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OPTIMIZATION OF METAL ORGANIC FRAMEWORK (MOF) SYNTHESIS FOR USE IN DRUG DELIVERY

Meyer Elazar, Ph.D
214 Haalon St., Matta, Israel
Correspondence e-mail: elime11g@gmail.com

Abstract. Synthesis optimization of the metal organic framework (MOF) UiO-66 has been carried out using 2-aminoterephthalic acid functional group, a zirconium salt and a modulator grafted into the UiO-66 framework. Reaction parameters such as the effects of temperature, reaction time, the nature of the zirconium salt and the ligand, the molar ratio between the zirconium salt and the ligand, the quantity of the modulator, the solvent and the effect of added water have been investigated. The synthesized MOFs have demonstrated excellent chemical and thermal stability, which ensured them to be used as carriers for drug delivery.

Keywords: Synthesis optimization, metal organic framework (MOF), functional group, zirconium salt, modulator, chemical and thermal stability, drug delivery.

Introduction

Molecular metal complexes have been used as catalysts in a variety of different applications such as for gas storage, chemical catalysis, molecular sensing and as carriers for drug delivery. Since the early reports on metal organic frameworks[1], there has been a growing interest in applying these materials in several chemical applications. However, one of the major problems of applying MOFs in industrial or commercial applications is the instability of many MOFs in aqueous environment or in media with high humidity as well as the poor structural stability of several MOFs that cannot not withstand reaction conditions requiring certain organic solvents, high temperatures or reagents having basicity or acidity properties.

MOFs comprised of organic ligands and metal clusters via coordinative bonds can be highly porous and crystalline materials[2]. There has been a remarkable progress over the last decades in the design of MOFs with variety of properties such as high porosity, surface functionalization and stability that make them suitable to be used as carriers for drug delivery.

UiO-66 zirconium MOF was first reported by Lillerud et al in 2008[3] having unique properties such as large surface area, tunable functional groups and an atomic-level control over pore structure, which are among the properties that make these materials suitable candidates for a variety of applications. Extensive research over the last two decades has revealed the potential of MOFs in, e.g., drug delivery, biomedicine, heterogeneous catalysis and hydrogen storage applications.

Lillerud et al have studied the chemical and physicochemical behavior of the UiO-66 MOF family obtained from different 1,4-benzenedicarboxylic acid linker ligands, demonstrating that this class of MOFs retains high thermal and chemical stabilities while functional groups are present at the linker units[4]. Lilerud et al have also investigated the link between synthesis parameters and the physicochemical properties of the product to afford UiO-66 having high thermal stability[5].

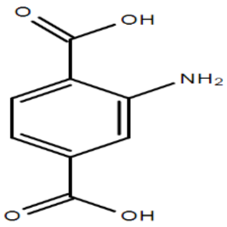
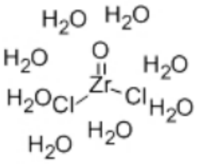
Materials and methods

There are still open questions with regard to the optimal conditions of carrying out the synthesis of UiO-66 MOF with regard to stability of the obtained MOF as a function of the reaction conditions such as the optimal molar ratio between the reactants, quantity of modulator, reaction temperature, reaction time and yield, the nature and optimal volume of the solvent, and testing the synthesized MOFs as carriers for conducting drug release experiments, as described, e.g., in Reference 6 of the present article.

The synthesis of UiO-66 MOF can be carried out by reacting a zirconium salt selected from, e.g., zirconium oxychloride octahydrate ($ZrOCl{\cdot}8H_2O$), zirconium chloride ($ZrCl_4$), zirconium bromide ($ZrBr_4$), zirconium iodide (ZrI_4), zirconium fluoride (ZrF_4), zirconium nitrate ($Zr(NO_2)_4$) and zirconium sulfate ($Zr(SO_4)_4$) with a linker selected from, e.g., 2-aminoterephthalic acid, 2-nitroterephthalic acid, 2-chloroterephthalic acid and 2-bromoterephthalic acid in a high boiling point solvent such as dimethylformamide (DMF) or γ-butyrolactone in the presence of a modulator selected from, e.g., acetic acid, formic acid, benzoic acid and trifluoroacetic acid (TFA).

Table 1 below depicts the structure of 2-aminoterephthalic acid and zirconium oxychloride octahydrate

Table 1

Compound	Formula
2-aminoterephthalic acid	
zirconium oxychloride octahydrate	

Results and Discussion

Preparation of UiO-66 MOF

The preparation of UiO-66 MOF was carried out by dissolving 21 mg of zirconium oxychloride ($ZrOCl_2{\cdot}8H_2O$) (0.065 mmole) in 3 ml of DMF (boiling point 153^{o}C) followed by adding 47 mg of 2-aminoterephthalic acid, (0.26 mmole, 4 fold excess) in 1 ml of DMF at room temperature and 2 ml of glacial acetic acid in a 20 ml glass vial. The vial containing the mixture was closed with a stopper and placed in an oven at 90^{o}C for 24 hours under static conditions. After 24 hours, the vial was left to cool to room temperature and the mixture was transferred into a plastic tube, vortexed and centrifuged. The resulting solid was treated three times each with 1 ml of DMF by vortexing the mixture followed by spinning down the solid by a centrifuge and repeating the same procedure with a mixture of DMF:water:ethanolamine 20:1:1 and with water. The obtained wet solid was lyophilized overnight to obtain the dry MOF as a while solid. The solid was weighed and samples were withdrawn for X-ray powder diffraction (XRPD) and scanning electron microscope (SEM) analysis and stored at room temperature.

The molecular formula of UiO-66 is $C_{48}H_{34}N_6O_{32}Zr_6$ and its molecular weight is 1754.1. The following Table 2 below includes data on the reactants and products of the reaction.

Table 2

Compound	Molecular formula	Molecular weight
Zirconium oxychloride octahydrate	$ZrOCl_2{\cdot}8H_2O$	322.25
2-aminoterephthalic acid	$C_8H_7NO_4$	181.15
MOF UiO66	$C_{48}H_{34}N_6O_{32}Zr_6$	1754.1

From the point of view of the material preservation act, the following equation may be written as: $6ZrOCl_2{\cdot}8H_2O + 6C_8H_7NO_4$ ------------> $C_{48}H_{34}N_6O_{32}Zr_6 + 12HCl + 6H_2O$, so the calculation of the reaction yield may be based upon the data included in Table 2, the product weight and the molar data included in the preparation procedure of UiO-66 MOF.

Using the prepared MOF as carrier for drug delivery

8 mg of UiO-66 MOF were dispersed in 1 ml of water followed by addition of 120 µl of SulfoCy5 solution and additional 1 ml of water. The mixture was vortexed and shaken overnight. The dispersion mixture was centrifuged and a solution of 400 nmol of DNA aptamer 1, dissolved in water, was added and additional 1 ml of water. The mixture was vortexed and shaken overnight. Then, the mixture was vortexed and centrifuged and the liquid was taken out. The MOF loaded particles were washed three times with water in order to remove unbound nucleic acids, dried by lyophilization and kept at +4^{o}C. Same procedure was repeated in parallel as control, without addition of the aptamer. 2 mg each of MOF loaded particles were shaken for 12 hours with 1 ml of 15 mM solution of the drug dissolved in water, prepared by dissolving 40.6 mg of the drug in 10 ml of water; 1 ml of 0.193 mM solution of rhodamine 6G in methanol; 1 ml of 0.12 mM solution of fluorescein in methanol and unloaded MOF (control), in total 2X4=8 mg. The mixtures were vortexed and shaken for 12 hours. Then, the vials were

vortexed, centrifuged and washed several times with water to remove the unloaded drug. Samples were dried by lyophilization and kept at +4°C for the next stage.

The DNA functionalized with aptamer 1 MOFs, were transferred into a phosphate buffer solution and hybridized with the complementary DNA aptamer 2, the pH-responsive tetrahedra, either a tetrahedra gated or the duplex-gated MOFs, which resulted in the locked state of the MOFs encapsulating the respective drugs/dyes.

The pH responsive loaded MOFs were washed several times with buffer solution. At appropriate time intervals samples of the mixtures were centrifuged to precipitate the MOF and the fluorescence of the released dye loads in the supernatant solution were measured using a Cary Eclipse Varian spectrophotometer. Centricon 3000 was used to obtain the filtrate containing the drug by inserting a sample into the reservoir of the filtering device to enable filtration by centrifugation, thus precipitating the DNA and obtaining the drug in an aqueous solution in the filtrate vial ready for spectral analysis.

Preliminary results

A. The effect of the reaction temperature

B. The effect of the reaction time

C. The nature of the zirconium salt and the ligand

D. The molar ratio between the zirconium salt and the ligand

E. The quantity of the modulator

F. The solvent effect

G. The effect of added water

H. Stability of the obtained MOF

A. The effect of the reaction temperate

The synthesis of UiO-66 MOF, using 1:4 molar ratio of zirconium salt to the ligand for 24 hours and addition of 2 ml of acetic acid as modulator was carried out at different temperatures. Carrying out the reaction at 75°C yields a product with poor X-ray powder diffraction (XRPD) spectrum. The obtained MOFs synthesized at different temperatures yield stable products in which the XRPD patterns are not changed after 6 months of storage at room temperature as depicted in Table 3 below.

Table 3

Reaction temperature	Yield, %	Stability over 6 months at room temperature
75^{o}C	14%	Not stable
90^{o}C	16%	Stable
105^{o}C	23%	Stable
120^{o}C	23%	Stable

B. The effect of the reaction time

The synthesis of UiO-66 MOF, using 1:4 molar ratio of zirconium salt to the ligand at a temperature of 90^{o}C and 2 ml of acetic acid as modulator was carried out at different reaction times. The obtained MOFs synthesized at different reaction times yield stable products in which the XRPD patterns are not changed after 6 months of storage at room temperature. The results are depicted in Table 4 below.

Table 4

Reaction time, hours	Yield, %	Stability over 6 months at room temperature
12	20	Stable
24	16	Stable
48	21	Stable
72	27	Stable
96	23	Stable

C. The nature of the zirconium salt and the ligand

Lillerud et al. and others have used zirconium chloride as the chosen salt for the reaction albeit, theoretically, other salts may be used such as zirconium oxychloride zirconium bromide, zirconium iodide and zirconium fluoride. The experiment described herein employed zirconium oxychloride. Several ligands have been proposed such as 2-aminoterephthalic acid, 2-nitroterephthalic acid and 2-bromoterephthalic acid.

D. The effect of the molar ratio between the zirconium salt and the ligand

The standard synthesis of UiO-66 MOF for 24 hours at 90^{o}C and using 2 ml of acetic acid as modulator was carried out using different molar ratios of zirconium salt to the ligand. The results are depicted in Table 5 below.

Table 5

Molar ratio	Yield, %
1:1	16
1:2	16
1:4	16
1:6	21

E. The quantity of the modulator

Modulators may be used to slow hydrolysis of the zirconium compound or the crystallization process and to allow for crystal nucleation and a controlled growth. These modulators may be a mono-carboxylic acid connected to a carbon chain of the formula R-COOH, for example if R equals methyl the modulator is CH_3COOH. The synthesis of UiO-66 MOF, using 1:4 molar ratio of zirconium salt to the ligand at 90°C for 24 hours was carried out using different quantities of acetic acid glacial used as modulator. The quantity of acetic acid used as modulator is per 21 mg of $ZrOCl_2{\cdot}8H2O$ (0.065 mmole) and 47 mg of 2-aminoterephthalic acid, (0.26 mmole, 4 fold excess). The results are summarized in Table 6 below.

Table 6

Volume in ml of acetic acid as modulator per 0.065 mmol of $ZrOCl_2{\cdot}$ 8H2O	Yield, %
1	Very low
2	16
2.5	27
3	25
4	17

It may be understood from the above mentioned results that without addition of modulator, the yield of the reaction may be very low and while adding excess modulator, the yield may be decreased and reaction may be inhibited.

F. The solvent effect

Traditionally DMF is used as solvent. However, carrying out the reaction in γ-butyrolactone yields a good product. Table 7 below summaries the results obtained when carrying out the reaction in different solvents.

Table 7

Solvent	Boiling point, deg. C	Yield, %	XRPD pattern
γ-butyrolactone	204°C	20	Goo
Dimethyl sulfoxide (DMSO)	189	No reaction	
Ethylene glycol	197	No reaction	
Dimethylacetamide (DMA)	165	Not yet tested	
N-methyl-pyrrolidone (NMP)	202	Not yet tested	

G. The effect of added water

The synthesis of UiO-66 MOF, using 1:4 molar ratio of zirconium salt to the ligand for 24 hours and 2 ml of acetic acid as modulator was carried out at a temperature of 90°C with addition of 200µl of water. The obtained MOF demonstrated good XRD pattern after 6 months of storage. The yield was 20%.

H. Stability of the obtained MOF

The obtained MOFs as described herein show good stability over at least 6 months while being kept at room temperature as demonstrated in Figures 1 and 2 below depicting XRPD curve and SEM picture respectively both taken 6 months after the synthesis.

Figure 1

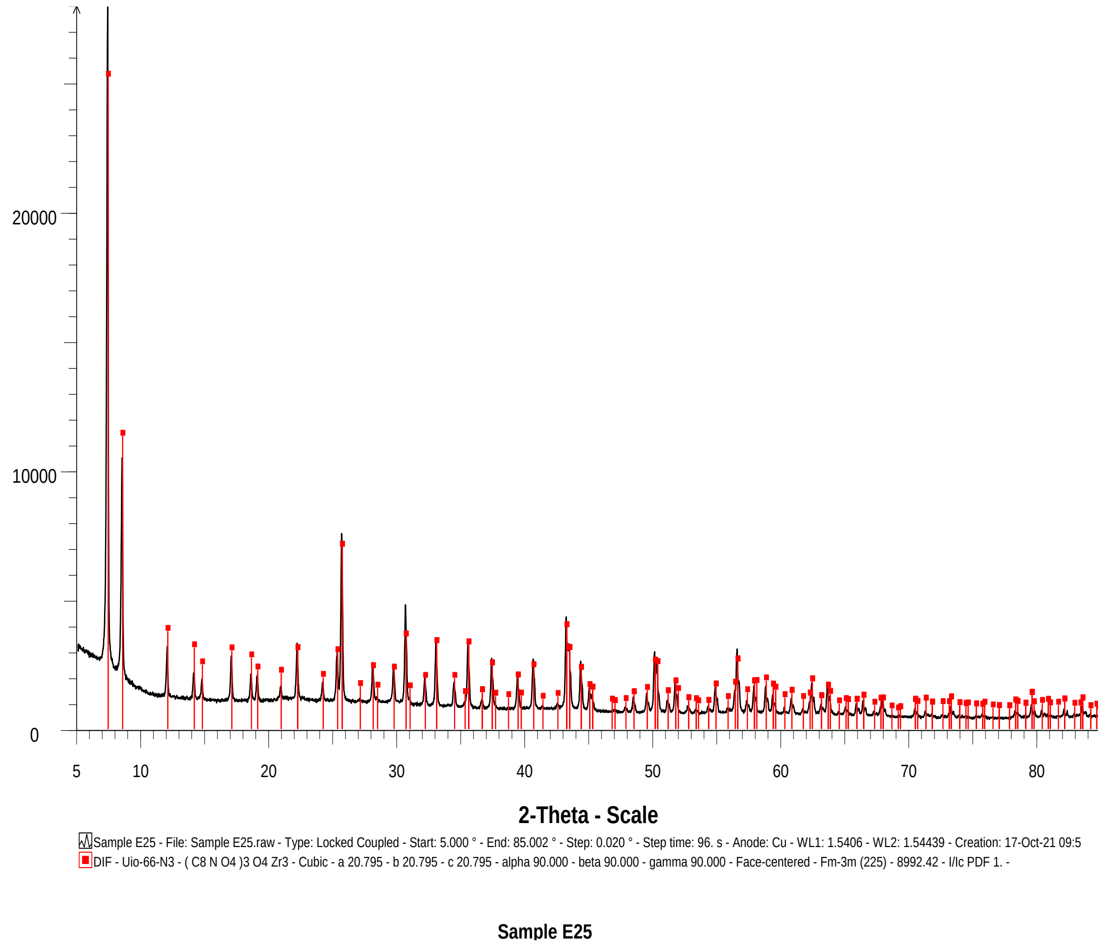
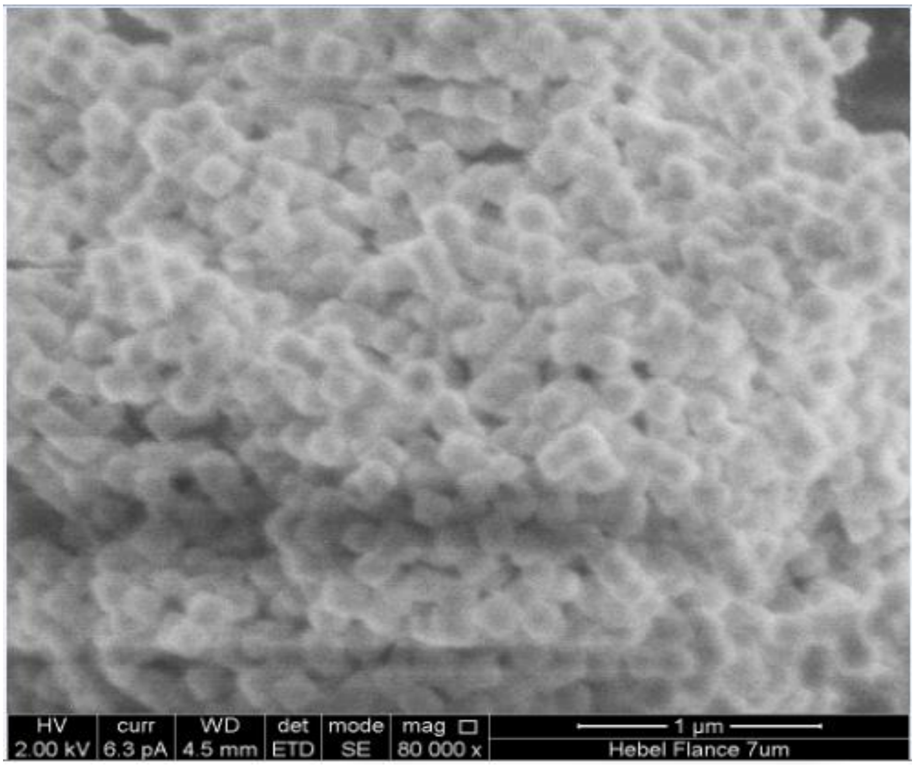


Figure 2



Conclusion

Optimal conditions were set for carrying out the synthesis of UiO-66 MOF with regard to the reaction time, choice of ligand, optimal molar ratio between the reactants, quantity of modulator, nature and optimal volume of the solvent and reaction temperature and yield. The UiO-88 MOF optimization enables a product showing good stability over at least 6 months while being kept at room temperature.

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