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A New Biocompatible Metal-Organic Framework Prepared by Green Chemistry Methods

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Abstract—A new biocompatible metal-organic framework $[Mg(Mal)(H_2O)](H_2O)$ (H_2Mal = malic acid) (**I**) was synthesized under solvothermal conditions, isolated in a pure state, and characterized by elemental analysis and X-ray diffraction. Compound **I**, which is the second example of a magnesium metal-organic framework based on malic acid, was prepared under drastic conditions of solvothermal synthesis. Cysteine or products of its decomposition were found to have a template effect on the formation of malic acid-based metal-organic frameworks under the chosen drastic conditions.

Keywords: biocompatible materials, metal-organic frameworks, X-ray diffraction, solvothermal synthesis
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INTRODUCTION

Metal-organic frameworks (MOFs) [1] are an important class of crystalline materials consisting of metal-containing nodes and organic linkers [2]. The possibility of controlling [3] their periodic structure [4] and, hence, physicochemical properties by selecting particular components brings about [5–9] unabated interest of the world community in these materials [10–14]. For example, MOFs are actively used for gas storage [15] and separation [16], for energy storage [17], for targeted drug delivery [18] and also as catalysts [19], sensors [20], and membranes [21–23]. Unfortunately, susceptibility of most known MOFs to hydrolysis [24, 25] considerably restricts their potential applicability in the presence of water.

In recent years, particular attention has been paid to biocompatible MOFs [26, 27], in which structural components are non-toxic metal ions and biomolecules such as amino acids [28], nitrogenous bases [29], oligosaccharides [30] or natural organic acids [31]. These materials are mainly in demand in biomedicine [32], where the relative stability of MOFs in aqueous solutions [33] and the absence of toxicity of both MOFs and the products of their decomposition [34] are important factors. The rejection of traditional synthetic linkers obtained from oil-refining products [35] in favor of biomolecules is a significant step towards decreasing the environmental pollution. Furthermore, broad structural diversity of biomolecules, which are rich in heteroatoms [36] and are often chiral, endows MOFs with unique properties [37–39].

Solvothermal synthesis is a popular method for the preparation of new MOFs [40] as high-quality single crystals needed for crystal structure determination [41] by X-ray diffraction. Biomolecules are readily soluble in green solvents such as water or ethanol [42]; the use of these solvents for the synthesis facilitates post-synthetic treatment of MOFs, since there is no need to remove toxic polar organic solvents (DMF, DMA), which are traditionally used in the solvothermal synthesis of MOFs [43].

In this study, the "green" protocol was used to prepare a new metal-organic framework $[Mg(Mal)(H_2O)](H_2O)$ (H_2Mal is malic acid) (**I**) consisting entirely of biocompatible components: magnesium ions (mineral needed for normal functioning of the muscle and nervous systems, blood pressure regulation, and support of the immune system) and malate anions (important metabolic intermediate in living organisms). This MOF was isolated in a pure state and characterized by elemental analysis and X-ray diffraction.

EXPERIMENTAL

All operations were performed in air using commercially available solvents and reagents. Analysis for carbon and hydrogen was carried out on a CarloErba microanalyzer, model 1106.

Synthesis of $[Mg(Mal)(H_2O)](H_2O)$ (I). A mixture of DL-malic acid (0.0268 g, 0.2 mmol), L-cysteine (0.0242 g, 0.2 mmol), and magnesium acetate tetrahydrate (0.0858 g, 0.4 mmol) was dissolved in a mixture

Table 1. Key crystallographic data and structure refinement details for **I**

Parameter	Value
Molecular formula	$C_4H_{10}O_8Mg$
M	210.43
System	Orthorhombic
Space group	*Pbca*
Z	8
a, Å	13.9730(2)
b, Å	8.1922(2)
c, Å	14.2476(3)
V, Å^3	1630.92(6)
ρ(calcd.), g cm^{-3}	1.714
μ, cm^{-1}	2.34
F(000)	880
$2\theta_{max}$, deg	61
Number of measured reflections	22655
Number of unique reflections	2508
Number of reflections with $I > 2\sigma(I)$	2357
Number of refined parameters	118
R_1 (for reflections with $I > 2\sigma(I)$)	0.0262
wR_2 (for all reflections)	0.0746
GOOF	1.095
Residual electron density (min/max), e Å^{-3}	−0.315/0.465

of ethanol and distilled water (1 : 1 v/v, 1 mL), and the solution was heated in a sealed glass tube up to 120°C at a rate of 200°C/h, kept at this temperature for 24 h, and then slowly cooled down to room temperature for 5 h. The colorless crystals thus formed were separated from the mother liquor, washed with distilled water and ethanol, and dried in air. The product yield was 0.026 g (62%).

For $C_4H_{10}O_8Mg$		
Anal. calcd., %	C, 22.83	H, 4.79
Found, %	C, 22.76	H, 4.88

Single crystal X-ray diffraction study of **I** was carried out for the sample taken out from the sealed tube immediately after it was cooled down to room temperature, on a Bruker Quest D8 diffractometer (MoK_α radiation, graphite monochromator, ω-scan mode) at a temperature of 100 K. The structure was solved using the ShelXT software [44] and refined by the full-matrix least-squares method on F^2_{hkl} with the Olex2 software [45] in the anisotropic approximation for non-hydrogen atoms. The hydrogen atoms of the OH groups and water molecules were located from difference Fourier maps, while positions of other hydrogen atoms were calculated geometrically, and all of them were refined in the isotropic approximation. Selected crystallographic data and structure refinement details are summarized in Table 1.

The full set of X-ray diffraction data for **I** was deposited with the Cambridge Crystallographic Data Centre (CCDC no. 2172323; http://www.ccdc.cam.ac.uk/).

RESULTS AND DISCUSSION

When magnesium(II) acetate with a mixture of malic acid and cysteine were kept in an ethanol–water mixture at 120°C for 24 h and then the mixture was slowly cooled down to room temperature, transparent single crystals were formed. According to X-ray diffraction data, this was a new MOF described as $[Mg(Mal)(H_2O)](H_2O)$ (**I**). Magnesium(II) ions serve as the metal nodes, while the organic linkers are represented only by doubly deprotonated malate

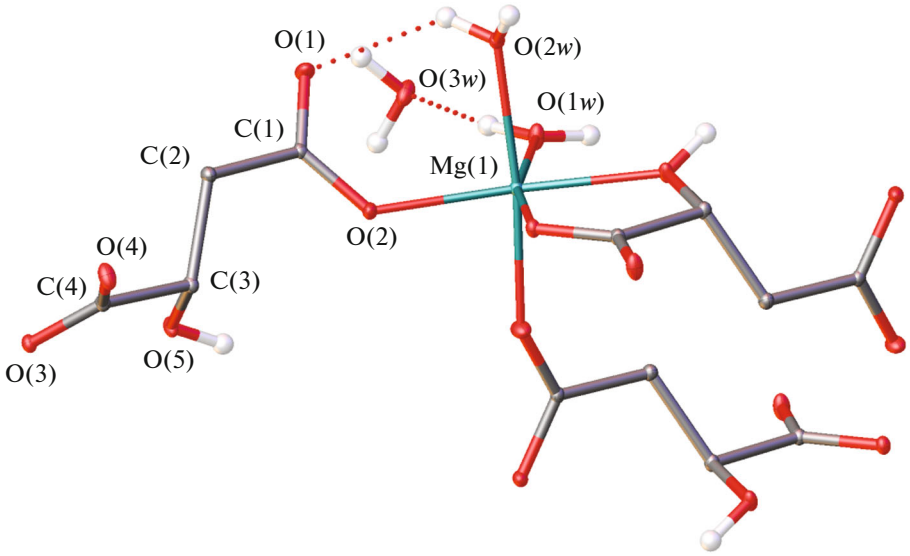

Fig. 1. Fragment of the crystal packing of MOF **I**, illustrating the coordination environment of the magnesium(II) ion. Here and below, the CH and CH_2 hydrogen atoms are not shown, the other atoms are shown as thermal ellipsoids (p = 30%); atom numbering is given only for symmetrically independent atoms. The dashed lines show the hydrogen bonds.

anions. Each magnesium(II) ion is connected to three such dianions and two water molecules (Fig. 1). The third water molecule is solvating. The coordination polyhedron is an octahedron (Table 2) in which the equatorial positions are occupied by the oxygen atoms of water molecules (Mg–O, 2.0269(7) Å), one hydroxyl group (Mg–O 2.0954(7) Å), and two carboxyl groups (Mg–O, 2.0455(7) and 2.0734(7) Å) of two dianions, while the axial positions are occupied by the carboxyl oxygen atoms of the third dianion (Mg–O, 2.0163(8) Å) and the second water molecule (Mg–O, 2.1252(7) Å). This is also confirmed by the "shape measures" S(OC-6) [46], which describe the deviation of the polyhedron shape from an ideal octahedron (Table 2). The lower this value, the better the polyhedron shape is described by the chosen polyhedron. In our MOF **I**, the S(OC-6) value estimated from X-ray diffraction data using the Shape 2.1 program [46] is 1.011, which implies that the shape of magnesium(II) polyhedron is close to an ideal octahedron. For comparison, a similar value relative to another six-vertex polyhedron, ideal trigonal prism (TP-6), is much higher (12.128).

The Mg–O coordination bonds with malate dianions give rise to a two-dimensional coordination layer along the *bc* crystallographic plane (Fig. 2), additionally stabilized by hydrogen bonds between the dianion hydroxyl group and the coordinated water molecule (O...O, 2.7164(10) Å; OHO, 170.27(5)°) and a bifurcated hydrogen bond formed by the same molecule

Table 2. Selected geometric parameters of **I**

Bond	d, Å
$M–O_{COO}$	2.0163(8)–2.0734(7)
$M–O_{OH}$	2.0954(7)
$M–O_{H_2O}$	2.0269(7) and 2.1252(7)
Polyhedron shape	Deviation from the ideal shape
S(OC-6)	1.011
S(TP-6)	12.128

* O_{COO}, O_{OH}, and O_{H_2O} are the oxygen atoms of the carboxylate and hydroxyl groups of the malate dianion and water molecules, S(OC-6) and S(TP-6) are deviations of the metal ion polyhedron shape from the ideal octahedron (OC-6) and ideal trigonal prism (TP-6).

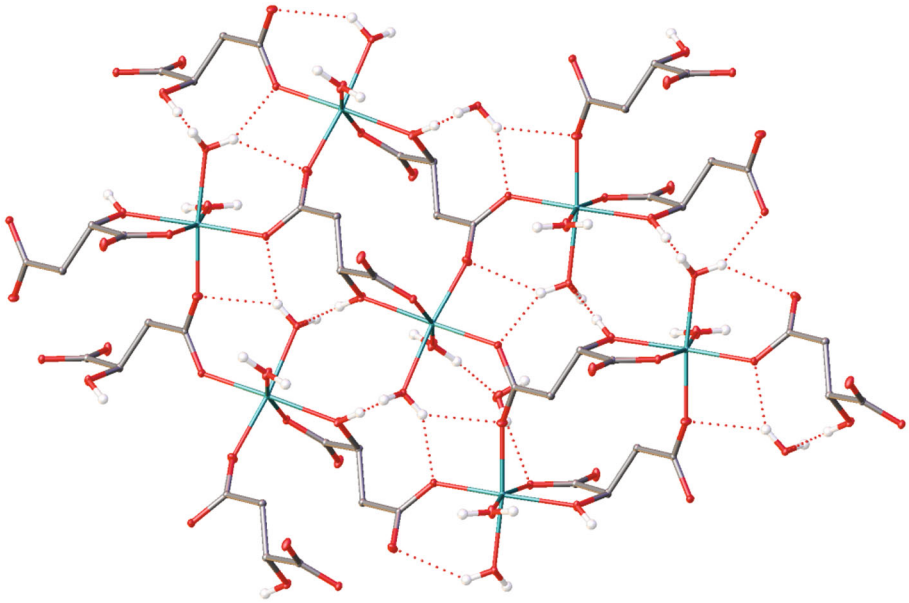

Fig. 2. Fragment of the crystal packing of MOF **I**, illustrating the formation of the two-dimensional coordination layer.

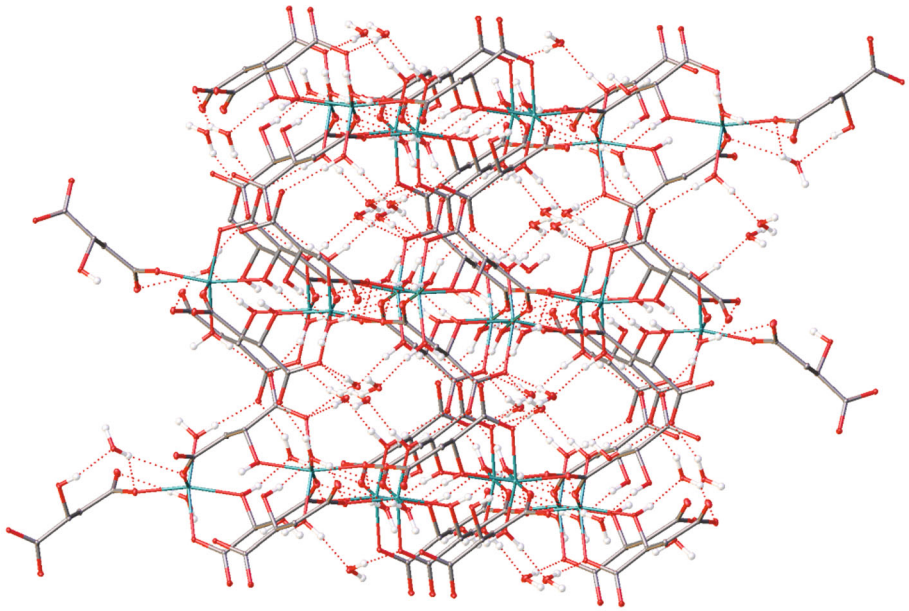

Fig. 3. Fragment of the crystal packing of MOF **I**, illustrating the arrangement of the two-dimensional coordination layers in the crystal.

with the carboxyl groups of two dianions (O...O, 2.8767(10) and 2.9428(9) Å; OHO, 137.61(5)° and 144.66(5)°). A similar function is performed by the hydrogen bonds of the solvating water molecule with the second coordinated water molecule (O...O, 2.6395(10) Å; OHO, 172.51(5)°) and with a carboxyl group of the dianion (O...O, 2.8555(10) Å; OHO, 176.59(5)°) in the two-dimensional coordination layer. The other hydrogen bonds that are formed by each of three water molecules with the carboxyl groups of the dianion (O...O, 2.6606(9)–2.8927(10) Å; OHO, 160.9(1)°–174.8(1)°) connect these 2D layers into a dense three-dimensional framework (Fig. 3) with a maximum pore volume of less than 4.19 $Å^3$, as follows from evaluation of the X-ray diffraction data by the OLEX2 software [45].

Note that 2D MOF **I** is the second example of magnesium MOF based on malic acid after previously described 3D MOF $[Mg(Mal)(H_2O)_2](H_2O)$ [47], which was also synthesized by the solvothermal

method, but without cysteine in the reaction medium. In our study, cysteine was used in order to prepare heteroligand MOF that could be incorporated into biocompatible composite films.

The formation of MOF **I**, instead of the known MOF $[Mg(Mal)(H_2O)_2](H_2O)$ is apparently caused by the template effect of cysteine or sulfur-containing products of its thermal decomposition in the course of solvothermal synthesis (120°C, 24 h). Indeed, when this reaction was carried out without cysteine, no MOF **I** or other crystalline products were obtained.

Thus, we synthesized the previously unknown MOF $[Mg(Mal)(H_2O)](H_2O)$ by solvothermal reaction using green solvents (water and ethanol) and biocompatible reagents (magnesium acetate, malic acid, and cysteine). This compound is the second example of magnesium MOF based on malic acid. An attempt to obtain this MOF in the absence of cysteine revealed the template effect of this amino acid or products of its decomposition under the chosen drastic conditions. The formation of $[Mg(Mal)(H_2O)](H_2O)$ instead of the target heteroligand MOF with malonate and cysteine linkers implies that milder conditions of the synthesis should be used, while maintaining its green character, which is required for developing new biocompatible MOFs for biomedical applications.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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