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Supporting Information for

Metal Organic Frameworks as Potential Multi-Carriers of Drugs

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1. Materials and methods

General reagents and solvents were commercially available and used as received. [Ru(*p*-cymene)Cl_2(pta)] (pta = 1,3,5-triaza-7-phospaadamantane), RAPTA-C,[1] and [Ni_2(2,5-dihydroxyterephthalate)$(H_2O)_2$]·$(H_2O)_8$, CPO-27-Ni,[2] were prepared according to published procedures. ^{1}H NMR were acquired on a 400 MHz Bruker Equipment using $CDCl_3$ as solvent. Thermogravimetric and differential calorimetric analyses were performed, under air atmosphere, on a NETZSCH TG 209 equipment, at a heating rate of 5 K min^{-1}. UV-vis spectra were collected on a Perkin Elmer Lambda 35 UV/VIS spectrometer. Centrifugation has been performed by means of a Sigma 3-30K centrifuge. The NO measurement experiments were performed using a Sievers NOA 280i chemiluminescence Nitric Oxide Analyzer. The infrared spectra were recorded using either a Perkin Elmer Spectrum GX IR spectrometer system or a Bruker Equinox 55 spectrometer (equipped with an MCT detector) with the spectral resolution of 2 cm^{-1}. XRPD data were collected in the 2θ range 5-50° with 0.02° steps on a Stoe Stadip diffractometer using monochromated CuKα radiation (λ = 1.5418 Å). The compounds were manually grounded in an agate mortar, then deposited in the hollow of a aluminium sample holder. N_2 adsorption isotherms were measured at 77 K on a Micromeritics Tristar 3000 volumetric instrument. Prior to measurement, powdered samples were activated by heating at 423 K for 12 h and outgassing to 10^{-4} bar.

2. Chemical stability tests on CPO-27-Ni

In a typical test, 30 mg of activated MOF has been suspended into 10 mL of the desired solvent for 3 days at room temperature. Afterwards, the solid was filtered off and dried at room temperature before XRPD acquisition (Fig. S1).

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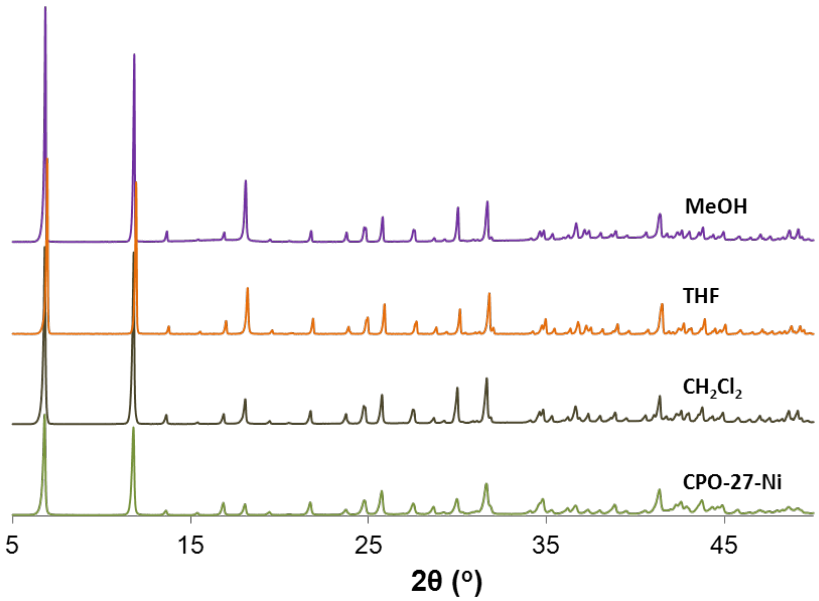

Fig. S1 XRPD patterns acquired on CPO-27-Ni as synthesized and after different chemical stability tests. The solid has been stirred in each solvent for 3 days at room temperature.

3. Adsorption and release of RAPTA-C from CPO-27-Ni

Evacuation of CPO-27-Ni: Prior to the loading of RAPTA-C into CPO-27-Ni, the as synthesized solid CPO-27-Ni was heated at 423 K for 12 h and outgassed to 10^{-4} bar. Under these conditions, the complete removal of the water guest molecules in order to obtain empty pores ready for NO and RAPTA-C adsorption could be achieved.

Loading of RAPTA-C at 298 K: RAPTA-C solutions (80% saturation) were prepared using different anhydrous solvents (methanol, tetrahydrofurane and dichloromethane). RAPTA-C solid-liquid adsorption experiment was performed at 298 K by suspending 90 mg of activated CPO-27-Ni into the RAPTA-C solutions under stirring for 24 h in order to assure that equilibrium was reached. Then, each sample was centrifuged at 4000 rpm for 10 minutes to achieve the separation of CPO-27-Ni@RAPTA matrix from the solution. The amount of RAPTA-C incorporated into CPO-27-Ni was indirectly calculated monitoring, by means of UV-vis, the decrease of RAPTA-C concentration in the solution. The highest loading was obtained with anhydrous dichloromethane.

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For the evaluation of the amount of RAPTA-C adsorbed into CPO-27-Ni MOF, the concentration of the metallodrug in solution before and after the incorporation was checked by UV-vis. The UV-vis maximum absorption bands for RAPTA-C in dichloromethane, methanol and tetrahydrofurane are found at 339, 338 and 336 nm with a tale peak at 470, 466 and 432 nm, respectively. In SBF, these two maxima are found at 350 nm and 441 nm, respectively. These peaks are attributed to [Ru(*p*-cymene)Cl(H_2O)(pta)] complex that is immediately obtained when RAPTA-C is hydrolized in water.[3]

The 2,5-dihydroxyterephtalic ligand, eventually leached during RAPTA-C incorporation, is soluble in SBF. Its UV-vis maximum absorption band is found at 530 nm, therefore, the free 2,5-dihydroxyterephtalic ligand cannot interfere with the UV-vis absorption of the RAPTA-C species. In any case, the leaching of the ligand has never been observed during the performance of our experiments.

Anal. calc. (using dichloromethane as impregnating solvent) for $Ni_2(H_2O)_2(C_8H_2O_6)(H_2O)_8(C_{16}H_{25}Cl_2N_3PRu)_{0,23}$ (H_2O) (CPO-27-Ni@RAPTA): C, 22.81; H, 4.88; N, 1.57; Anal. Found: C, 22.20; H, 4.22; N, 1.90. Considering Z = 18, the functionalization degree of CPO-27-Ni@RAPTA is 4.14 RAPTA-C molecules *per* unit cell.

Loaded RAPTA-C calculated from UV-vis: 0.23 mol of RAPTA-C per formula unit.

Release of RAPTA-C: The delivery of RAPTA-C in simulated body fluid (SBF) has been studied at 310 K. SBF was prepared according to literature methods.[4] With this purpose, we prepare two solutions, A and B (Table S1) that must be mixed just before each experiment in order to avoid the possible precipitation of some poorly soluble inorganic salts.

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	Sol. A (g/L)	Sol. B (g/L)
NaCl	6.213	6.213
$NaHCO_3$	5.948	
KCl	0.450	
$Na_2HPO_4 \cdot 2H_2O$		0,498
$K_2HPO_4 \cdot 3H_2O$	0.462	
$MgCl_2 \cdot 6H_2O$	0.622	
$CaCl_2$		0.584
Na_2SO_4	0.144	

Table S1. Composition of the A and B solutions used for the preparation of the solution of simulated body fluid.

The study of RAPTA-C delivery process was carried out for both CPO-27-Ni@RAPTA samples before and after NO incorporation. For this purpose, we suspended 20 mg of these samples (CPO-27-Ni@RAPTA and CPO-27-Ni@RAPTA@NO) in 20 mL of SBF, incubated at 310 K, under stirring. Aliquots (3 mL) of the supernatant solution were analyzed by means of UV-vis (λ = 350 nm) at different periods of time (10, 20, 30, 45 min, 1, 1.5, 2, 3, 5, 7, 9, 24 h) in order to determine the amount of released RAPTA-C and the kinetics of the process. Each aliquot was centrifugated at 4000 rpm for 2 minutes, then both the solution and the solid were joined to the mother solution to keep the volume constant.

4. IR spectrometry for RAPTA-C identification

RAPTA-C, CPO-27-Ni and CPO-27-Ni@RAPTA (2 mg) were manually grounded with dry potassium bromide in an agate mortar and then pressed into a disc.
IR spectroscopic analysis showed the presence of RAPTA-C in the CPO-27-Ni@RAPTA loaded polymer. Indeed, the most intense peaks observed in the RAPTA-C infrared spectrum also appear in that of CPO-27-Ni@RAPTA sample (Fig. S2).

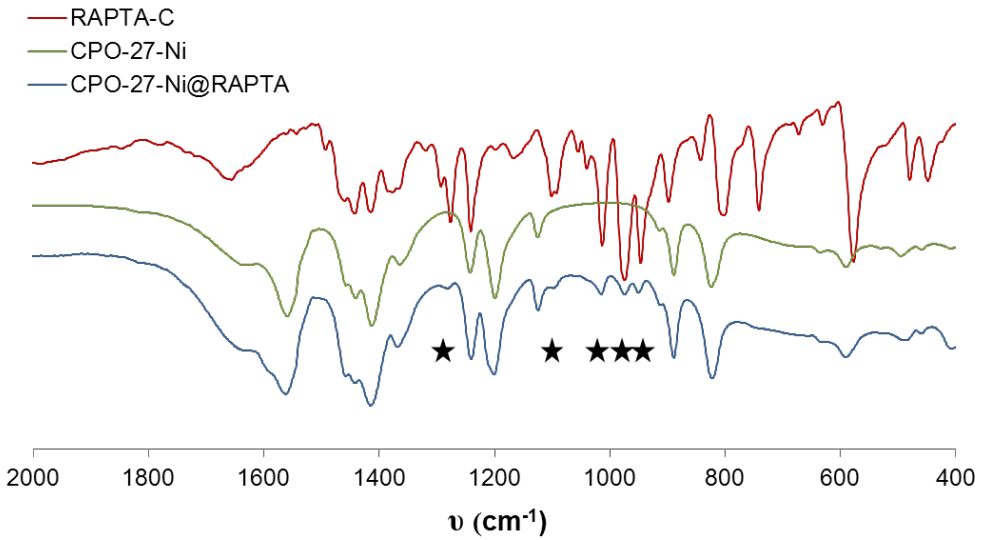

Fig. S2 IR spectra of RAPTA-C, activated CPO-27-Ni and CPO-27-Ni@RAPTA samples.

5. Thermal analysis on CPO-27-Ni and CPO-27-Ni@RAPTA

The thermal stability of free RAPTA-C, CPO-27-Ni and CPO-27-Ni@RAPTA (CH_2Cl_2 loaded) has been evaluated under an air stream.

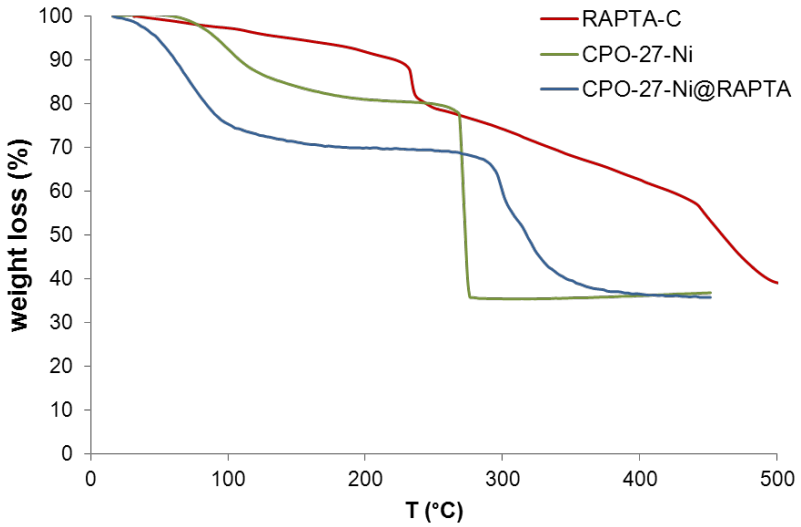

Fig. S3 TG traces for RAPTA-C, CPO-27-Ni and CPO-27-Ni@RAPTA and under air atmosphere.

Calculated residue after thermal treatment of CPO-27-Ni@RAPTA: $(NiO)_2(RuO_2)_{0.23}$: 32.49%; Found: 32.84%.

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6. X-ray powder diffraction for CPO-27-Ni and CPO-27-Ni@RAPTA

The loaded form CPO-27-Ni@RAPTA has been obtained suspending 30 mg of activated CPO-27-Ni into 10 mL of an anhydrous dichloromethane RAPTA-C solution (0.011 M), stirring at 25º C for 24 hours to ensure that the equilibrium is reached. The solid was filtered, washed with anhydrous dichloromethane and dried under reduced pressure. XRPD measurements confirm that the crystal structure of the porous matrix is maintained (Fig. S3).

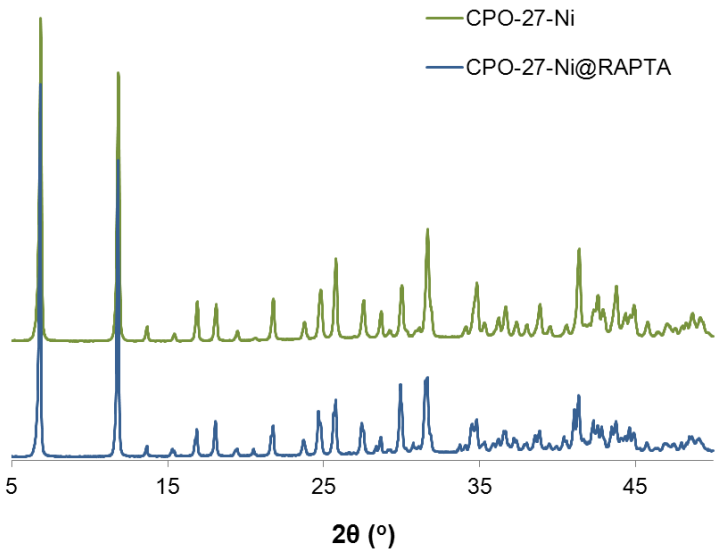

Fig. S4 XRPD patterns of activated CPO-27-Ni and loaded CPO-27-Ni@RAPTA species.

7. Measurement of the adsorption-desorption isotherms of NO

NO adsorption/desorption isotherms for CPO-27-Ni and CPO-27-Ni@RAPTA were measured using a gravimetric adsorption system. The microbalance was thermally stabilized to eliminate external effects. The microbalance had a sensitivity of 0.1 μg and a reproducibility of 0.01% of the load. The pressure of the absorption system was monitored by two BOC Edwards active gauges with ranges of 10^{-8} to 10^{-2} and 10^{-4} to 10^{3} mbar, respectively. 25 mg of sample was initially subjected to the vacuum before being degassed at 423 K under a pressure of 10^{-4} mbar overnight, until no further weight loss was observed. The temperature was then decreased to 298 K and kept constant by a circulating water bath with temperature accuracy of 0.02 K. The counterbalance

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temperature was kept the same as that of the sample in order to minimize the influence of temperature differences on weight readings, and the sample temperature was monitored using a K-type thermocouple located close to the sample bucket (< 5 mm). The variation in sample temperature was minimal (< 0.1 K) throughout the experiment. NO gas was introduced into the adsorption system until the desired pressure was achieved, and the mass uptake of the sample was measured as a function of time until the adsorption equilibrium was reached. In this manner, an adsorption isotherm was collected by introducing dried NO gas (Air Liquid, 99.5%) with gradual system pressure increments with the uptake of NO noted at the equilibrium mass of the material at each increment point. Desorption of the NO gas absorbed in the samples was performed by gradually decreasing the system pressure to 10^{-2} mbar.

8. Loading and measurement of the kinetic of NO release by chemiluminescence

Powdered samples of CPO-27-Ni and CPO-27-Ni@RAPTA (~ 20 mg) were dehydrated at 423 K under a pressure of 10^{-4} mbar overnight. They were cooled to room temperature and exposed to an atmosphere of NO (Air Liquid, 2 bar) for 1 hour. The samples were then evacuated and exposed to dry argon. This evacuation and exposure to argon was repeated 3 times to ensure the total removal of excess NO.

In order to measure the kinetic of release of NO by chemiluminiscence, the instrument was calibrated by passing air though a zero filter (Sievers, < 1 ppb NO) and 89.7 ppm NO gas (Air Products, balance nitrogen). The flow rate was set to 180 mL/min with a cell pressure of 0.011 bar and an oxygen pressure of 0.42 bar. To trigger the desorption of NO from the CPO-27-Ni@NO and CPO-27-Ni@RAPTA@NO samples, wet nitrogen gas (controlled humidity 11% RH) was passed over the powders at room temperature. The eluted flow was directed into the analyser and the concentration of NO recorded as a function of time.

9. IR spectrometry for NO identification

Nitric oxide gas was distilled by freeze and thaw cycles before adsorption to remove any traces of moisture and impurities.

For IR studies, samples of CPO-27-Ni and CPO-27-Ni@RAPTA were pressed into thin wafers and activated in situ in an IR cell. First, samples were evacuated at room

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temperature for 30 min, and then temperature was raised with a heating rate of 5 K/min until 423 K and kept at this temperature under vacuum for 12 h.

The adsorption measurements were carried out by means of an IR cell with calibrated volume (ca. 5 cm^3). Then, nitric oxide was introduced into the IR cell to expose the sample to an atmosphere of NO.

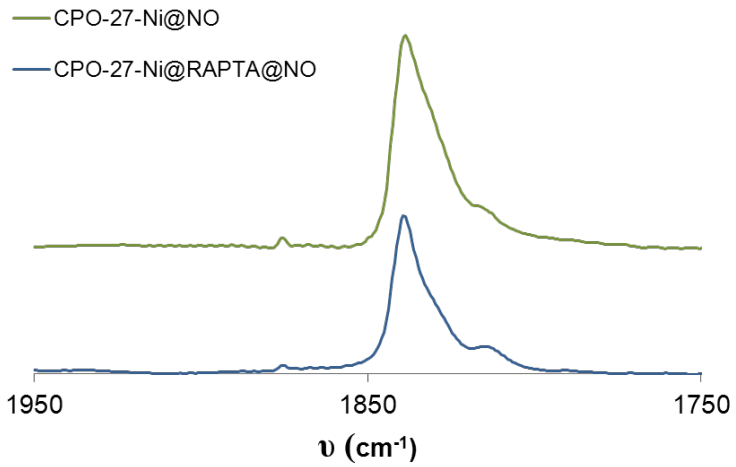

Fig. S5 IR spectra acquired on activated CPO-27-Ni and CPO-27-Ni@RAPTA upon exposition to NO. These spectra show that the metal sites are accessible to NO even after adsorption of the RAPTA molecule.

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