Novel Zinc Phosphate Phases Formed with Chiral *d*-Glucosamine Molecules

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Chiral syntheses and separations of both intermediate and final compounds are currently extremely important areas of research, especially for the chemical, pharmaceutical, agrochemical, and biomedical industries. We are investigating the synthesis of new inorganic porous materials for enantiomeric selectivity. We present a study of inorganic zinc phosphate crystalline phases templated with the chiral molecule *d*-glucosamine hydrochloride. The crystallization of these phases is highly dependent on reaction time, temperature, and stoichiometry. Resultant new phases include a mesoporous phase and a layered phase. Data indicates that the walls of the new 32 Å sized mesoporous phase are crystalline and ordered. Characterization techniques applied include powder X-ray diffraction, TEM, and ^{31}P MAS NMR.

Introduction

Chirality, or "handedness", is four different groups attached to a carbon atom of a molecule that has two *nonsuperimposable mirror-image* forms (each called an enantiomer). The two forms of the chiral molecule can possess very different biological activity. Chiral synthesis and separations of both intermediate and final compounds are currently extremely important areas of research, especially for the chemical, pharmaceutical, agrochemicals, and biomedical industries.[1] In the pharmaceuticals industry (where chiral drug production alone is a $40 billion/year business) rising drug development costs and regulatory requirements have translated into both slower licensing of new drugs and rapid rise in prescription drug costs. This industry is looking for both catalysts (where much work is focused on combinatorial chemistry approaches) and separations material to greatly aid in the production of enantiomerically pure final products. The development of tunable, highly sensitive, and selective molecular recognition materials for important chemical drug species will require enantioselective capabilities.

In an effort to produce enantioselective materials, we have undertaken a study to design chiral inorganic molecular sieves. We have employed the knowledge and successes of recent work[2−10] by templating an inorganic structure with organic molecules. Zeolitic-type structures with chiral tetrahedral framework topologies have previously been synthesized.[11−13] Furthermore, chiral organometallic templates have been used to synthesize zeolitic and layered frameworks.[14−16] Amine molecules have been effective in templating zinc phosphates due to the readily available H-bonding between the nitrogen of the amine and the "dangling" hydroxide of terminal phosphate groups found on the walls of a pore.[17,18] The inherent need for an enantioselective framework, and our past experiences with nonaluminosilicate molecular sieves,[19−21] led us to study the zinc phosphate system. We have explored the transfer of size, shape, and chirality of our templating molecule to the crystalline

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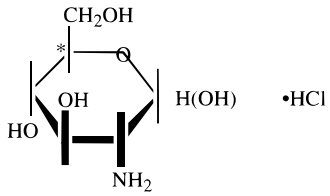

Figure 1. Structure of glucosamine hydrochloride; an asterusk marks the chiral carbon atom.

zinc phosphate system. The resultant materials from the synthetic approaches we describe are envisioned to either become enantioselective chromatography materials or be developed into membrane separations barriers.

Experimental Section

Synthesis of Chirally Templated Zinc Phosphate Phases. The phase space explored for this work is defined by the ratios of zinc, phosphorus, and hydroxide per template. The reactions are performed at room temperature, with reaction times of 3, 6, and 24 h. The starting materials are 4 M H_3PO_4, 25 wt % tetramethylammonium hydroxide (TMAOH) in water, *d*-glucosamine hydrochloride ($C_{12}NO_5H_{26}$·HCl; DGA; see Figure 1), and 2 M $Zn(NO_3)_2$.

Typical synthesis parameters for the *hexagonal phase* were as follows: 1.179 g of 4 M H_3PO_4, 3.6435 g of TMAOH, and 1.08 g of DGA are mixed in a capped Teflon bottle. To the clear solution is added 1.94 g of 2 M $Zn(NO_3)_2$. The thixotropic mixture was shaken until milky and allowed to stand at room temperature. The phase precipitated out of a gel-like solution in 24 h. The product was then recovered by vacuum filtration, washed repeatedly with deionized water, and allowed to dry in air. Typical synthesis parameters for the *layered phase* were as follows: 1.179 g of 4 M H_3PO_4, 4.008 g of TMAOH, and 1.08 g of DGA are mixed in a capped Teflon bottle. To the clear solution is added 1.94 g of 2 M $Zn(NO_3)_2$. The thixotropic mixture was shaken until milky and allowed to stand at room temperature. The phase precipitated out of a gel-like solution in 3 h. For both crystalline phases, the template could not be removed by high vacuum at room temperature, calcination, or solvent extraction (1 M HCl/EtOH) without collapse of the structures. However, the template could be removed from the mesoporous phase after exposure to mild, drying atmospheric conditions for long periods of time (≥1 month).

Characterization. *Powder X-ray diffraction data* were collected at room-temperature on a Siemens Model D500 automated diffractometer, with $\theta-2\theta$ sample geometry, Cu Kα radiation, between $2\theta = 5°$ and 60°, and step size 0.05°. Data presented were collected on "as-synthesized" materials. *Transmission electron microscopy (TEM)* was performed on a JEOL 1200EX at 120 keV. Images were collected using a Gatan 694 retractable multiscan CCD camera. (Template was removed prior to TEM studies. Failure to remove template resulted in the structure "bursting", caused by electron beam heating of organic material in the pores.) *^{31}P cross-polarization magic angle spinning (CP/MAS) and Bloch-decay MAS NMR* data were acquired at 121.4 MHz on a Varian Unity Plus spectrometer using a 7 mm supersonic probe manufactured by Doty Scientific. Typical experimental parameters were 6.0 kHz spinning speed, 6 μs rf pulse lengths ($\pi/2$ pulse for both ^{31}P and ^{1}H), and prepulse delays of 30s for CP/MAS experiments and between 120 and 600s for Bloch-decay experiments. ^{1}H decoupling was performed during all experiments.

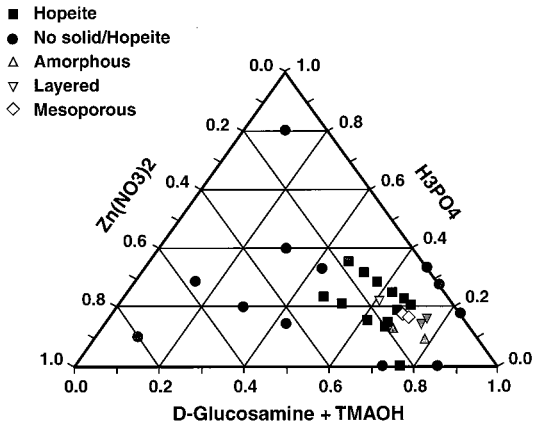

Figure 2. Synthesis−space diagram of (*d*-glucosamine + TMAOH):zinc:phosphate structures established by powder X-ray diffraction patterns.

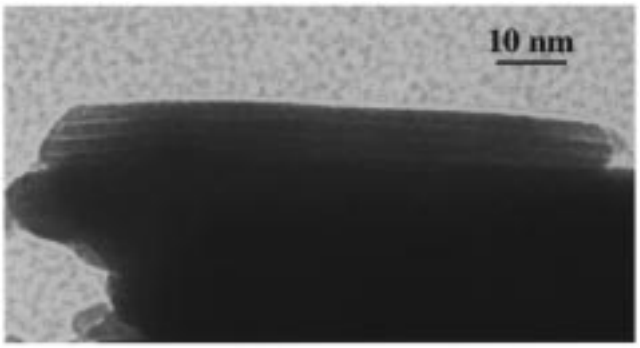

Figure 3. TEM of chirally templated zinc phosphate layered phase. A 10 nm bar is shown for scale.

Results

Within the strict phase reaction limitations, we formed either (1) no precipitated phase; (2) hopeite ($Zn_3(PO_4)_2$·$4H_2O$; a thermodynamically stable, small-pored mineral); (3) a layered material (with intralayered distances of ≈17 Å); or (4) a mesoporous phase, with a hexagonal crystal lattice. (See Figure 2) Note that layered materials of differing intralayer distances can be synthesized, depending on reaction conditions. Only one is presented here. (See Figure 3.) Powder X-ray diffraction allowed us to identify and monitor the growth of different crystalline phases: a mesoporous phase (similar X-ray pattern to hexagonal MCM-41[4]), a layered phase, and the hopeite phase. (See Figure 4) For "fingerprinting" purposes, the identifiable peaks in the powder X-ray diffraction patterns ($2\theta = 1.5-10°$) for the mesoporous, layered, and hopeite phases are $d = 31.223$, 17.404, and 9.141 Å, respectively. The X-ray data is reinforced by TEM data. Distinct, measurable intralayer spacings on the interim layered phase, the mesoporous phase (see Figure 5), and crystalline hopeite are observed.

An investigation of the phase space indicates there is a very narrow range of reactants that provide for the synthesis of the mesoporous and layered phases. The phase space described here had a reaction time of 24 h, with partial studies at 3 and 6 h reaction times (to monitor phase growth). The reaction conditions studied indicate that 24 h at room temperature will produce the mesoporous phase with reactants in the following ratio: $0.3H_3PO_4$:$0.5Zn(NO_3)_2$:0.8(TMAOH + DGA). The

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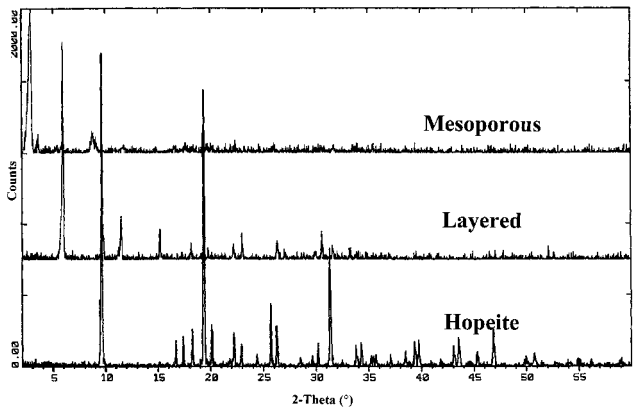

Figure 4. Powder X-ray diffraction patterns of three phases synthesized in the zinc:phosphate:(*d*-glucosamine + TMAOH) phase space. The different phases are products of time, reactant ratios, pH, and temperature.

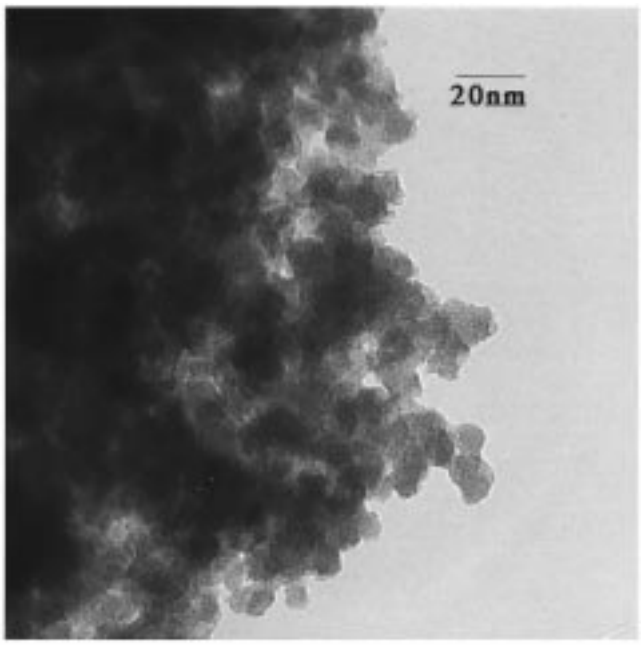

Figure 5. TEM of chirally templated zinc phosphate mesoporous phase. The white spots are 32 Å pores, and the walls are zinc phosphate. The template was removed under mild vacuum with time. A 20 nm bar is shown for scale.

layered phases were less well defined in ratio for crystallization and tended to surround the region for mesoporous crystallization. There are also distinct regions for hopeite crystallization and no precipitation of a phase. We observed a transition in phase growth which is dependent on time of reaction. Much like was observed in the M41S studies,[6] we observed an evolution of phase growth beginning with the interim layered templated-zinc phosphate phase (observed at 3 h) with a primary *d* spacing of 33(±1) Å. This layered phase disappears with an additional few hours of reaction time. After 24 h of reaction, the mesoporous phase was observed, with identifiable *d* spacings of 35 and 25(±1) Å. When the reaction was allowed to continue until 48 h, hopeite was the only crystallographic phase present. (See Figure 6) The system appears to drive toward the thermodynamically stable, probably more favored, hopeite phase.

Working in the zinc phosphate phase space, we found that we could synthesize a structure with a 3-dimensional pored system. Of particular interest to us was the TEM data. The coherent spacings were all approximately 32 Å, the pore sizes are consistent, and the pores are distinct. The repeat distance of the pores was approximately 36 Å. This corresponds to $2d_{100}/\sqrt{3}$ of the (100) peak (assignment of the 31.2 Å powder X-ray diffraction peak to the (100); see Figure 6). The remaining XRD peaks do not correspond to (110) or (200) peaks and may be due to impurity phases. There is a degree of shorter range ordering to the pores; however, there is a lesser degree of long-range coherent crystalline pore ordering. Much like some water:cosolvent silica/surfactant disordered mesophases (d-H),[22,23] the liquid crystalline packing of the *d*-glucosamine molecules may have a disordered arrangement of cylinderical 1-d pores (quasihexagonal) that are intersecting disordered unimodal channels. Both systems exhibit similar long-range disorder of the hexagonal-packed pores in TEM images and the (100) diffraction peak in powder X-ray diffraction.

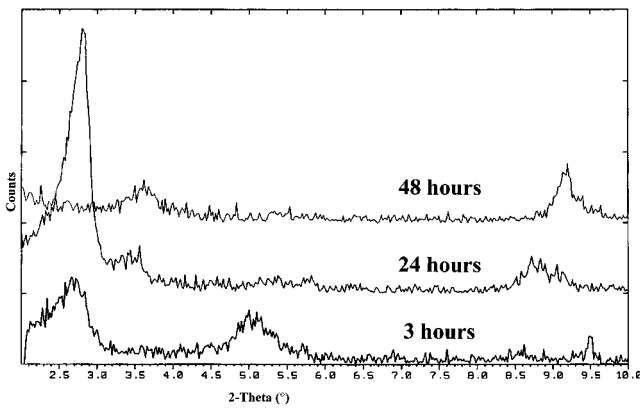

Figure 6. Powder X-ray diffraction patterns detailing the effect of time on reaction products for $0.3H_3PO_4$:$0.5Zn(NO_3)_2$:0.8(*d*-glucosamine + TMAOH). 3 h = layered phase; 24 h = mesoporous phase; 48 h = hopeite phase.

^{31}P MAS NMR data indicate a crystalline framework for the mesoporous phase (as opposed to the all silicate MCM[4,6] mesoporous materials, which have amorphous walls). The three peaks (8.0, 4.5, and 2.5 ppm chemical shifts) are all consistent with tetrahedral monophosphate species with varying degrees of distortion of the tetrahedral unit (see Figure 7). The resonances are assigned as follows: the peaks at 8.0 and 4.5 ppm correspond to an impurity phase, consisting of hopeite (4.5 ppm) and an unknown hopeite-related phase (8.0 ppm), and the peak at 2.5 ppm is attributed to the framework of the mesoporous phase. Note that the hopeite-related phase is present only during and after NMR spinning (as monitored by XRD). The narrow peak widths (hwhm = 0.75 ppm) suggest, at most, a very small degree of variation in the geometry of the phosphate tetrahedra within the framework and thus show no evidence for the formation of an amorphous phosphate phase. Instead, data show that the walls of this zinc phosphate mesoporous phase have an ordered arrangement of its tetrahedral atoms. Cross polarization and relaxation studies suggest that the mesoporous

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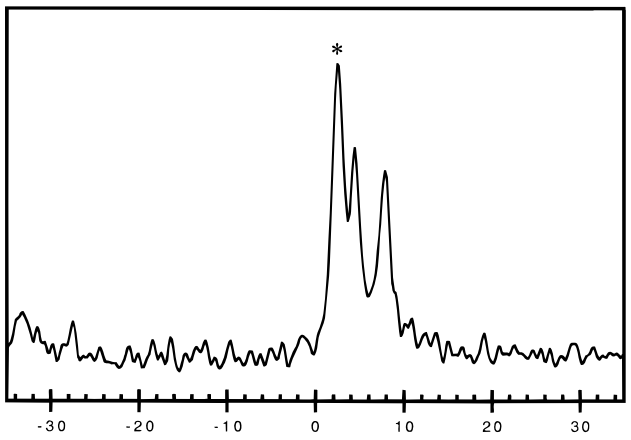

Figure 7. ^{31}P MAS NMR of mesoporous phase (with impurities), referenced to 85% H_3PO_4. An asterisk indicates the mesoporous zinc phosphate peak.

and hopeite phases are phase separated on the nanometer scale or greater. The chemical shift for the mesoporous phase was found to be close to that of the ^{31}P MAS NMR data for crystalline ZnPO-X molecular sieves (5.8 ppm).[24] The data strongly suggest that the walls of this zinc phosphate mesoporous phase have an ordered arrangement of its tetrahedral atoms.

Discussion

The ability to rapidly synthesize enantiomerically pure final products is clearly a desirable goal. However, this requires highly selective and active chiral catalysts. Typically, the asymmetric synthetic route to a drug or intermediate is so difficult that separation of the racemate turns out to be the cost-effective solution. The ability to design a chiral separations material is required. Furthermore, many drug molecules are larger than the average zeolitic pore (>15 Å) and therefore will be excluded from any separations. Chiral separations of large drug molecules through a chiral framework mesoporous phase should not be limited by the size of the drug molecules. With our mesoporous phase, the size of the pores and the possible chirality of the framework are important if this phase is to be used as a separations material.

Characterization results show that the zinc phosphate mesopore we describe is successfully templated by the chiral *d*-glucosamine hydrochloride. Powder X-ray diffraction data showed a hexagonally packed mesoporous phase, with short-range coherent order. The ^{31}P MAS NMR data indicated that the walls of the phase are crystalline and similar in local structure to Zn/P zeolite analogues, as opposed to the amorphous walls found in the silicate MCM mesopores phases. The single unidirectional pore size and shape of this mesopore also substantiate the possibility of the chirality in the framework, in a fashion similar to the earlier predicted chiral polymorph of Zeolite B and of reported Co/P, ABW, and HEX phases.[12,14] With those reported materials, the crystallographic screw axis (which describes the chirality of the tetrahedral framework atoms) is shown to run in the direction of the channel system of the largest pore opening. Furthermore, by using one enantiomer of the chiral template in the reactions, we have attempted to ensured that structure direction will be enantiomerically pure.

The role of the chiral template is still being studied, to better understand how this small template is able to space fill extremely large intracrystalline voids. Much like the crystalline guanadine zinc phosphate phase reported by Harrison and Phillips,[18] it is possible that a number of DGA cations "cooperate" in a type of planar conformation, whereby they collectively are large enough to fill the 31.2 Å pore of the mesoporous phase. In much the same way, hydrogen-bonding interactions between the amine group of the template to the oxygen atoms of the framework may account for the stability of the unit. However, there is also the possibility that protons from the hydroxyl groups of the sugar are weakly hydrogen bonding to the "dangling" phosphate groups of the framework. This would account for a much weaker interaction between the template and the framework. This theory is of interest to us because of our ability to remove the template through mild (long term) dehydration (see above), contrary to many amine-templated zinc phosphate systems. Another theory for template geometry is that the *d*-glucosamine molecules are forming a large liquid crystalline (LC) cholesteric mesophase. This LC mesophase is comprised of helical aggregates of molecules, which contain a chiral center, and is referred to as a "twisted nematic mesophase".[25] In this case, chirality is maintained in the resulting superstructured template. Characterization and enantiomeric separation studies are on going to further resolve the issue of template molecular ordering.

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