

Crystallization of nanostructured curcumin MOF in supercritical CO₂

Núria Portolés-Gil,^{a*} Núria Aliaga,^{a,b}
Jose Antonio Ayllón,^c Ana M. López-Periago,^a Concepcion Domingo.^a

^a Instituto de Ciencia de Materiales de Barcelona (ICMAB-CSIC), Campus UAB s/n, Bellaterra
08193, Spain

^b ICREA, Institució Catalana de Recerca i Estudis Avançats, Passeig Lluís Companys 23, 08010
Barcelona, Spain

^c Departamento de Química Analítica, Universidad de Barcelona, Martí i Franques 1–11, 08028
Barcelona, Spain

*nportoles@icmab.es

ABSTRACT

To date, scCO₂ has generally been applied in the activation of metal-organic frameworks (MOFs) by emptying pore space [1]. In our research group, a new methodology for the preparation of MOFs in scCO₂ has been recently developed [2]. Taking into account that curcumin pigment can be efficiently extracted by scCO₂ with ethanol from the turmeric rhizome [3]; the possibility of preparing curcumin MOFs by reactive crystallization in this medium was examined. To favor the reaction, Zn(acac)₂, with a significant solubility in scCO₂, was used as the metal complex to be reacted with curcumin. A solid stable in air was crystallized in scCO₂, using a 1-5 v% ethanol, at 313-333 K, 15-20 Pa in different experimental runs lasting from 1 h to 72 h. The obtained solid was identified as a 3D structure with a stoichiometry 1:1 for Zn and curcumin. The obtained crystalline powder has a BET surface area measured by N₂ adsorption of *ca.* 300 m²g⁻¹, which is a considerably high value for as-synthesized products. This article also shows the control in the different morphologies of this 3D BioMOF as a function of the parameters used during the supercritical synthesis.

INTRODUCTION

Metal-organic frameworks (MOFs) are typically built from transition metals and highly symmetric petrochemical-derived organic molecules, as carboxylate acids and pyridine derivatives and imidazole.[4] The attained success in controlling the structure, functionally and porosity of these materials has led to the development of numerous potential applications for MOFs, most notably in gas adsorption, energy and medicine. Medical applications would require constructions made of biocompatible building blocks, which drive on the development of the topic of metal-biomolecule frameworks or bioMOFs.[5] These materials find applications as drug delivery systems, either by transferring an adsorbed active agent or directly by building them with the specie to be released.[6] At present, natural molecules such as amino acids, peptides, proteins, nucleobases, carbohydrates, cyclodextrins, porphines and some biological carboxylic acids have shown their abilities to bond metal ions and form extended bioMOFs.[7] Among the many possible natural products, symmetric molecules are preferred to build bioMOFs, since it has been demonstrated that the organic linker symmetry is a key parameter to prepare highly porous frameworks.[8]

This work focusses in the use of curcumin to synthesize a bioMOF. Curcumin is a polyphenolic pigment present in the turmeric root and it is interesting from a pharmaceutical point of view in the treatment of chronic illnesses including cancer, anti-inflammatory and neurological diseases.[9] Curcumin is unique in its structure for possessing two isomers, enol and β -diketone tautomeric forms.[10] It has three different metal-binding sites, exhibiting multiple possible coordination modes, a feature that increases potential structural diversity. On this basis, several complexes of metals with curcumin or curcuminoids have been described [11]; and also a highly porous 3D MOF with empirical formulae $[\text{Zn}_3(\text{curcumin})_2.7(\text{DMA})_3(\text{ethanol})]$ (DMA = N,N'-dimethylacetamide).[12] This MOF was solvothermally synthesized in a mixture of DMA and ethanol, and as a result the as-synthesized structure occludes large amounts of DMA solvent that is a substance of Very High Concern.

To increase the sustainability of the solvothermal processes used for MOFs preparation, the use of more environmentally friendly approaches, such as working in aqueous or alcoholic solutions, supercritical fluids or ionic liquids, and in solventless conditions, is desirable.[13] The use of scCO_2 in the field of MOFs has been mainly limited to the post-synthesis activation by cleansing entrapped undesired byproducts or solvents. [1] In a totally different investigation, we have demonstrated that 1D to 3D coordination polymers can be prepared in scCO_2 through reactive crystallization by the right choice of building blocks with some solubility in this fluid.[2] In this work, we extended the synthetic protocols in scCO_2 to the construction of a MOF exclusively from biologically friendly components, such as Zn(II) and bioactive curcumin. Ethanol (Class 3 solvent with low toxicity) was used as a co-solvent. A new structure of the curcumin-Zn(II) was obtained. Research is focused on tuning and controlling the crystal habit and size in the nanometric range.

MATERIALS AND METHODS

Materials and reagents

Zinc acetylacetonate hydrate ($\text{Zn}(\text{acac})_2$) and Curcumin, (1E,6E)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (Fig. 1), were purchased for Sigma Aldrich and used without further purification. Ethanol (EtOH) was purchased from Panreac. Compressed CO_2 (99.95 v%) was supplied by Carburos Metálicos S.A. (Spain).

Equipment and synthesis

MOFs preparation in scCO_2 was carried out in a high pressure vessel of 100 mL. In each experiment, the autoclave was charged with *ca.* 200 mg of reagents and 2 mL of EtOH. The solid reagents were added into a 10 mL Pyrex vial together with a small magnetic stir bar. The ethanol was added either into the vial mixed with the solid reagents or out at the bottom of the reactor physically separated from the solids. In all the cases, the vial was capped with filter paper. The autoclave was then filled with liquid CO_2 at 6 MPa, while stirring at 500 rpm. In a typical experiment, the system was pressurized at 20 MPa (Teledyne Isco 260D syringe pump) and then heated at either 313 or 333 K using resistances. The reactor was kept stirred only during the first 20 min, although in some experiments it was maintained until the end of the process. These working conditions were maintained for a period ranging from 1h to 72 h. Finally, the reactor was depressurized to atmospheric pressure and cooled to room temperature.

Characterization

Prepared samples were structurally characterized by routine XRD patterns recorded on a Siemens D-5000 diffractometer with Cu K α radiation, in the 2 θ range of 5-30°. Samples chemical composition was assessed by elemental analysis (EA) carried out using a Thermo (Carlo Erba) Flash 2000 analyzer. The BET surface area was determined by N₂ adsorption at 273 K using an ASAP 2000 Micromeritics Inc. Samples were first degassed at 393 K for 24 h. Morphological features were examined by scanning electron microscopy (SEM) with a Quanta Fei 200 microscope. The microscope is equipped with an Energy Dispersive X-ray (EDX) system for chemical analysis.

RESULTS

In this study Zn(acac)₂ was chosen as an organometallic complex due to the significant solubility in scCO₂. Curcumin as an organic linker owing that this natural product is extracted from turmeric rhizome by mixtures of scCO₂ and EtOH. MOF crystallization experiments were performed by adding EtOH as a co-solvent, since in its absence the target product was not obtained.

XRD characterization indicated that the solid was crystalline (Fig 1) and EDX microanalysis point out to a high concentration of Zn, together with two other light elements, C, and O. The elemental analysis of this sample (C_{exp} = 53.95 and H_{exp} = 4.41 Wt%) match a MOF composition of [Zn(curcumin)_x(H₂O)]_x = (1.5-2) (C_{cal} = 53.90 and H_{cal} = 4.74 Wt%). Both XRD and EA indicated that a new compound different from the described MOF in the literature [Zn₃(curcumin)₂7(DMA)3(ethanol)].[12] Besides this solid activated at 393K under vacuum give a BET surface area of 331 m²g⁻¹, most of them in the area of the micropore. This value was also different than the described MOF.

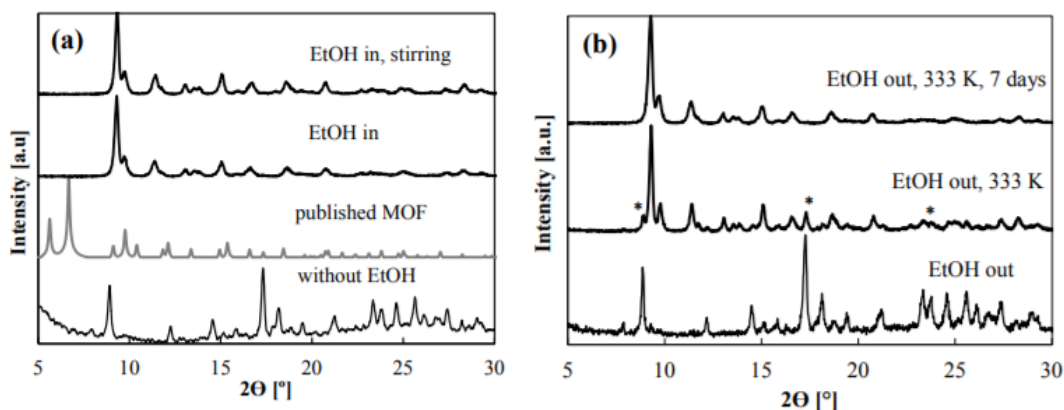


Figure 1. XRD of precipitated solids at different experimental conditions (a) without EtOH, with EtOH in contact with the solid reagents at 313 K, and published phase in ref. 12; and (b) with EtOH added out of the vial of the solid reagents at 313 and 333 K, (*) in the middle pattern indicates peaks of residual curcumin.

SEM micrographs showed different morphologies depending on the working conditions. For the experiments where the ethanol was in contact with the reagents and the agitation was kept only the first 20 minutes of reaction, microstructure consisting in monodispersed spherical particles, with a flower-like morphology, and several microns in diameter (Fig 2.1a, 1b) were obtained. These microcrystals were built from tens of 2D nanosheets on the nanometer scale slightly curved and densely interpenetrated. In

similar experiment but with continuous stirring the micrographs showed agglomerated nanoplatelets. (fig 2. 1c,1d)

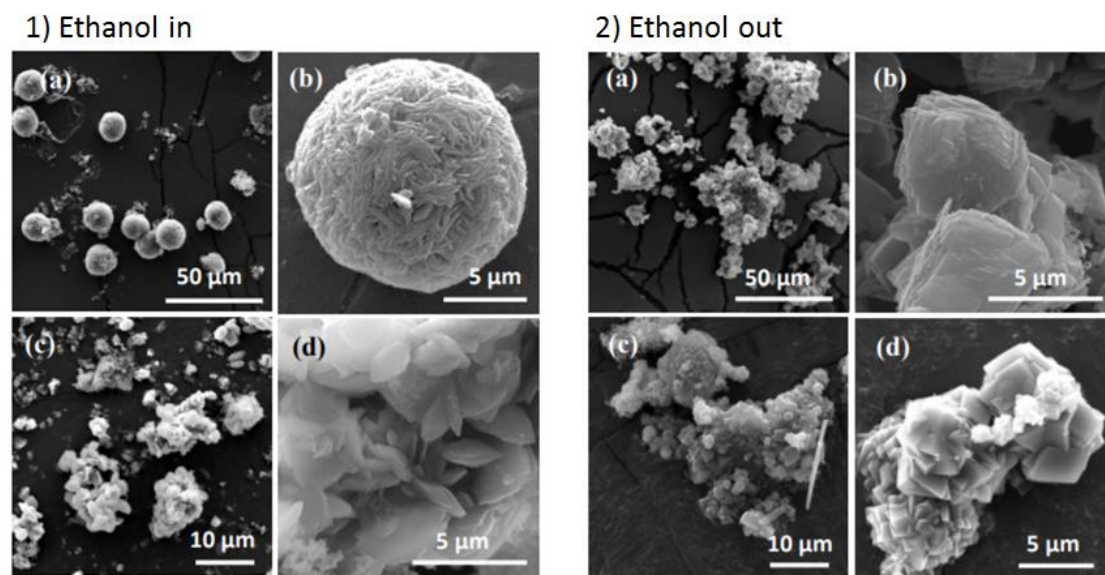


Figure 2. 1) SEM micrographs taken from samples prepared adding the EtOH in contact with the solid reagents: (a,b) stirring only the first 20 min, and (b,c) stirring during all the experimental time. 2) SEM micrographs taken from samples prepared adding the EtOH out of the vial containing the solid reagents and using different running times: (a,b) 3 days, and (b,c) 7 days.

In the experiments where the ethanol was added out of the vial, avoiding the physical contact with the reagents, it was crystallized the same MOF but with a different morphology. In 72h at 333K micrographs of this sample showed the formation of incipient micrometric polyhedral (Fig 1. 2a,2b). When reaction time was increased to 7 days larger and well-shaped micrometric polyhedral were crystallized. (Fig 1. 2c, 2d). In all the cases XRD demonstrate that the same compound was crystallized.

CONCLUSIONS

The presented analysis involves a systematic study of the synthesis of a 3D bioMOF, built with curcumin and Zn(II) and obtained by reactive crystallization in $scCO_2$. Moreover, the designed $scCO_2$ process avoids the use of toxic organic solvents, difficult to recover additives, and large excesses of expensive linkers. The obtained phase has a stoichiometry assessed by elemental analysis (EA) of $[Zn(\text{curcumin})_xH_2O]$ ($x = 1.5-2$) different from the published MOF of curcumin.[12] A complex crystal growth pathway was observed leading to an habit represented by hierarchical nanostructured micrometric flowers.

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