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Asymmetric Crystallization

Nucleotide-Catalyzed Conversion of Racemic Zeolite-Type Zincophosphate into Enantioenriched Crystals**

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Homochirality is a ubiquitous feature in living systems and plays a crucial role in biological processes. Many naturally occurring biochemical molecules such as proteins, nucleic acids, and carbohydrates are homochiral.[1] In comparison, homochirality in inorganic compounds is quite a rare phenomenon. For example, even though quartz is chiral, it is found in nature in both right- and left-handed forms.[2] Also, unlike homochiral organic molecules,[3] chirality in inorganic systems often depends on the crystallization process that allows the generation of chirality through the organization of achiral inorganic units into the enantiomorphous space group. This crystallization process, however, almost always generates a mixture of right- and left-handed crystals, even though statistical fluctuations may occasionally result in enantioenriched bulk samples.[4]

There has long been a strong interest in creating crystalline homochiral porous materials that may be utilized in processes such as heterogeneous enantioselective catalysis and separation.[5–8] With few exceptions, the homochiral porous solids prepared to date acquired homochirality through the incorporation of enantiopure organic ligands that are bonded to the crystalline framework either as a cross-linking ligand or a pendant ligand. Induction by chiral additives or solvents has also been found to generate homochirality in crystals of a few metal–organic coordination polymers in which metal–ligand interactions may be responsible for the chiral induction.[9,10] Clearly, these methods are not suitable for the synthesis of homochiral zeolite-type materials that are constructed entirely from inorganic building blocks.[11]

The bulk asymmetric crystallization of inorganic open-frameworks from achiral precursors into three-dimensional open-framework materials has not been reported to date, but is a highly desirable process because of its implication in heterogeneous asymmetric catalysis.[12,13] Crystallization of some simple salts such as sodium chlorate under the influence of chiral co-solute (e.g., D-glucose) was reported a long time ago, although its enantioselectivity was recently disputed.[4] Such chiral mineral–biomolecule interactions have also been linked to the origin of biological homochirality.

The homochiral crystallization of inorganic salts (e.g., $NaClO_3$) from achiral precursors has also been reported to occur in the absence of chiral induction agents.[14] These experiments can lead to bulk homochiral crystals on the basis of statistical fluctuation of crystallization events. However, the absolute chirality is generally not predictable from run to run. In addition, these homochiral structures bear no similarity to materials with 3D zeolite-type topology.

We are interested in the development of synthetic methods that can lead to the bulk asymmetric crystallization of inorganic zeolite-type frameworks because of the potential applications of such materials in heterogeneous enantioselective catalysis. For inorganic crystals, the generation of chirality through crystallization is not uncommon, when it is considered that many crystals with enantiomorphous space groups are known. What is uncommon and difficult to achieve is the controlled generation of homochiral or enantioenriched bulk samples. Since one of the most prominent families of inorganic zeolite-type materials are metal phosphates,[15,16] we began our work by investigating methods to create asymmetric crystallization in the zeolite-type metal phosphate system. For this work, we selected one zeolite-type topology chiral zincophosphate (CZP), which has an intrinsically chiral topology. CZP is based on a hydrated sodium zincophosphate (**1**, $NaZnPO_4{\cdot}H_2O$, space group: $P6_122$ or $P6_522$),[17] and has large-pore 12-membered-ring channels along the hexagonal *c* axis. Even though it is chiral, CZP has never been reported in enantiopure or enantioenriched forms.

In devising synthetic strategies to create homochiral or enantioenriched CZP crystals, we hypothesized that if a nucleotide is employed as a chiral induction agent, it may undergo enantioselective interaction with the crystal nuclei through its phosphate group. Such enantioselective interactions between the enantiopure nucleotide molecules and the racemic CZP crystals should offer an opportunity to achieve the asymmetric crystallization of zeolitic CZP crystals. Furthermore, the chiral interactions between biomolecules and inorganic crystals have always been of interest because of their relevance to the origin of biological homochirality. Herein, we report the chirality-induction effect of a ribonucleotide (uridine-5′-monophosphate disodium (ump; Figure 1) on the catalytic asymmetric crystallization of **1**.

Upon mixing ZnO (0.052 g), H_3PO_4 (0.092 g, 85% aqueous solution), and H_2O (2 mL), followed by the adjustment of the pH to 11 using 6 M NaOH (ca. 17 drops), a polycrystalline white powder was obtained and subsequently identified as **1** by X-ray powder diffraction. The same sample showed no solid-state CD signal, which suggests that the bulk

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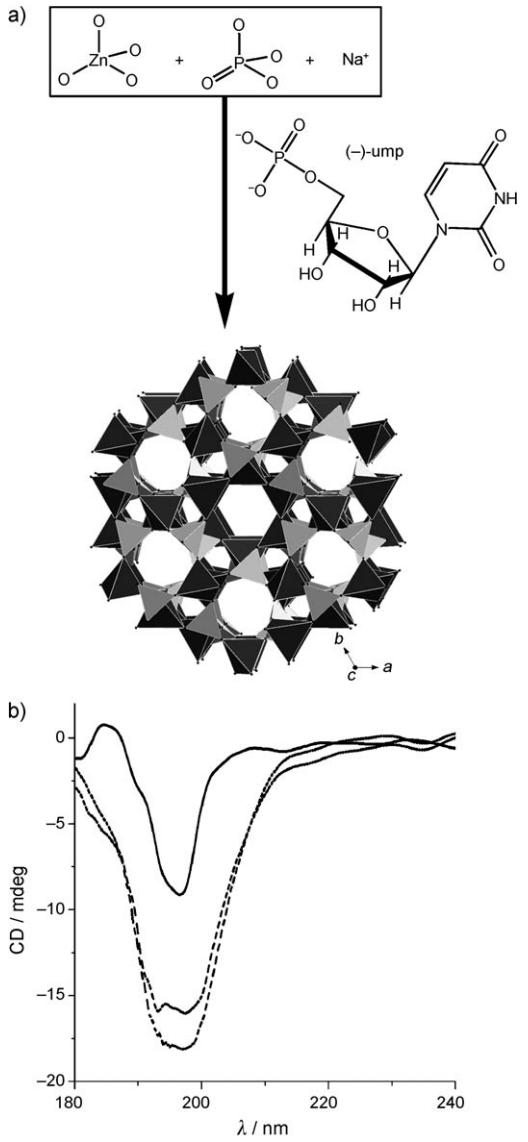

Figure 1. a) Asymmetric crystallization of CZP zeolite-type crystals (crystal structure shown in polyhedral style) induced by the ump catalyst. b) Solid-state CD spectra of the enantioenriched bulk samples (the three curves represent three different samples prepared in three separate syntheses).

was racemic. When a small amount of ump (0.0472 g) was added to the fresh heterogeneous mixture, followed by hydrothermal treatment in a vial at 80 °C for 4 days, crystals suitable for single crystal X-ray diffraction were obtained. All the available evidence suggests that the asymmetric crystallization of CZP crystals (or more specifically, conversion of racemic crystals into enantioenriched crystals) occurred. Such asymmetric crystallization was catalyzed by the enantiopure nucleotide and could be repeated many times.

The first piece of evidence for the asymmetric crystallization was provided by single-crystal structure refinement. Crystal structures of 15 randomly selected crystals were refined using single-crystal X-ray diffraction data. The Flack parameter of each refinement indicates that 14 crystals belong to the $P6_122$ space group while only one crystal adopts the opposite $P6_522$ space group (Table S1 in the Supporting Information). This result suggests that the *ee* value is approximately 85 % in favor of the $P6_122$ form when ump is used as the catalyst.

The second piece of evidence for the asymmetric crystallization comes from the solid-state CD spectroscopy. The CD spectra for samples obtained from three separate synthetic batches catalyzed with ump show that the bulk samples of (−)-**1** consistently exhibit negative CD signals at around 197 nm (Figure 1).

The third piece of evidence for the asymmetric crystallization is provided by a comparative study of the crystallization processes performed in the absence of ump. In this case, the resulting bulk sample is a conglomerate. The single-crystal X-ray diffraction study of six randomly selected crystals shows that right- and left-handed CZP crystals are present in the same amount (Table S2 in the Supporting Information). Furthermore, no CD signal was detected for the bulk sample prepared in the absence of ump.

To probe the nature of this unusual chiral induction effect, we also investigated both uridine and D-ribose (chiral parts of ump) as the chiral induction agent, in order to determine whether the chiral sugar unit can exert a direct influence on the crystal growth. We found that neither uridine nor D-ribose exhibits the chiral induction effect (Figure S1 in the Supporting Information). This result suggests that there is probably a cooperative effect between the binding of the phosphate group in ump to CZP crystal nuclei and the generation of the absolute chirality of CZP crystals.

The use of a different nucleotide provides additional insight into the mechanism of the chirality induction. We found that the nucleotide inosine-5′-monophosphate disodium (imp) is ineffective in the chirality induction. We believe that the difference between the catalytic induction abilities of ump and imp is related to their base groups. It has been shown that imp has a strong tendency to bind to the metal cation through the base group hypoxanthine, which is related to purine with a fused ring structure,[18] while ump tends to bind to metals through its phosphate group.[19] Therefore, we suggest that the enantioselective interaction occurs between the CZP crystal nuclei and ump at the solid–solution interface (Figure 2 a) and that for imp, the interaction between the base group and metal cations could disrupt the metal–phosphate interaction and lead to the loss of enantioselectivity on CZP crystals (Figure 2 b).

The mechanism of the chirality induction can be further probed by studying the effect of the reaction temperature. When the synthesis was performed at 120 °C under otherwise identical synthetic conditions, the resulting bulk sample became racemic. The loss of the chiral induction effect is likely due to the hydrolysis of ump into phosphate groups and uridine. This hypothesis is supported by the fact that crystals of **1** can also be grown by using ump as the sole phosphate source at 120 °C. In this case, the reaction of a mixture of ump, $Zn(NO_3)_2{\cdot}6H_2O$, and 1,3-bis(4-piperidinyl)propane (pH 11.3) at 120 °C led to crystals of **1**, thus confirming that ump hydrolyzes at 120 °C to provide the PO_4^{3-} source for the crystal growth of **1**.

Many theories exist on the origin of homochirality in biological systems. One such theory suggests that the enan-

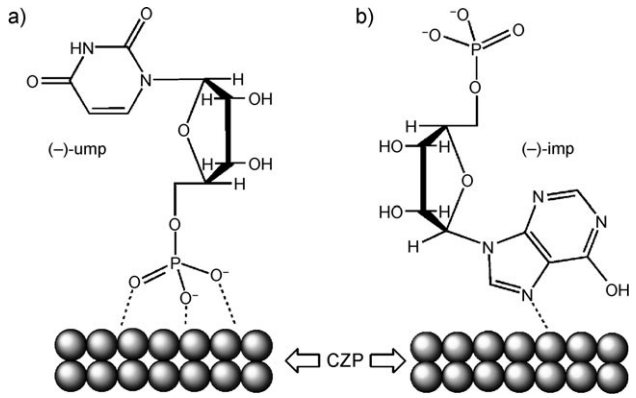

Figure 2. Possible interactions between a) ump and CZP crystal nuclei and b) imp and CZP crystal nuclei.

tioselective adsorption of small organic molecules on the chiral surface of minerals such as quartz may play a role in the initial enantiomeric excess of some biomolecules. In this aspect, it is of interest to note that the chirality of enantiopure biomolecules controls the absolute chirality of mineral-like chiral inorganic crystals in the chiral induction effect reported here. Such a process is the reverse of the mineral induction effect in the "origin-of-homochirality" theory. As such, an interesting question is raised about whether there is a mutual chirality amplification effect during the generation of homochirality in biomolecules in the prebiotic period.

In conclusion, we have reported an unusual example of the asymmetric crystallization of an inorganic zeolite-type material. The asymmetric crystallization is achieved by using a nucleotide as the chirality-induction agent, and is based on a strategy that matches the functional groups of the chirality-induction agent with the bonding features of the chiral crystals. Additional evidence such as effects of other nucleotides, nucleosides, D-sugars, and reaction temperature provides further support that the mechanism of the chirality induction occurs through the cooperative effect between the phosphate binding to the crystal nuclei and absolute chirality control from the sugar unit. We believe the method reported here represents a new paradigm in the development of homochiral crystalline materials and may help to provide new insights into the chiral mineral–biomolecule interactions.

Experimental Section

Single-crystal structure analysis: Each crystal was glued to a glass fiber with epoxy resin and mounted on a Bruker APEX II diffractometer equipped with a fine focus, 2.0 kW sealed tube X-ray source ($Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å) operating at 50 kV and 30 mA. Each structure was solved by direct methods followed by successive difference Fourier methods.

Measurement of solid CD spectra: The mixture of sample (ca. 3 mg and dried KBr powder (40 mg) was well ground and then pressed into a disk for use in the CD measurement, which was obtained using a J-810 spectropolarimeter.

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