The Properties, Synthesis, and Medical Applications of Nanoscale Metal Organic Frameworks

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Abstract. Metal-organic frameworks (MOFs) are self-assembled nanomaterials formed from coordination bonds between metal cations and organic ligands. MOF-74 are a unique group of MOFs with large surface area and high loading capacity. Nanoscale MOF-74 have a great potential for drug loading and MRI scanning. This review summarizes the synthetic methods, properties, and medical applications of MOF-74.

1. Introduction
Metal-organic frameworks (MOFs) are a group of porous crystalline materials with a periodic framework structure formed by the organic-inorganic coordination of transition metal ions or ion clusters with organic ligands.

MOF-74, also called CPO-27, consists of the central metal cation (M) and the organic ligand DHTP$_4^-$ (2,5-dihydroxyterephthalate). As shown in its structure, DHTP$_4^-$ has high binding ability, and a central metal ion is bonded to five O. In this way, metal cations and ligands form straight helical secondary building units (SBUs). The high stability leads to a wide range of applications, including gas adsorption, catalyst, hydrogen preservation, drug loading, and MRI scanning.

![Figure 1. The structure of DHTP$_4^-$.](image-url)
2. Synthesis

2.1. General synthesis
A typical synthesis of MOF-74 involves a two-step solvothermal method, which refers to the coordination between organic ligands and metal ions in a solvent at a suitable temperature and autogenous pressure, and involves the reaction of an organic solvent and reaction material under high temperature pressure hydrothermal to generate crystals. In 2005, Rosi et al. [2] first reported the synthesis of MOF-74 along with 13 other types of MOFs. They prepared a solid mixture of 0.096 mmol 2,5-dihydroxyterephthalic acid with 0.203 mmol Zn(NO$_3$)$_2$·4H$_2$O. The solid mixture was dissolved in 2.0 ml DMF, 0.1 ml 2-propanol, and 0.1 ml water, and then placed in a Pyrex tube, frozen, evacuated, heated to 105 °C for 20 h and cooled to room temperature. The experiment produced yellow needle crystals of MOF-74. Tranchemontagne et al. [3] developed a room-temperature synthetic method of MOF-74 by mixing 1.20 mmol 2,5-dihydroxyterephthalic acid with 3.12 mmol Zn(OAc)$_2$·2H$_2$O dissolved in 20 ml DMF. The diacid solution was added to the stirring zinc salt solution over 10 min, then the mixture was stirred for another 18 h. At this point the mixture showed pure MOF-74 in PXRD analysis compared with simulated pattern.

2.2. Synthesis of nanoscale MOF-74
A high bioactivity requires nanoscale MOFs (nMOFs) to be synthesized. Besides traditional solvothermal method, the small size of MOF-74 can be achieved by several new synthetic methods. The most common synthetic method of nanoscale MOFs is the traditional two-step solvothermal method. It refers to The formation of nanoscale crystals can be triggered by controlling temperature, concentration, reaction time, pH value, stoichiometric relationship between metal and ligands, and adding conditioning assistants. Hu et al. reported that by lowering reaction temperature to 45–60 °C and reducing reaction time to 69 h, the products will have smaller and denser pores. The size and distribution of pores can be controlled by regulating these parameters.[4] Deprotonating assistants, e.g. triethylamine (TEA) and polyvinylpyrrolidone (PVP), influences the morphology and size of MOF crystals. [4][5]

Direct precipitation refers to the method of mixing the reactants under root temperature. nMOFs that are able to be produced with this method are MOF-5, MOF-74, MOF-177, and HKUST-1.

Microwave-assisted synthesis relies on the interaction between microwave and charges to generate heat. In aqueous solutions, the interaction between electromagnetic waves and polar molecules may result in extreme temperature, thus the selection of microwave frequency and solvents is crucial. The advantages of microwave-assisted synthesis is: 1) High temperature and pressure accelerates the
nucleation and crystal growth of nMOFs, therefore shortening reaction time. 2) The products have high purity. In 2008, Bae et al. used both conventional method and microwave-assisted method to synthesize $\text{Zn}_2(\text{NDC})_2(\text{DPNI})$, and tested their ability of gas adsorption and selectivity. According to their research, microwave-assisted method resulted in slightly lower capacity yet much higher selectivity of $\text{CO}_2$ over $\text{CH}_4$, which is among the highest selectivities reported for $\text{CO}_2$ and $\text{CH}_4$.[6] Wu et al. reported that compared with traditional methods, microwave-assisted synthesis can reduce the reaction time from 1 d to as short as 100 min. [7]

Similar to microwave-assisted synthesis, sonochemical synthesis also promotes more rapid reaction and more uniform morphology. Yang et al. compared the capability of separating $\text{N}_2$ and $\text{CO}_2$ of nMOFs synthesized by both conventional route and sonochemical route. By adding TEA as a deprotonating agent, crystal size is reduced. The nMOFs showed a high adsorption capacity for both $\text{CO}_2$ and water (350 mg/g and 593 ml/g respectively), and were able to separate $\text{CO}_2$ from $\text{N}_2$ at a capacity of about 179 mg/g. Their stability and reversible adsorption-desorption process are confirmed through cyclic $\text{CO}_2$ adsorption-desorption experiments.[1]

3. Medical Application

Since its synthesis, the medical application of nMOFs have been widely investigated because of its following properties: 1) nMOFs are highly biocompatible and degradable, and can be easily decomposed in and excreted from the human body. 2) High porosity leads to high adsorption capacity. 3) The structure of nMOFs is highly customizable; the application of magnetic central metal ions ($\text{Fe}_{3}^{3+}$, $\text{Gd}_{3}^{3+}$) leads to its capability as contrast agent in MRI scanning.

3.1. Applications in drug loading

MOFs as drug loading agents keep drug concentration at a certain level for a long time period, promoting safety and efficiency. Drugs form multiple attraction forces with the framework, including ionic bonding, coordinate bonding, $\pi-\pi$ interaction, van der Waal’s forces, and hydrogen bonding. Among these forces, ionic bonding—the electrostatic attraction between cations and anions—attracts the most attention because drug release in human bodies mainly involves the interaction between ions. The capability of MOF-74 as drug loading agents is mainly a result of its high porosity: the dehydrated samples of MOF-74 contain hexagonal 1D channels with a diameter of around 1.10 nm along the c axis.[8]
3.1.1. Drug loading in Fe-MOF-74. Hu et al. synthesized and investigated the drug loading capacity of Fe (III)-based MOF-74 using ibuprofen. The nMOFs were synthesized by the oxidation of FeCl$_2$, and show matching XRD pattern curve with the simulated data. The study revealed a drug loading capacity of approximately 0.21 g drug per gram of dried materials. The group also evaluated the cytotoxicity of Fe-MOF-74 using PC12 cells. The cells’ viability maintains at about 100% after incubating in MOFs probes with a concentration of 5 μg/ml, and there is no difference in either cell density or cell morphology between MOF-treated group and control group. [9]
3.1.2. Drug loading in Mg-MOF-74. Hu et al. investigated the drug loading capacity and biocompatibility of Mg-MOF-74. The MOFs were obtained using traditional two-step solvothermal method and coated with polydopamine (PDA) to improve its biocompatibility. An anti-cancer drug, α-cyano-4-hydroxycinnamate (CHC) was loaded, giving an adsorption capacity of 625 mg/g of CHC/dehydrated Mg-MOF-74, or 62.5wt%. The cytotoxicity of MOFs were evaluated by Cell Counting Kit-8 (CCK-8) Assay on HeLa cells. The cell viability of Mg-MOF-74@PDA after an 6 h incubation remains 60% at a high concentration of 50 μg/ml. [10]
Figure 6. Cellular viability of HeLa cells with Mg-MOF-74 (black) and Mg-MOF-74@PDA (red).[10]

3.2. Applications in MRI scanning
Magnetic resonance imaging (MRI) is a non-invasive, non-ionized imaging technique that produces a high-resolution image of target tissues. The relaxivity of a contrast agent is measured in two dimensions: the longitudinal relaxivity value ($R_1$) or the transverse relaxivity value ($R_2$). To produce a larger contrast in tissues, contrast agents are often administered in high doses.

In 2006, Rieter et al. first proposed the potential of Gd-nMOFs as contrast agents. These MOFs contain a large number of Gd$^{3+}$ centers, marking a high per-particle relaxivity. By suspending MOF samples in water containing 0.1% xantham gum, the team obtained an $R_1$ value of 35.8 s$^{-1}$ per mmol dm$^3$ of Gd$^{3+}$, and an $R_2$ value of 55.6 s$^{-1}$ per mmol dm$^3$ of Gd$^{3+}$. The $R_1$ value was unprecedented.[11] However, the framework hydrolyses, releasing highly toxic Gd$^{3+}$. Rieter et al. later developed a method to encapsule the MOFs in amorphous silica. The surface modification improved water dispersibility and biocompatibility of Gd-nMOFs.[12]

Figure 7. $R_1$ and $R_2$ relaxivity data of synthesized nMOF of 100 nm in length and 40 nm in diameter.[11]
Compared with other MOFs, the application of MOF-74 in MRI scanning is less reported. Hu et al. synthesized a bimetallic framework—Zn$_{0.7}$Mn$_{0.3}$-MOF-74—and investigated its relaxivity. The $r_1$ value and $r_2$ value of the framework is 6.5 s$^{-1}$ per mmol dm$^3$ and 28.7 s$^{-1}$ per mmol dm$^3$ respectively, which is greater than commercially used Gd-based contrast agent. The team improved the biocompatibility of nMOFs using chitosan (CS) coating. The cell viability after 6 h incubation was 50% at a concentration of 80 μg/ml. [4]

![Figure 8. $T_1$ and $T_2$ relaxivity plot of aqueous suspension of nanoparticles. [4]](image)

![Figure 9. Cellular viabilities of HeLa cells with Zn$_{0.7}$Mn$_{0.3}$-MOF-74 (black) and Zn$_{0.7}$Mn$_{0.3}$-MOF-74@CS (red)](image)

4. Conclusion
In conclusion, we review the properties, synthetic methods, and latest medical applications of nanoscale MOF-74 materials.

The attributes of MOF-74 contribute to its extraordinary adsorption capacity among similar porous materials. In particular, these attributes include high specific surface area, high porosity, highly stable structure, and high capacity for adjustments.

Nanoscale MOF-74 can be synthesized through many approaches; one of them being the traditional solvothermal method, which is rather time-consuming but highly variable. The reaction conditions can
be altered actively to change size and porosity. In recent years, alternative synthetic methods emerged, including direct precipitation, microwave-assisted, and sonochemical synthesis. Compared with traditional methods, microwave-assisted synthesis result in shorter reaction time and higher product capacity; however, the frequency and solvents should be carefully selected to prevent extreme heat. Alternative synthetic methods are highly prospective, considering their short reaction time and reduced energy consumption.

The application of MOFs include gas storage, catalysis, drug loading, and MRI scanning. Previous studies on the drug loading capacity showed their high biocompatibility and capacity. Studies on MRI scanning showed their potential as contrast agents. However, reports on the medical application of MOF-74 is relatively limited; more in-depth research is necessary for further industrial application of MOF-74.

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