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Facile, fast and green synthesis of a highly porous calcium-syringate bioMOF with intriguing triple bioactivity†

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A facile, fast and green strategy based on ethanol is utilized to prepare a new bioMOF, namely, CaSyr-1, with particular characteristics of full biocompatibility given by using just calcium and syringic acid, the latter being a phenolic natural product found in fruits and vegetables, permanent porosity with an outstanding surface area $>1000 \text{ m}^2 \text{ g}^{-1}$, and a micropore diameter of 1.4 nm close to mesopore values. Collectively, these data establish CaSyr-1 as one of the most porous bioMOFs reported to date, with high molecular adsorption capacity. The CaSyr-1 adsorptive behavior is revised here through the reversible adsorption of CO_2 and the encapsulation of bioactive ingredients in the structure. Remarkably, CaSyr-1 enables the development of triple therapeutic entities, involving bioactive Ca^{2+} , syringic acid and an impregnated drug.

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1. Introduction

Metal organic frameworks (MOFs) are fascinating crystalline materials with remarkably high porosity and versatile chemistry.¹ Biological MOFs, known as bioMOFs, are composed of biocompatible metals and organic biomolecules as linkers, and are suitable for applications as diverse as gas adsorption² and medicine.³ The research on bioMOFs for biomedical applications, with particular interest in the development of drug delivery systems, is currently a hot topic in biomaterials science.⁴ For this purpose, bioMOFs can be used either as-synthesized or after encapsulation of specific active pharmaceutical products.⁵ Some interesting bioMOFs, constituted by non-toxic endogenous cations, e.g. Ca^{2+} , Zn^{2+} , Mg^{2+} or $\text{Fe}^{2+/3+}$,

and naturally occurring ligands have already been reported.⁶ Nevertheless, the integration of exclusively biocompatible units in the framework of a MOF is not a straightforward task, since most biomolecules possess low symmetry that prevents the formation of porous and stable networks, often requiring the use of (toxic) auxiliary ligands.⁷ Hence, the utilization of bioMOFs in the biomedical area has been limited by the difficulties found in preparing fully biocompatible compounds, considering not only the nature of the building units, but also the size of the particles as indicators of overall cytotoxicity.⁸ Regarding the latter, bioMOFs must be developed as nanoparticles, with a well-defined shape and narrow particle-size distribution, which are modulated by optimizing the experimental conditions during synthesis.⁹

An important point to consider in the development of bioMOFs is the chosen synthetic route. A typical reaction path designed to develop MOFs relies on the use of high boiling point basic solvents, as those derived from formamide, under solvothermal conditions.¹⁰ This method is widely used because it provides crystals of high quality suitable for structural elucidation. However, the overall process generally involves harsh reaction conditions, long reaction/activation periods and large amounts of hazardous solvents that tend to get trapped in the internal cavities of the MOF, parameters that hinder not only their biomedical application, but also their scale-up production.¹¹ Currently, more sustainable methods are under research, such as those based on the use of non-toxic solvents, e.g., water or ethanol, and applying easy scalable mechanochemical or spray-drying technologies.¹²

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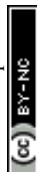
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To advance the molecular design and synthetic aspects of bioMOFs, this work presents a facile, fast and green strategy for the preparation of a novel porous 3D framework, named here as CaSyr-1, composed of a calcium cation (Ca^{2+}) as the metal node and a syringate dianion (Syr^{2-}) as the organic linker (Fig. 1), with unique textural properties and intriguing sorption and biomedical applications.

The incorporation of Ca^{2+} into MOFs has recently gained significant attention, with more than 150 crystal structures already reported.¹³ This interest is attributed to multiple health benefits,¹⁴ together with the mostly unexplored unique properties that this cation can provide, which are different from the well-known features of the universally employed transition metals. Syringic acid (H_2Syr) is a phenolic compound, often found in fruits and vegetables, with anti-oxidant, anti-inflammatory, anti-cancer and anti-hypertensive therapeutic properties.¹⁵ Contrary to Ca^{2+} , the utilization of Syr^{2-} in coordination chemistry has been scarce and absent in porous compounds.¹⁶

2. Results and discussion

2.1. Synthesis

Porous CaSyr-1 nanopowder was synthesized in this work with a large space–time yield following an eco-friendly route in the green solvent ethanol (EtOH).¹⁷ Remarkably, the material could be prepared in only a few min (*i.e.*, 10 min) by simply mixing quantitative molar amounts of reactants, calcium acetylacetonate ($\text{Ca}(\text{acac})_2$) and H_2Syr , in a reduced volume of the solvent (1 mmol of each reactant in 1 or 10 mL of EtOH , corresponding to reactants: EtOH with molar ratios of 1:8 and 1:80, respectively) at room temperature. Powder X-ray diffraction (PXRD) indicates that the obtained product was in both cases the explored phase CaSyr-1 (Fig. 2a and S1† for 1:80 and 1:8 molar ratios, respectively). However, narrow particle-size distributions, most appropriate for biomedical uses, were obtained in the system with an increase in the volume of EtOH (Fig. 2b, c and S2, S3†), which allows a better control over supersaturation and subsequent nucleation and crystal growth. CaSyr-1 was thus precipitated as isometric porous nanoparticles with a mean diameter of 64 ± 11 nm (Fig. 2b and c). According to dynamic light scattering (DLS) measurements, the mean hydrodynamic diameter in suspension was *ca.* 150 nm when suspended in EtOH (Fig. S4†). Moreover, the

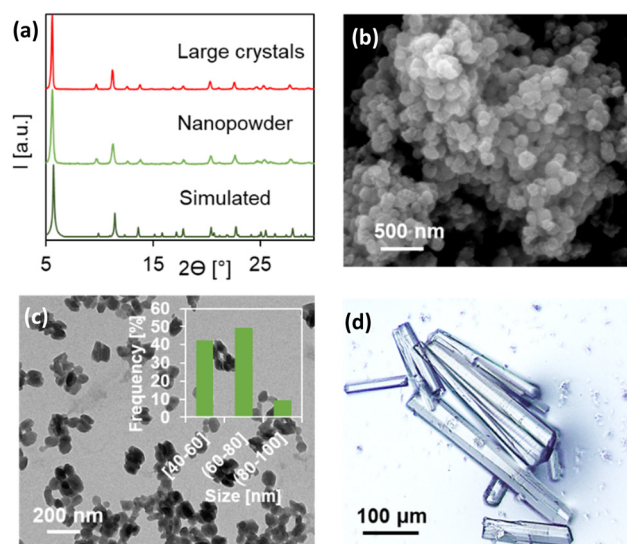


Fig. 2 (a) PXRD pattern of CaSyr-1 species compared with the simulated, (b) SEM and (c) TEM with the particle size histogram of the nanopowder, and (d) an optical microscope image of large crystals.

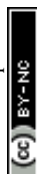
particle-size distribution was extremely narrow (100–200 nm), which indicates that CaSyr-1 exhibits adequate dimensional properties for biosystems designed for flowing in blood vessels.¹⁸ The synthetic protocol was optimized to reduce the cost and time of the process, but conserving the desired dimensional, morphological and textural properties of the end product.

2.2. Crystal structure

In order to elucidate the crystalline structure of CaSyr-1, crystals of suitable quality (Fig. 2d) were prepared in dimethylformamide (DMF) at 393 K and characterized by synchrotron XRD. The resolved crystalline structure has the formula $[\text{Ca}_2(\text{Syr})_2(\text{H}_2\text{O})_2]_n \cdot \text{C}(\text{solvent})$, which was confirmed by elemental analysis (Table S1†). A simulated PXRD pattern from the single crystal data matched those of both bulk large crystals precipitated in DMF and the nanopowder obtained in EtOH (Fig. 2a). The CaSyr-1 framework consists of interconnected dimeric units containing two crystallographically independent Ca^{2+} ions, two independent Syr^{2-} linkers and two ancillary H_2O ligands (Fig. 3a). A detailed description of the crystalline structure can be found in the ESI.† Briefly, regarding the calcium sphere, it is worth highlighting the double clamp-like coordination mode of Syr^{2-} that is responsible for the connection between Ca1 and Ca2 (through two μ_2 -oxo bridges, O2 and O5) and, thus, for the formation of the dimer. This coordination mode is powered by the adjacent methoxy-phenolate-methoxy groups present in the ligand. Although isolated methoxy groups are extremely weak ligands, when positioned next to a coordinating group, such as phenolate, they tend to form this robust clamp-like coordination.¹⁹ With respect to syringate, the role of the dicarboxylate groups is also noteworthy in the extension of the structure (Fig. 3b), since they serve as



Fig. 1 Occurrence and bioactivity of CaSyr-1 building blocks.



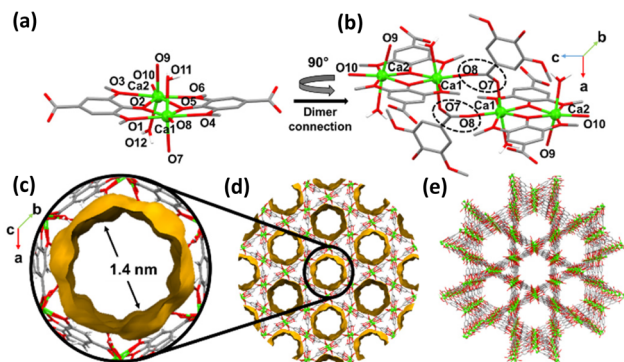


Fig. 3 Structure of CaSyr-1: (a) dimeric unit, (b) connections through dicarboxylate bridges, (c) pore structure, (d) void arrangement, and (e) 3D framework.

bridges of two different dimeric units and promote the formation of the 3D porous framework (Fig. 3c–e). The resulting network displays two types of prisms, triangular and hexagonal (ratio 2 : 1), with a disposition in the space that resembles the Kagome lattice, frequently found in natural minerals, but also in many MOFs.²⁰

Void volume measurement using Mercury software (probe radius 1.2 Å) indicates that the porosity arises only from the hexagonal section, in the form of unidimensional channels with a diameter of 1.4 nm. Note that CaSyr-1 has the largest pore diameter value described for microporous bioMOFs, close to that of mesoporous bioMOFs.²¹ Additionally, a highly porous architecture of open pores is obtained, with 36 v% void space.

2.3. Porosity and thermal stability

CaSyr-1 porosity was experimentally confirmed by N₂ physisorption at 77 K, giving an isotherm of type I (Fig. 4a). The high adsorption values at a very low relative pressures indicate microporosity (micropore volume of 0.32 cm³ g^{−1}), which is in accordance with the size of the cavities observed in the resolved crystalline structure. N₂ uptake at high relative pressures, accompanied by hysteresis, is assigned to interparticle mesoporous voids. A high value of an apparent BET surface

area of 1080 m² g^{−1} (Langmuir 1205 m² g^{−1}) was derived from the isotherm, which is exceptional in comparison with other reported bioMOFs that are considered totally biocompatible (Table 1), as CaSyr-1, not including either toxic auxiliary ligands in the framework and/or impregnated or coordinated harmful solvents in the pores. The measured surface area value for CaSyr-1 is just comparable with that reported for the γ -cyclodextrin macrocyclic CD-MOF-1. Regardless, CaSyr-1 exhibits a notably larger pore aperture diameter (1.4 nm) in comparison with CD-MOF-1 (0.42 and 0.78 nm), which would extend for the former, the scope of possible bioactive ingredients to be encapsulated.^{6a,c,22}

The lighter weight of Ca²⁺ with respect to transition metals offers gravimetric advantages for gas loading, which together with the large affinity of Ca²⁺ for CO₂, makes Ca-based MOFs suitable materials for CO₂ sorption. Uptakes in the order of 1–2 mmol g^{−1} (100 kPa and 273–298 K) are reported,¹³ which could only be increased by synthesizing mixed-metal MOFs.²³ Remarkably, the monometallic CaSyr-1 bioMOF described in this work, with a CO₂ sorption of 3.7, 2.4 and 1.8 mmol g^{−1} at 100 kPa and 273, 298 and 313 K (Fig. 4b), respectively, outperform the values previously described for Ca-based MOFs (Table S2†). Actually, the found value of CO₂ sorption for CaSyr-1 is closer to that of basic adenine bioMOFs, specifically designed for this application,²⁴ and the industrially used activated carbon or zeolite 13X (*ca.* 4 mmol g^{−1}).²⁵ From the data extracted at different adsorption temperatures, the CO₂ enthalpy of adsorption (*Q_{st}*) could be estimated, giving rise to a value of *ca.* 18 J mmol^{−1} (Fig. S7†) in the range of physisorption. The PXRD spectra of CaSyr-1 after these analyses indicate that CO₂ was desorbed without any structural modification of the adsorbent. For environmental and process cost reasons, in the application of CO₂ capture, the use of inexpensive renewable biolinkers for MOF design, such as that in CaSyr-1, is preferred *vs.* those derived from non-renewable petrochemical feedstocks.²

For adsorption-related applications, thermal stability plays an important role in ensuring the integrity of MOFs during interaction with an adsorbate and in the regeneration process of the material for further reuse.²⁶ Here, the thermal stability of CaSyr-1 was evaluated through thermogravimetric analysis (TGA) under N₂ flow (Fig. S8†). The weight decay at *ca.* 330 and 420 K is ascribed to the loss of EtOH and water molecules, respectively, both trapped in the cavities of the bioMOF during synthesis and manipulation, resulting in a total weight loss of about 20 wt%. The weight decrease does not involve any structural change in the framework of CaSyr-1, which was confirmed by a variable-temperature PXRD (VTPXRD) analysis, measured continuously from 298 to 500 K. Actually, no significant differences among the patterns recorded at the different temperatures were noticed (Fig. S9†). Hence, the removal of the solvent from the voids does not compromise the stability of the porous framework. The TGA suggests that CaSyr-1 is thermally stable up to *ca.* 600 K, the temperature at which the pyrolysis of the bioligand induces the degradation of the network. This notable thermal stability is usual in Ca-based

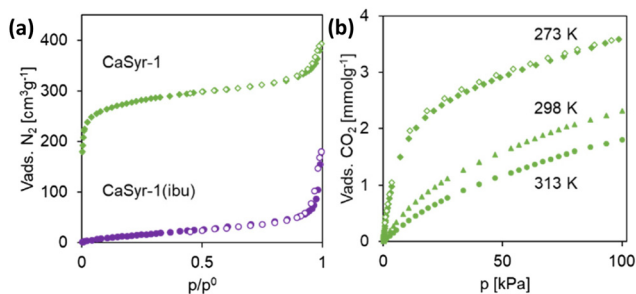


Fig. 4 Adsorption behavior: (a) N₂ isotherms at 77 K for pristine CaSyr-1 and impregnated CaSyr-1(ibu), and (b) CO₂ isotherm at 273, 298 and 313 K of CaSyr-1.



BioMOF	Bioligand	Apparent BET surface area (m ² g ⁻¹)	Micropore volume (cm ³ g ⁻¹)	Pore aperture diameter (nm)	Ref.
CaSyr-1	Syringate	1080	0.32	1.4	This work
CD-MOF-1	γ -Cyclodextrin	1220	0.47	0.42/0.78	6a
sc-CCMOF-1	Curcumine	350	0.10	N/A	6c
[Cu ₂ (μ_3 -ade) ₂ (μ_2 -OOCCH ₃) ₂] \cdot H ₂ O	Adenine/acetate	505	0.17	N/A	22a
{[Zn(FDC)] \cdot H ₂ O} _n }	2,5-Furandicarboxylate	780	N/A	0.63	22b
MOF-1201	L-Lactate	430	0.18	0.78	22c

Drug encapsulation in $scCO_2$

CaSyr-1

Triple bioactivity

Legend:

- Ca^{2+} (red sphere)
- Syringate (white sphere)
- Drug (purple sphere)

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Variable-temperature PXRD. The variable-temperature PXRD (VTPXRD) measurements were performed at the BL16-NOTOS

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beamline of the ALBA synchrotron, from 298 up to 500 K. Data were collected at 20 keV (0.62074 Å wavelength) in the transmission mode using a Mythen-II detector (6 modules at 535 mm from the sample). The powdered sample was placed inside an *ad hoc* capillary reaction cell (fused silica capillary with 0.7 and 0.85 nm inner and outer diameters, respectively) with a capillary connected online to both a gas-handling and a vacuum line. An Oxford Cryostream 700 instrument was used to control the temperature of the sample.

Microscopy. CaSyr-1 large crystals were optically analyzed with an Olympus IX53 inverted microscope connected to a XC30 camera. The crystal morphology of the nanopowder was observed by scanning electron microscopy (SEM) in a Quanta FEI 200 FEG-ESEM microscope. For better resolution, the sample was coated with Au/Pd. The histograms of the particle-size distribution were obtained by measuring >200 discrete particles in images taken with a transmission electron microscope (TEM; JEOL 1210) using the ImageJ program.

Dynamic light scattering. The particle-size distribution in suspension was estimated by the dynamic light scattering (DLS) method, using a Zetasizer Nano ZS Malvern Inst. Prior to the measurement, CaSyr-1 was suspended in EtOH and sonicated for 1 h.

Gas adsorption. The porosity of the samples was determined by analysing the N₂ adsorption–desorption isotherms recorded at 77 K using ASAP 2020 Micromeritics Inc. equipment. The apparent specific surface area was calculated by applying the BET (Brunauer–Emmett–Teller) equation or the Langmuir model. The micropore volume was determined by the *t*-plot method. The CO₂ sorption capacity was assessed by analysing the isotherms at 273, 298 and 313 K up to 0.1 MPa. In both cases, the samples were first degassed at 373 K under high vacuum (10 Pa) for 20 h. The CO₂ enthalpy of adsorption (Q_{st}) was determined through the graphical representation of the pressure logarithm ($\ln p$) for a given adsorbed amount (n) as a function of the reciprocal temperature ($1/T$). The Q_{st} at a specific adsorbate loading was then estimated using the Clausius–Clapeyron equation (eqn (1)):

$$Q_{st}(n) = -R \ln(p_2/p_1)(T_1 T_2 / (T_2 - T_1)) \quad (1)$$

Elemental analysis. The chemical composition of CaSyr-1 nanopowder, regarding carbon and hydrogen, was estimated by elemental analysis (EA). Data were recorded in a Flash SmartTM elemental analyzer. The results were compared with the theoretical values calculated from the crystallographic formulae contained in the generated CIF from single crystal structural data (without considering the solvent in the pores).

Thermogravimetric analysis. The thermal stability of CaSyr-1 was evaluated by thermogravimetric analysis (TGA) under N₂ flow using a SDT 650-TA instrument.

¹H-nuclear magnetic resonance. Proton nuclear magnetic resonance (¹H-NMR) was employed to quantify the content of ibuprofen in the impregnated sample CaSyr-1(ibu). In order to release all the ibu and H₂Syr from CaSyr-1(ibu), 20 mg of the sample was suspended in methanol, and 4 drops of HF (40 v%

in water) were added. The mixture was heated at 333 K overnight to evaporate the solvent and excess HF, resulting in a crude product that contained CaF₂, protonated H₂Syr and ibuprofen. DMSO-d₆ was added to dissolve the organic components, and the subsequent suspension was filtered before transferring it to the ¹H-NMR tube in order to remove the precipitated calcium salt. The analysis was carried out in a Bruker Avance NEO 300 MHz. Both, ibuprofen and syringic acid exhibited well-defined 6H signals in the ¹H-NMR spectrum, corresponding to two methyls and two methoxides at δ = 0.86 and 3.80 ppm, respectively (Fig. S14 and S15[†]). Hence, in CaSyr-1(ibu), the molar ratio of ibu with respect to H₂Syr can be estimated by comparing the integration of the signal at 0.86 ppm with the integration of the signal at 3.80 ppm (Fig. S16[†]).

4.4. Bioactive release and biocompatibility assays

Bioactive release. The release of the organic bioactive components present in CaSyr-1(ibu) was tracked by ¹H-NMR, utilizing the same spectrometer as in the previous section. For that, 25 mg of CaSyr-1(ibu), corresponding to the IC₅₀, was suspended in 5 mL of PBS in D₂O (buffer pH = 7.4) under stirring at 200 rpm for 1 day at 310 K. The system was maintained under inert conditions to avoid the exchange of D₂O with H₂O from the air. During this period, four aliquots were collected at different times, *i.e.*, 10 min, 1, 3 and 24 h, and centrifuged to remove the precipitate and characterized by ¹H-NMR. The molar ratio of the syringate with respect to ibuprofen was estimated as in the previous section.

Cell culture. Biocompatibility was tested on a human osteosarcoma cell line (MG63, ATCC CRL1427). MG63 cells were cultured on the MEM NEAA medium (Sigma Aldrich), supplemented with 10 wt% of fetal bovine serum (FBS, Sigma), 1 wt% penicillin/streptomycin (Invitrogen) and 2 wt% L-glutamine (Invitrogen). Cells were cultured at 310 K and 5 v% CO₂ in a humidified chamber until confluence before the assays. Cells were used from 4 to 8 passages in all the experiments.

Toxicity tests. For pristine syringic acid and ibuprofen compounds, MG63 cells were cultured on a 96 well-plate at 100 000 cells per cm³ and incubated at 310 K and 5 v% CO₂. After 24 h, the medium was replaced by serial dilutions of syringic acid in culture medium and ibuprofen in 1 v% DMSO added to the culture medium. The cells were incubated at 310 K and 5 v% CO₂ for 24 h. MG63 cells in culture medium and 1 v% DMSO in culture medium were used as the control systems. After 24 h, the medium was replaced by the culture medium without phenol red (Sigma Aldrich).

For CaSyr-1 and CaSyr-1(ibu), 200 μ L of MG63 cells was cultured on transwell insets (collagen coated, cut-off = 0.4 μ m, diameter = 6.5 mm, Costar) at 100 000 cells per cm³. The insets were incubated in a 48-well plate with 400 μ L of culture medium and at 310 K and 5 v% CO₂. After 24 h, the medium of the inset was replaced by fresh medium, and the medium of the well plate was replaced by serial dilutions of CaSyr-1 and CaSyr-1(ibu) in culture medium (starting at 25 mg cm⁻³). After



24 h, all the media were replaced by culture medium without phenol red.

Cell viability. In the different studied systems, cell viability was analysed by adding Alamar Blue (1) ISO 10993-5:2009 (AB, Invitrogen)³⁹ at 10 v% and culturing the cells at 310 K for 4 h. After this time, the cell viability was measured using a plate reader (Biotek Synergy HT spectrophotometer) with laser excitation at 590 nm and measuring the emitted fluorescence at 530 nm. The cell viability (%) was calculated using the following equation (eqn (2)):

$$\text{Cell viability (\%)} = 100 \times (\text{ODS} - \text{ODB}) / (\text{ODC} - \text{ODB}) \quad (2)$$

where ODS, ODB, and ODC represent the emitted fluorescence at 530 nm for the sample (S), blank (B, culture medium without cells), and control (C), respectively. The experiments were conducted in triplicate for each sample, and the data obtained were expressed as mean values \pm SD.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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