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Histidine-Controlled Two-Dimensional Assembly of Zinc Phosphite Four-Ring Units

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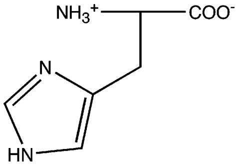
Despite there being numerous examples of metal−organic frameworks in which metal centers or clusters are joined together by bi- or polydentate ligands into extended structures, biologically important amino acids, histidine in particular, are rarely known to serve as bridging ligands for the construction of open-framework architectures. Here, we report hydrothermal self-assembly between neutral zwitterionic histidine molecules and inorganic secondary building units (i.e., (Zn−O−P−O)$_2$ four-rings) into a crystalline solid containing infinite two-dimensional arrays. We demonstrate that the acid−base and coordination chemistry of histidine can be controlled to promote the formation of open architectures with bridging histidine ligands instead of the commonly observed metal−chelates with chelating histidine ligands. Crystallographic data for Zn(HPO$_3$)(DL-C$_6$H$_9$N$_3$O$_2$)(H$_2$O)$_{1/2}$, *C*2/*c*, $a = 15.1307(3)$ Å, $b = 8.4230(2)$ Å, $c = 16.6322(4)$ Å, $\beta = 100.420(1)°$, $V = 2084.75(8)$ Å^3, $Z = 8$.

Introduction

Histidine is one of the naturally occurring essential amino acids and is often found at the active site of proteins. Compared to other amino acids, one unique structural feature of histidine is that its side chain bears a basic imidazole group. The histidine residue in a protein can therefore function as a monodentate ligand through its side imidazole group. The histidine imidazole−metal (e.g., Fe, Cu, or Zn) coordination chemistry is vital for many biological functions of histidine-containing metalloproteins, including hemoglobin, hemocyanin, and hemerythrin.[1]In the monomeric form, histidine is a polydentate ligand. In addition to the imidazole group, histidine can also coordinate to metal centers through its amino and carboxyl groups. In most known metal−histidine complexes, histidine binds with metal centers (e.g., V, Co, Ni, Cu, and Zn) in chelating modes using two or all three available functional groups (i.e., amino, carboxyl, imidazole).[2,3] Because of its strong tendency to form metal chelates, histidine is rarely known to function as the bridging ligand for the creation of open-framework materials.[4,5,6] One rare example of the bridging histidine is [Ag(Hhis)]$_n$, in which Ag$^+$ and anionic histidine alternate along the chain.[7]

Scheme 1. Molecular Structure of Histidine in the Neutral Zwitterionic Form



In this work, we seek to take advantage of the unique acid−base and coordination chemistry of histidine for the construction of the open-framework architecture. The realization of this objective requires the exploration of new histidine−metal coordination chemistry in which histidine serves as a divergent (bridging) ligand rather than convergent (chelating) ligand, as commonly observed in histidine−metal complexes.

The use of histidine (amino acids and peptides in general) as building blocks for the construction of crystalline open-framework solids has a number of advantages. Such systems are expected to exhibit rich metal−amino acid coordination chemistry that could serve as model systems for the study of important biocoordination compounds (e.g., metalloproteins). Open-frameworks developed through the integration of biomolecules such as amino acids (or peptides) and inorganic primary or secondary building units may allow for the creation of novel materials that combine the high chemical and thermal stability of inorganic oxides with the biological functionality of biomolecules. Furthermore, the direct incorporation of chiral amino acids into the framework may allow for the creation of noncentrosymmetric or chiral solids that could have potential applications in enantioselective catalysis and separation or nonlinear optical applications.[8,9] Because of these advantages, there has been extensive interest in using amino acids as building blocks to create

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Table 1. Summary of Crystal Data and Refinement Results

name	$ZnPO_3$−His
formula	$Zn(HPO_3)$(DL-$C_6H_9N_3O_2$)$(H_2O)_{1/2}$
size (mm^3)	0.20 × 0.12 × 0.10
T (K)	298
a (Å)	15.1307(3)
b (Å)	8.4230(2)
c (Å)	16.6322(4)
β (deg)	100.420(1)
V ($Å^3$)	2084.75(8)
Z	8
space group	$C2/c$
$2\theta_{max}$ (deg)	68.6
total no. of data points	18701
no. of unique data points	4349
data, $I > 2\sigma(I)$	3587
no. of params	194
$R(F)$ (%)	3.17
$R_w(F^2)$ (%)	8.10
GOF	1.06

hybrid inorganic−organic framework solids and a number of amino acids have been explored already, including asparagine, histidine, and asparic and glutamic acids.[10,11,12,13,14]

Here, we report a rare extended open-framework solid in which histidine functions as a cross-linking ligand. To the best of our knowledge, this is the first time that inorganic secondary building units (four-membered rings as commonly observed in zeolites) are assembled with histidine bridges into an extended framework structure. In this new compound (denoted $ZnHPO_3$−His), neutral zwitterionic histidine exhibits a rather unusual coordination mode: bidentate linker between two tetrahedral metal centers. This coordination mode is in contrast with monodentate or bi- and tridentate chelating ligands coordinating to a single metal center, as commonly observed in many metal histidine complexes.

Experimental Section

Synthesis. L-Histidine (0.9311 g) was added to a solution prepared by mixing 0.3731 g of zinc carbonate, 0.7455 g of phosphorous acid (H_3PO_3), 1.5075 g of water, 1.5137 g of ethylene glycol, and 0.0690 g of hydrogen fluoride pyridine. The mixture was stirred for 45 min (pH = 3.77), sealed in a Teflon-lined stainless steel autoclave, and heated at 120 °C for 7 days. After the mixture was cooled to room temperature, clear rectangular-prismatic crystals (0.6570 g, 70.5% yield) were obtained.

Single-Crystal Structure Analysis. A crystal was glued to a thin 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 Kα radiation, $\lambda = 0.71073$ Å), operating at 50 kV and 30 mA. The empirical absorption correction was determined on the basis of equivalent reflections, and other possible effects, such as absorption by the glass fiber, were simultaneously corrected. The structure was solved by direct methods followed by successive difference Fourier methods. All hydrogen atoms were located from difference Fourier maps and refined isotropically; all non-hydrogen atoms were refined anisotropically. Computations were performed using SHELXTL and final full-matrix refinements were against F^2. The crystallographic results are summarized in Table 1.

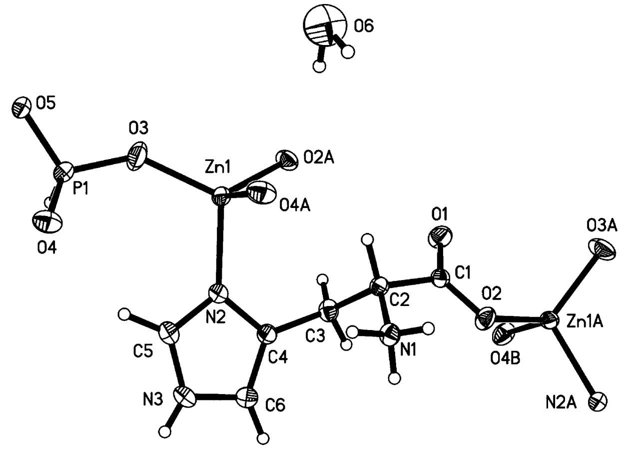

Figure 1. ORTEP diagram of $ZnHPO_3$−His showing the local coordination environment and connectivity between inorganic and organic components. Hydrogen atoms are shown as small open circles attached to thermal ellipsoids.

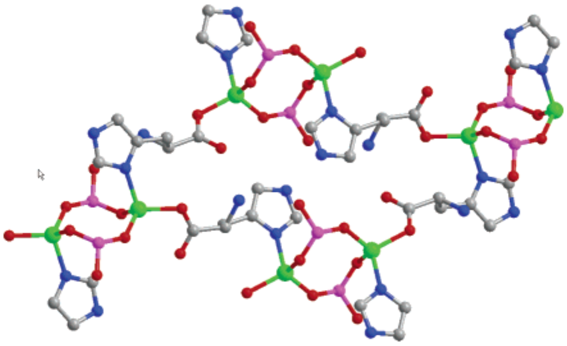

Figure 2. Four neutral inorganic four-rings made from $[(ZnHPO_3)_2]_2$ are cross-linked by four neutral histidine molecules into a "super" four-ring unit. Green, Zn; Purple, P; Blue, N; Red, O; and Grey, C. Hydrogen atoms are not shown.

Thermal Analysis. The simultaneous DSC-TGA thermal analysis was performed on a TA Instruments SDT Q600 under a flowing nitrogen atmosphere. The flow rate of the nitrogen gas was controlled at about 100 L per minute. The sample was prepared by grinding single crystals into fine powder. A total of 7.004 mg was heated between room temperature and 1000 °C at a heating rate of 5 °C/min.

Results and Discussion

The crystal structure of $ZnHPO_3$−His is determined from single-crystal X-ray diffraction data with 2θ values as high as 69°. All hydrogen atoms can be determined unambiguously from difference Fourier maps, which confirms that histidine functions as the bidentate ligand (using the carboxyl and imidazole groups) in the neutral zwitterionic form (Figure 1). Such a bridging coordination mode by histidine is unusual because in the histidine−metal system, histidine has a strong tendency to form metal chelates.

A main structural motif is the four-membered ring (4-ring, $(ZnHPO_3)_2$) commonly observed in zeolite-type structures (Figure 2).[15,16] The neutral 4-ring (four cationic polyhedral centers, not counting oxygen bridges) is formed from two

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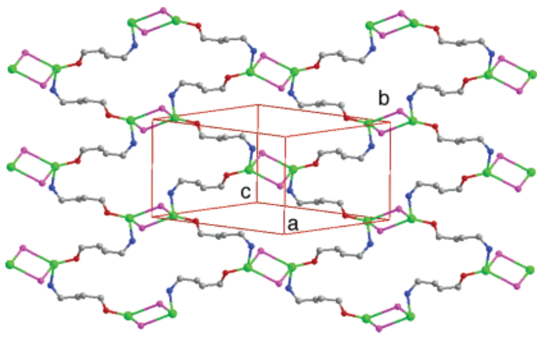

Figure 3. Neutral zwitterionic histidine molecules cross-link $(ZnHPO_3)_2$ four-rings into an infinite two-dimensional sheet. For clarity, $(ZnHPO_3)_2$ units are represented as (Zn−P−Zn−P) four-rings and histidine molecules are shown with some atoms removed to highlight their bidentate and bridging connectivity. Green, Zn; Purple, P; Blue, N; Red, O; and Grey, C.

tetrahedral Zn^{2+} cations and two HPO_3^{2-} phosphite anions, resulting in a neutral $(ZnHPO_3)_2$ 4-ring. Each P site within the 4-ring is only two-connected because its two other bonds are terminated by two dangling groups (P−H and P═O). In comparison, each Zn^{2+} site is 4-connected to two phosphite anions and two neutral histidine molecules.

The above inorganic 4-rings are further connected by neutral zwitterionic histidine molecules into a hybrid inorganic−organic super 4-ring. Such hybrid super 4-ring consists of four inorganic 4-rings interlinked by four histidine molecules (Figure 2). Each histidine molecule serves as a simple bidentate bridge between one pair of inorganic 4-rings. These super 4-rings are extended into infinite two-dimensional sheets (Figure 3) that are stacked in the crystallographic (101) direction.

It is worth noting that histidine functions as a bridge between inorganic secondary building units, not just simple isolated metal sites. The direct cross-linking of Zn^{2+} sites with neutral zwitterionic histidine molecules would result in the formation of a positive framework that is generally not favored under hydrothermal conditions. Thus, the main role of phosphite anions is to help create inorganic secondary building units that are either neutral or negative. Some zinc phosphite frameworks that do not contain cross-linking amino acids are already known.[17] On the basis of such understanding, we are currently investigating whether other anions such as phosphonates and selenites can function in a similar capacity.

One apparent difficulty with the synthesis of metal−histidine open-framework materials is the relative ease with which histidine can form metal chelates. With three functional groups, a total of four permutations are possible when more than one functional group participates in the metal−histidine coordination: NH_2 and COO^-, NH_2 and imidazole, COO^- and imidazole, and all three groups. The formation of stable metal−histidine complexes can be achieved in three of the above four permutations: (1) the formation of six-membered rings between a metal center and two nitrogen sites (one from the amino group and one from the imidazole group), (2) the formation of a five-membered ring between a metal center with both amino and carboxyl groups; and (3) the formation of both a five-membered ring and a six-membered ring using all three functional groups of histidine. The formation of stable six- or five-membered rings competes with the formation of histidine-based open-framework materials, which explains the rarity of open-framework materials built from bridging histidine.

Because all three of the above modes require the participation of the amino group, the key to the creation of histidine-based open-frameworks is to remove the coordinating ability of the amino group. For the formation of an open-framework architecture, the divergent coordination mode using the imidazole and carboxyl groups are preferred. This is feasible because the chelate formed from the imidazole and carboxylic groups would have a seven-membered ring and is much less likely to form.

In this study, to achieve the divergent coordination, we systematically varied the pH of the reaction system. More specifically, the synthetic strategy here is to select a pH value low enough that the amino group is protonated and unable to bond to the metal. In the meantime, the pH should be high enough to produce an adequate concentration of the zwitterionic form. The optimum pH range for this purpose was found to be between 3.7 and 7.0, below the isoelectric point (7.6) of histidine (the pK_a values of three functional groups, −COOH, $^+NH_3$, and protonated imidazole, are 1.8, 9.1, and 6.1, respectively). A higher pH is undesirable because it would significantly increase the concentration of the anionic form, leading to the crystallization of the pentahydrate phase, $Zn(His)_2{\bullet}5H_2O$ ($a = 16.41$ Å, $b = 14.76$ Å, $c = 10.99$ Å, $\beta = 129.60°$, $C2/c$), that has been found in our experiments when higher pH values are used.[18] Even though enantiomerically pure L-histidine was employed as the reactant, the product crystals are centrosymmetric and contain both D and L forms. The exact reason for the racemization is unclear and remains under investigation.

$ZnHPO_3$−His is stable until about 287 °C in the nitrogen atmosphere. No weight change or heat change was observed until 287 °C, at which a weight loss of 11.8% accompanied an endothermic reaction. This was likely due to the loss of water molecules and the partial loss of neutral histidine molecules. The slow weight loss (15.2% in total) continued until 880 °C. Between 880 and 1000 °C, there was a sharp weight loss of 56.4%. The temperature (287 °C) for the water loss is quite high. This is likely due to the hydrogen bonding between water molecules and framework oxygen sites (O−H···O type). In addition, the protonated amino group (NH_3^+) is also capable of forming hydrogen bonding with water molecule (N−H···O type). The shortest distances between the water oxygen site and framework oxygen site and between the water oxygen site and framework nitrogen site are 2.929 and 3.152 Å, respectively. Such distances are close enough for the formation of hydrogen bonds.

In conclusion, zwitterionic histidine has been used as the structural building block and bidentate ligand to assemble inorganic secondary building units into a two-dimensional open-framework architecture. This is the first time that the biologically important histidine molecule has been assembled

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in the bridging mode with inorganic secondary building units into the metal–organic hybrid framework. The synthetic strategy is based on the control of the charge on both inorganic secondary building units and histidine molecules. In particular, the control of the reaction pH to promote the coordination ability of the imidazole group while suppressing the coordination ability of the amino group is important for preventing the formation of metal–histidine chelates and for achieving the cross-linking function of histidine. This work opens up new opportunities for the synthetic design of novel materials that integrate zeolite-like structural building units with biologically functional molecules.

Supporting Information Available: Crystallographic data including positional parameters, thermal parameters, and bond distances and angles (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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