of **1** and **2** are 14 and 12 $m^2\cdot g^{-1}$, respectively. Such small surface areas indicate that organic groups are closely packed in the interlayer spaces of **1** and **2**.

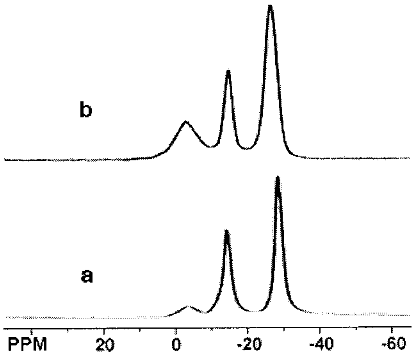

Figure 2. ^{31}P MAS NMR spectra of: (a) γ-ZrPMP (**1**) and (b) γ-ZrPMT (**2**) ($\delta = -28.8$ ppm for PO_4^{3-}, -15.5 ppm for $H_2PO_4^-$, and -5.4 ppm for $R\text{-}PO_3H^-$)

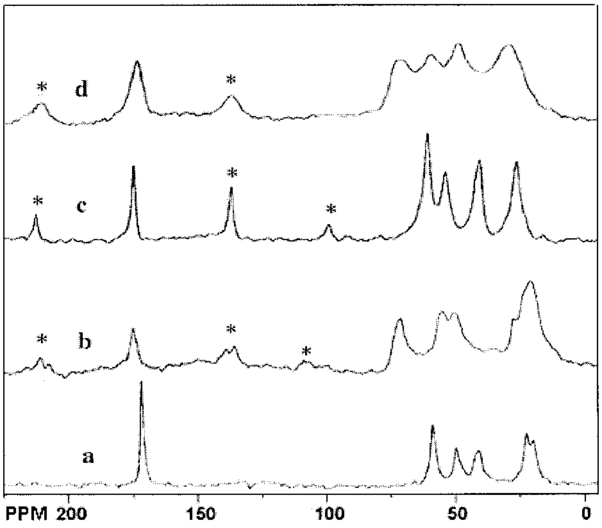

Figure 3. ^{13}C CP/MAS NMR spectra of: (a) H_3PMP, (b) γ-ZrPMP (**1**), (c) H_3PMTA, and (d) γ-ZrPMT (**2**) (asterisks denote spinning sidebands)

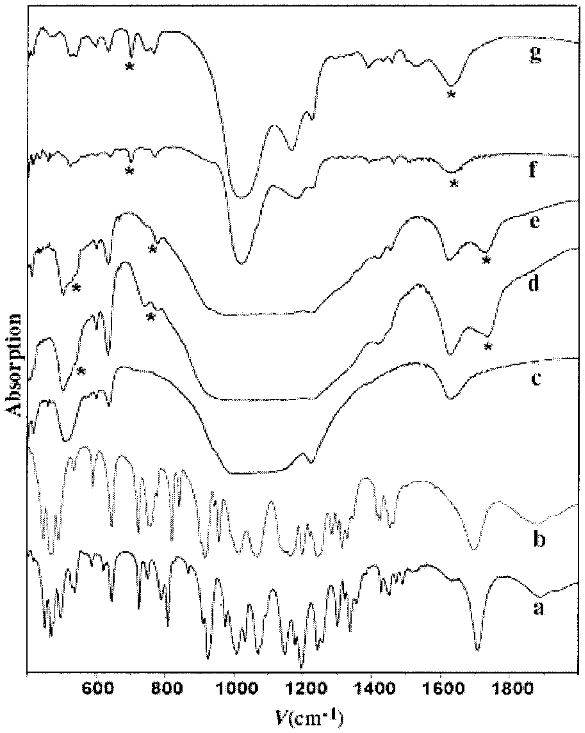

Figure 4. FT-IR spectra of: (a) H_3PMP, (b) H_3PMTA, (c) γ-ZrP, (d) γ-ZrPMP (**1**), (e) γ-ZrPMT (**2**), (f) **3** and (g) **4**; the bands at 1710 and 1730 cm^{-1} are attributed to CO_2H (a−e), and those at 1635 cm^{-1} to $-CO_2^-$ and 701 cm^{-1} to $C_6H_5CH(CH_3)NH_2$ (f and g)

Based on the above experimental data and the structure of γ-ZrP, a schematic representation of the proposed structural character of **2** is shown in Figure 5 (**1** is similar to **2**). In **2**, the nitrogen atoms are protonated by $H_2PO_4^-$ groups. These results are supported by the ^{13}C MAS NMR and IR spectra of **2** (Figures 3 and 4).

Molecule modeling of **2** is carried out based on γ-zirconium phosphate. Figure 6 shows the simulated structure model of **2**. This model shows that the heterocycles are closely packed, in good agreement with small BET surface areas.

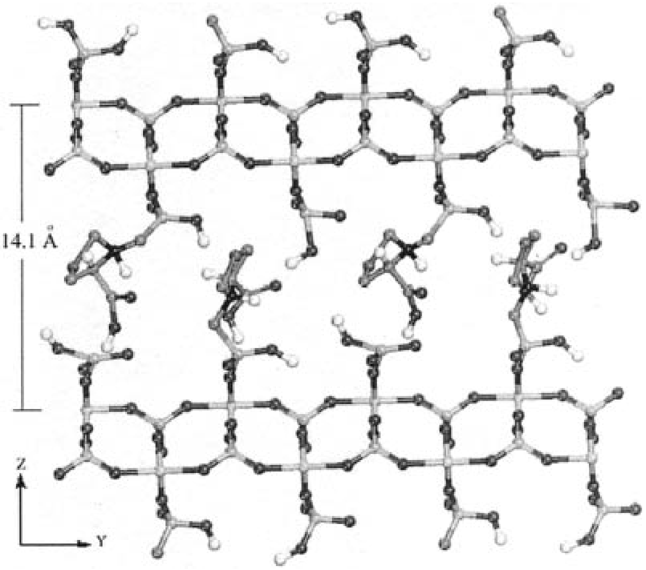

Figure 6. Simulated structural model of γ-ZrPMT (**2**) on the basis of γ-ZrP

Intercalation Capability and Optical Activity of γ-ZrPMP (1) and γ-ZrPMT (2)

A racemic mixture of 1-phenylethylamine [$C_6H_5CH(CH_3)NH_2$] (PEA) was used for the intercalation studies. The compounds [$Zr(PO_4)(H_2PO_4)_{0.53}(HO_3PCH_2NC_4H_7COOH)_{0.47}\cdot 0.56C_6H_5CH(CH_3)NH_2\cdot 0.75H_2O$] (**3**) and [$Zr(PO_4)(H_2PO_4)_{0.50}(HO_3PCH_2NCH_2SC_2H_3COOH)_{0.50}\cdot 0.51C_6H_5CH(CH_3)NH_2\cdot 0.90H_2O$] (**4**) were prepared from **1** and **2**, respectively, upon intercalation of PEA in ethanol solution at 55 °C for 24 h and 35 °C for 48 h, respectively. The *d*-spacings of intercalated **3** and **4** are 21.65Å and 20.94 Å, respectively (Figure 1d and e). In the IR spectra of **3** and **4**, the peaks at 1457, 1383 and 701 cm^{-1} are new and the

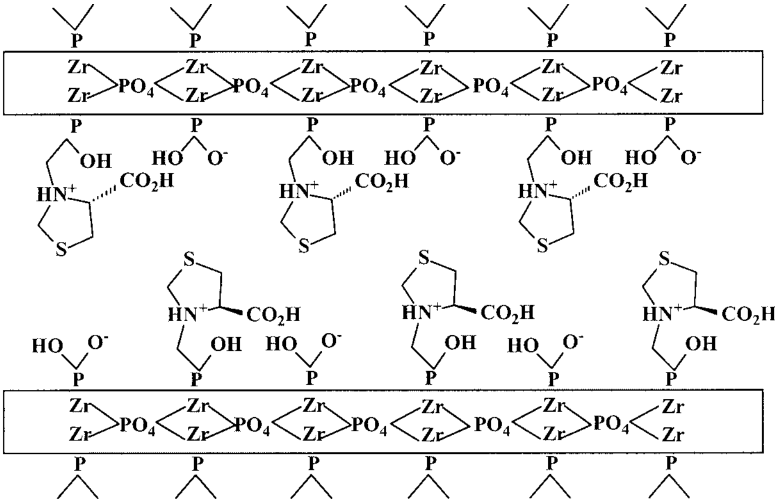

Figure 5. Schematic representation of the interlayer arrangement of γ-ZrPMT (**2**)

peaks at 1730 cm^{-1} disappear. (Figure 4f and g), which suggests that PEA exists inside the layers.[16]

Deintercalation was achieved by suspending **3** or **4** in 0.5 M HCl at 55 °C. The $[\alpha]_D{}^{25}$ values of deintercalated **3** and **4** are −15.6 and −21.2 (c = 1.3 in aqueous HF solution; pH ≈ 1.0), respectively. Compared to the $[\alpha]_D^{25}$ values of −16 for **1** and −21 for **2**, these results show that no racemization occurs during the whole experimental process.

Optical measurements show that the mother liquor obtained after the intercalation or deintercalation has no optical activity, which suggests that neither enantiomer is preferred under the above intercalation condition. In-depth studies of enantioseparation need appropriate guests and special techniques, such as high-performance liquid chromatography (HPLC).[3a,17]

Conclusion

In summary, two new compounds, formulated as $[Zr(PO_4)(H_2PO_4)_{0.53}(HO_3PCH_2NC_4H_7COOH)_{0.47}{\cdot}2.0H_2O]$ (**1**) and $[Zr(PO_4)(H_2PO_4)_{0.50}(HO_3PCH_2NCH_2SC_2H_3COOH)_{0.50}{\cdot}1.6H_2O]$ (**2**) were obtained. The host materials possess intercalation-deintercalation properties and optical activity.

Experimental Section

Materials and Methods: L-Proline, L-cysteine and 1-phenylethylamine $[C_6H_5CH(CH_3)NH_2]$ (PEA) were purchased from Acros, and used as received; PEA was racemic. The content of zirconium and phosphorus was analyzed with a Perkin−Elmer 3300 DV ICP analyzer, and C, H and N by a Perkin−Elmer 2400 analyzer. The IR spectra were recorded as KBr pellets with a Nicolet Impact 410 FT IR spectrometer. X-ray powder diffraction data were collected with a Siemens D5005 diffractometer with Cu-K_α radiation (λ = 1.54178 Å), a 0.03° 2θ-step size, and a 1-s counting time in the 3−40° 2θ range. Thermogravimetric analysis was performed with a NETZSCH STA 449C thermoanalyzer under a 20 mL min^{-1} air flow with a heating rate of 10 °C·min^{-1}. ^{13}C and ^{31}P MAS NMR spectra were recorded with a Bruker-MSL 400 MHz spectrometer. Solution ^{31}P NMR spectra were recorded with an AVANCE 500 spectrometer. BET was carried out under an N_2 flow with a Micro ASAP 2010 M at 77 K. Specific rotation was measured with a WWW-1S digital spectrometer. Solid **1** or **2** was dissolved in about 1.0 mL of HF (40% in water), and deionized water was added up to 50.0 mL. The path length was 20 cm.

Preparation of H_3PMP: This compound was obtained using our modified method based on a literature procedure.[13] CH_2O (40 mmol, 36% in water) was added dropwise to a mixture of L-proline (10 mmol), H_3PO_3 (11 mmol) and HCl (30 mL of a 6.0 M aqueous solution) under reflux. The resultant solution was then heated at reflux for a further 12 h. A white solid with a yield of 96% was recovered after removal of water, and recrystallized from an EtOH/propylene oxide (2:1, v/v) mixture. M.p. 257−259 °C. $C_6H_{12}NO_5P$ (209.14): calcd. C 34.44, N 6.69, H 5.74; found C 34.25, N 6.80, H 5.67. $[\alpha]_D{}^{25}$ = −63 (c = 1.6, in water). ^{31}P MAS NMR (161.9 MHz, 298 K): δ = 8.7 ppm.

Preparation of H_3PMTA: A mixture of L-cysteine (10 mmol), CH_2O (11 mmol, 36% in water) and HCl (10 mL of a 1.0 M aqueous solution) was allowed to stand at room temperature for 24 h. HCl (10 mL of a 6.0 M aqueous solution) and H_3PO_3 (11 mmol) were then added. CH_2O (40 mmol, 36% in water) was added dropwise to the resultant mixture at reflux over 5 min. The solution was then heated at reflux for a further 5 min. The product (yield: 85%) was recovered by removing the water. M.p. 198−200 °C. $C_5H_{10}NO_5PS$ (227.17): calcd. C 26.44, H 4.44, N 6.17, S 14.11; found C 26.49, H 4.62, N 6.01, S 13.95. $[\alpha]_D^{25}$ = −105 (c = 1.0, in water). ^1H NMR (D_2O + K_2CO_3, 500 MHz, 298 K): δ = 2.23−2.48 (m, 2 H), 3.02−3.20 (m, 2 H), 4.01 (d, $J_{H,H}$ = 6.50 Hz, 1 H), 4.12 (d, $J_{H,H}$ = 9.5 Hz, 1 H), 4.32 (d, J = 9.5 Hz, 1 H) ppm. ^{13}C NMR (D_2O + K_2CO_3, 125.8 MHz, 298 K): δ = 31.9, 53.1 (d, $J_{C,P}$ = 147.7 Hz), 60.3, 76.1, 178.9 ppm. ^{31}P NMR (D_2O, 202.4 MHz, 298 K): δ = 7.7 ppm (t, $J_{H,P}$ = 12.1 Hz). MS: calcd. 228.12 $[M + H]^+$; found 228.14.

Preparation of γ-ZrPMP (1): H_3PMP (0.17 g) and γ-ZrP (0.25 g) were added to a distilled water/acetone solution (1:1, v/v; 35 mL). The resultant solution was kept at 80 °C in a Teflon-lined container in an oil bath for 14 d. A white crystalline solid was recovered after washing with water and drying at room temperature. $Zr(PO_4)(H_2PO_4)_{0.53}(HO_3PCH_2NC_4H_7COOH)_{0.47}{\cdot}2H_2O$ (371.39): calcd. C 9.11, H 2.75, N 1.77, P 16.69, Zr 24.56; found C 9.23, H 2.55, N 1.72, P 16.32, Zr 24.17. $[\alpha]_D^{25}$ = −16 (c = 1.2 in HF aqueous solution, pH = 1.5).

Preparation of γ-ZrPMT (2): The experimental procedure for the preparation of **2** was similar to that of **1**, but with H_3PMTA (0.19 g) instead of H_3PMP. $Zr(PO_4)(H_2PO_4)_{0.50}(HO_3PCH_2NCH_2SC_2H_3COOH)_{0.50}{\cdot}1.6H_2O$ (376.52): calcd. C 7.97, H 2.31, N 1.86, P 16.47, S 4.25, Zr 24.23; found C 7.89, H 2.40, N 1.78, P 16.19, S 4.40, Zr 24.09. $[\alpha]_D^{25}$ = −21 (c = 1.4 in HF aqueous solution, pH = 1.5)

Intercalation and Deintercalation Studies with γ-ZrPMP (1). Formation of γ-ZrPMP·$0.56C_6H_5CH(CH_3)NH_2$ (3): Compound **1** (100 mg, 0.27 mmol) was intercalated with 1-phenylethylamine (0.14 mL, 1.08 mmol, c = 0.108 mol·L^{-1}) in ethanol solution (10 mL) at 55 °C for 24 h. Compound **3** (91 mg) was recovered by centrifugal separation, and dried at room temperature for 24 h. $Zr(PO_4)(H_2PO_4)_{0.53}(HO_3PCH_2NC_4H_7COOH)_{0.47}{\cdot}0.56C_6H_5CH(CH_3)NH_2{\cdot}0.75H_2O$ (416.88): calcd. C 21.01, H 3.33, N 3.46, P 14.87, Zr 21.88; found C 21.42, H 2.98, N 3.16, P, 15.03, Zr 22.41. Deintercalation was achieved by suspending **3** in 0.5 M HCl at 55 °C for 2 h. $[\alpha]_D^{25}$ = −15.6 (c = 1.3 in HF aqueous solution, pH ≈ 1.0).

Intercalation and Deintercalation Studies with γ-ZrPMT (2). Formation of γ-ZrPMT·$0.51C_6H_5CH(CH_3)NH_2$ (4): Compound **2** (102 mg, 0.27 mmol) was intercalated with PEA (0.14 mL, 1.08 mmol, c = 0.108 mol·L^{-1}) in ethanol solution (10 mL) at 35 °C for 48 h. Compound **4** (88 mg) was recovered by centrifugal separation, and dried at room temperature for 24 h. $Zr(PO_4)(H_2PO_4)_{0.50}(HO_3PCH_2NCH_2SC_2H_3COOH)_{0.50}{\cdot}0.51C_6H_5CH(CH_3)NH_2{\cdot}0.90H_2O$ (425.59): calcd. C 19.96, H 3.03, N 3.32, P 14.57, S 3.76, Zr 21.43; found C 20.21, H 2.80, N 3.11, P 14.91, S 3.32, Zr 21.31. Deintercalation was achieved by suspending **4** in 0.5 M HCl at 55 °C for 2 h. $[\alpha]_D^{25}$ = −21.2 (c = 1.3 in HF aqueous solution, pH ≈ 1.0).

Molecular Modeling: Computer modeling procedures were employed for the structure study. Using the Cerius^2 program,[18] a supercell was created including four cells of γ-ZrP (a = 5.3825, b = 26.5348, c = 12.4102 Å), and then 50% of $H_2PO_4^-$ was replaced by H_2PMTA. The H_2O molecules were not taken into account in the modeling procedures. The lattice parameters *a* and *b* of the supercell were fixed, and *c* was changed to 14.1 Å on the basis of X-ray powder diffraction analysis. After fixing the inorganic matrix, the organic moieties were optimized to achieve the minimum geometry using the Universal Forcefield[18] supplied as part of the Cerius^2 program package.

Acknowledgments

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