Journal of
Materials Chemistry B

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# Template role of caffeine in its one-step encapsulation in MOF $NH_2$-MIL-88B(Fe)

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## Abstract

A simple and efficient one-step encapsulation of caffeine was carried out in MOF $NH_2$-MIL-88B(Fe) and compared to the traditional three-stage synthesis-activation-encapsulation procedure. Caffeine was added to the synthesis solution of the MOF whose structure was formed around the caffeine itself. The caffeine loading was 35 wt%. The presence of this molecule in the synthesis solution led to swollen CAF@$NH_2$-MIL-88B(Fe) when a different framework ($NH_2$-MIL-53(Fe)) was obtained without caffeine. For comparison, the ex situ encapsulation of caffeine was also carried out in $NH_2$-MIL-88B(Fe), once this material was obtained upon activation of $NH_2$-MIL-53(Fe). The release of caffeine and aminoterephthalic acid (the ligand used to obtain the MOFs) from the different materials was studied both in water and PBS. Caffeine plays the role of a structure directing agent or template since its presence led to the obtaining of a different MOF. In addition, caffeine contributed to the liquid phase stability of the MOF, as demonstrated through the release of the ligand from both CAF@$NH_2$-MIL-88B(Fe) (slower release) and $NH_2$-MIL-88B(Fe) (faster release). Chemical and structural evidence indicated hydrogen bonding interactions between caffeine and MOF.

**Keywords**: Metal organic framework, MIL-88B, Encapsulation, Caffeine, Drug release.

## Introduction

Metal-organic frameworks (MOFs) are a class of hybrid materials composed of metal centers linked to organic molecules forming a highly porous structure. Thanks to their great porosity[1] and the possibility of functionalizing the organic linkers to tune the pore,[2] shape[3, 4] and final functionality,[5] MOFs are considered as potential materials in several application fields such as adsorption,[6] medicine,[7] membranes,[8] catalysis[9] and separation and storage of gases and vapors.[10]

Special interest has been paid in biomedical applications, where it is essential that the MOF components (cation and organic linker) are biocompatible. Previous studies highlighted the good biocompatibility of several MIL-n(Fe) materials,[11] considered as the best choice for drug delivery applications. However, the encapsulation of molecules in porous matrices can go beyond the medical field, as demonstrated, for instance, in the encapsulation of additives in zeolite for polyamide fiber modification.[12]

The common or ex situ encapsulation in MOFs is a long process which involves at least three stages: MOF synthesis, porosity activation and encapsulation itself.[13] The activation step is especially problematic. It usually includes the use of the highly toxic solvent dimethylformamide (DMF) to exchange the occluded carboxylate molecules[14] so that finally it is necessary to remove the encapsulated DMF, making sure that no trace of it remains.

To avoid such a complex process, the possibility of an in situ encapsulation where the synthesis of the MOF and the drug encapsulation are carried out in only one step would be of considerable interest.[15] In addition to achieving a simplified process, the use of DMF would be avoided. In general, MOFs can be prepared in relatively milder conditions (in terms of solvent, pH and temperature) than other materials such as zeolites or even certain

MOFs, so that expensive and sensible drugs may not be affected during the (in situ or ex situ) encapsulation process. This would also mean that reactants excess could be reused. Considering caffeine as a model drug, we have already encapsulated this molecule in one step in both ZIF-8[15] and silica materials.[16] Now we have applied the same principle to $NH_2$-MIL-88B(Fe). This MOF has attracted much attention due to its great swelling capacity in the presence of specific molecules. A change in the swelling amplitude up to 132 % has been demonstrated.[17] Taking into account that the flexibility of this MOF is governed by the host-guest interactions, it is expected that caffeine with –C=O and –C=N groups would interact with amino groups in the MOF leading to a very open framework.[18] Caffeine is a very useful molecule used not only as model drug due to its chemical structure and amphiphilic nature[19] but also as an active ingredient in many cosmetic[20] and pharmaceutical[21] formulations. Caffeine has already been encapsulated in two steps into MIL-88B type,[18] MIL-53 and MIL-100[11] MOFs with Fe as the metal and in UiO-66[22] with Zr as the metal. The most important challenge for caffeine is to achieve a controlled drug delivery in water, in which caffeine is very soluble.

In this work we have observed how the presence of a caffeine molecule in the synthesis solution led to swollen CAF@$NH_2$-MIL-88B(Fe) when a different framework ($NH_2$-MIL-53(Fe)) was obtained without caffeine. This CAF@$NH_2$-MIL-88B(Fe) corresponds to a one-step encapsulation material. For comparison, the ex situ encapsulation of caffeine has been carried out in $NH_2$-MIL-88B(Fe) obtained upon activation of $NH_2$-MIL-53(Fe). The caffeine encapsulating materials were submitted to different release experiments both in water and PBS. In addition, the simultaneous degradation/dissolution of the MOFs was studied. Caffeine would have a clear role here as a structure directing agent or template, very common in the synthesis of zeolites but not often claimed for

MOFs. In this respect, ion templating effects have been used to control MOF topology,[23] ionic liquids have been used as both solvent and template in the case of ionothermal synthesis,[24] synthesis of inorganic-organic hybrids based on polyoxometalates has been carried out,[25] and a MOF structure has been derived from another by ligand replacing.[26] Nevertheless, to the best of our knowledge, this is the first time in which caffeine (a versatile molecule due to its amphiphilic character) acts as template for the synthesis of a porous crystalline material. Additionally, when hosting certain non-coordinated molecules[15, 27] template effects can be also claimed, as well as when the MOF synthesis was carried out in a micelled medium[28] and surfactant molecules acted as cooperative templates to create mesoporous MOFs,[29] even though hierarchical structures can be obtained without the use of secondary immiscible solvents or sufactants.[4] Summarizing, we not only used the in situ approach, as in our previous work related to CAF@ZIF-8,[15] to obtain different materials with carboxylate based MOFs showing high releasing time but also discovered that caffeine played template (as quaternary amines in the case of zeolites) and stabilizing roles.

## Experimental

*Synthesis of materials*

To synthesize CAF@$NH_2$-MIL-88B(Fe)_IN (one-step encapsulation), $FeCl_3 \cdot 6H_2O$ (0.54 g) with 2-aminoterephthalic acid (0.27 g), caffeine (0.3 g), and deionized water (75 mL) were added to a spherical flask. The reaction was continuously stirred at 80 ºC for 24 h and the final suspension obtained was centrifuged at 10000 rpm for 15 min. The product was dried in an oven at 60 ºC overnight.

The same procedure was followed without caffeine and in such conditions no $NH_2$-MIL-88B(Fe) framework was obtained. $NH_2$-MIL-53(Fe) was the product recovered after the reaction.

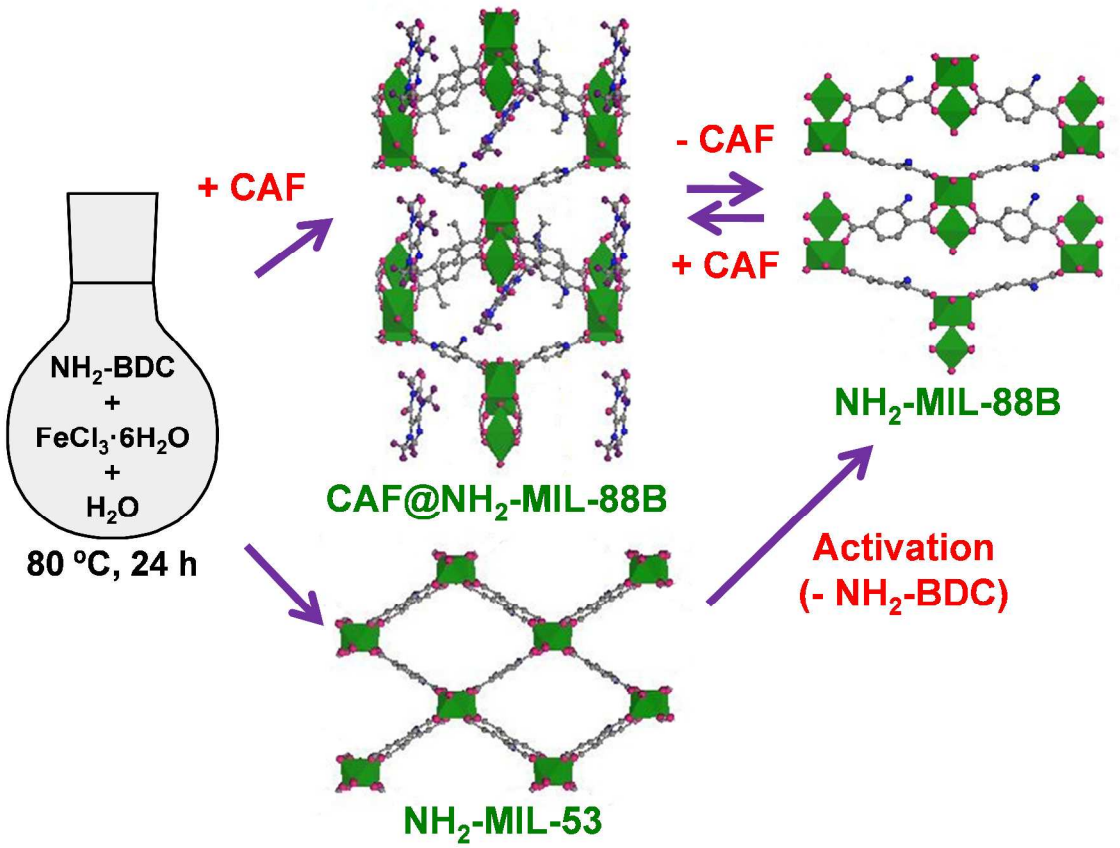


Figure 1. Relation between the samples prepared here. $NH_2$-BDC corresponds to 2-aminoterephthalic acid.

The $NH_2$-MIL-53(Fe) (0.5 g) was activated with ethanol (100 mL) at 80 ºC for 24 h. This activation process gave rise to $NH_2$-MIL-88B(Fe). Ex situ encapsulation of caffeine was carried out with this material as follows: 0.5 g of previously activated MOF was placed in a 100 mL aqueous solution of caffeine (10 g/L) at 80 ºC for several time periods (8 h, 24

h, 3 days and 7 days). Once centrifuged as described above, the sample obtained designated CAF@$NH_2$-MIL-88B(Fe)_EX was dried at 60 ºC overnight.

Both the CAF@$NH_2$-MIL-88B(Fe)_IN and EX gave rise to $NH_2$-MIL-88B(Fe) upon ethanol treatment at 80 ºC for 24 h, i.e. under the same conditions as used for the activation of $NH_2$-MIL-53(Fe). Figure 1 shows the relationship between the samples produced.

*Characterization*

The materials were analyzed by X-ray diffraction (XRD) using a D-Max Rigaku X-ray diffractometer with a copper anode and a graphite monochromator to select the $CuK_\alpha$ radiation ($\lambda$= 1.5418 Å). The step size was 0.03º in the 2.5-40º 2 theta range

The structure refinement of the different materials prepared was carried out from the X-ray diffraction patterns with 1250 experimental points each. Accelrys Materials Studio 4.3 software supplied by Accelrys® was used for the purpose. A combination of Rietveld[30] and Pawley[31] refinement methods was used for the optimum determination of the structures. Initially, Pawley refinement was performed until no improvement for the weighted profile factor (*Rwp*) was observed. The order for the parameter refinement was the following: first, base line; second, parameters related to peak shape with the Pseudo-Voigt for peak profile and Berar-Baldinozzi for asymmetry models. Then the lattice parameters were refined, and finally all the parameters were refined together. For the Rietveld refinement, all the occupancies were first refined, followed by peak shape parameters and lattice parameters. Finally, all the parameters were refined at the same time. The optimum structure was selected based on the minimum achieved *Rwp*. Caffeine was added to the model inside the pores, and its position was refined together with the peak profile and asymmetry parameters.

Thermodiffractometry was performed under vacuum with the CAF@$NH_2$-MIL-88B_IN sample in a furnace coupled with a D-Max Rigaku X-ray diffractometer with a copper anode and a graphite monochromator to select the $CuK_\alpha$ radiation. Each powder pattern was recorded in the 3-40º range (2θ) (at room temperature, 50, 100, 150, 200, 225, 250, 275 and 300 ºC) with a 2 s/step scan, corresponding to an approximate duration of 1 h for each pattern at the corresponding temperature. The temperature ramp between two patterns was 5 ºC/min.

Thermogravimetric analyses were performed using Mettler Toledo TGA/SDTA 851e equipment. Samples placed in 70 µL alumina pans were heated in a $N_2$ flow up to 750 °C with a heating rate of 10 °C/min.

The Fourier transformed infrared spectroscopy (FTIR) absorption spectra were acquired at room temperature with an Iraffinity Shimadzu spectrophotometer. Spectra of the samples corresponded to 30 scans at a resolution of 4 $cm^{-1}$, using the KBr pellet technique.

*Drug delivery and MOF degradation experiments*

Drug delivery experiments were performed in water and in PBS (phosphate-buffered saline) 0.01 M at pH 7.4. In the case of release in water, CAF@$NH_2$-MIL-88B(Fe)_IN or EX (10 mg) was stirred in suspension in a spherical flask with 100 mL of water. The experiment began at 37 ºC, to simulate the human body temperature. Once the release of caffeine was stabilized, the temperature was raised up to 60 $^oC$ and, when the caffeine concentration in water was again stable, the temperature was finally raised up to 80 ºC until complete caffeine release.

Release of caffeine in PBS media was carried out following the same procedure as that developed for water. CAF@$NH_2$-MIL-88B(Fe)_IN (10 mg) was placed in a spherical

flask with 100 mL of PBS 0.01 M at pH 7.4 under stirring. In this case the temperature was maintained at 37 ºC due to the fast release of the drug in PBS.

In both the water and PBS measurements, the abovementioned flask was connected to UV-VIS equipment (a V-670 Jasco UV-VIS spectrophotometer) by means of an accessory with a peristaltic sipper (Peristaltic Sipper NPF 721). Measurement parameters were set in the Time Course Measurement software (an accessory within the Spectra Manager Program): flow, suction, drain and wait times were established at 1.5, 1, 2, and 1 s, respectively. The measurements of absorbance at the wavelength of maximum caffeine absorption (272.5 nm) were taken every 5.5 h. When the release of 2-aminoterephthalic acid was followed, 360 nm in water and 330 nm in PBS were selected. Before starting the absorbance measurements, a blank measurement was made with deionized or PBS solutions under the same conditions as described above. Figure S1 shows typical UV-VIS spectra in water for caffeine, 2-aminoterephthalic acid and the liquid extract from CAF@$NH_2$-MIL-88B(Fe).

From caffeine and 2-aminoterephthalic acid absorbances, concentrations were calculated from calibration curves prepared with several caffeine-water or PBS solutions in the 0-30 mg/L concentration range. For 2-aminoterephthalic acid, two calibration curves were prepared, in water or PBS media, in the 0-14 mg/L concentration range.

The analysis of the 2-aminoterephthalic acid ligand allowed the MOF degradation during the caffeine release experiments to be assessed. For this purpose, the caffeine release experiments in water and in PBS were repeated in exactly the same way but following the wavelength absorbance corresponding to the 2-aminoterephthalic acid (360 nm in water and 330 nm in PBS). Also, MOF degradation without encapsulated caffeine was studied by following the 2-aminoterephthalic (330 nm) release in PBS at 37 ºC. $NH_2$-MIL-88B(Fe)

(10 mg) was placed in 100 mL of PBS 0.01 M at pH 7.4 under stirring until the complete dissolution of the MOF.

To verify the caffeine release values obtained by UV-VIS absorbance, GC-MS analyses were carried out with an Agilent 6850 gas chromatograph with a 5975C VL MSD mass spectrometric detector. Caffeine was separated by means of a HP-5MS capillary column, 30 m × 0.25 mm I.D. and with 0.25 μm phase thickness. The He carrier gas was set at a constant flow-rate of 1 mL(STP)/min, and 1 μL of the sample solution was injected with a 1:50 split ratio. Injector and detector temperatures were set at 250 and 280 °C, respectively. The GC oven was maintained at 120 °C for 2 min, ramped at 40 °C/min to 240 °C and held at this temperature for 2 min. The mass spectrometer was operated in the electron impact mode (EI, 70 eV) and m/z 194 ion was selected for monitoring. Caffeine was identified by direct comparison with the caffeine standard on the basis of the retention time and mass spectral ion ratios. Finally, 1 mL of the solution to be analyzed was 25 times diluted in ethanol.

## Results and discussion

As shown in Figure 1, caffeine behaves as a structure directing agent or template, since its presence allowed the synthesis of a different phase (CAF@$NH_2$-MIL-88B(Fe)) from that obtained in its absence ($NH_2$-MIL-53(Fe)). The one-step or in situ encapsulation of caffeine led to CAF@$NH_2$-MIL-88B(Fe)_IN, while the ex situ encapsulation of caffeine carried out in $NH_2$-MIL-88B(Fe), obtained upon activation of $NH_2$-MIL-53(Fe), led to CAF@$NH_2$-MIL-88B(Fe)_EX. Both CAF@$NH_2$-MIL-88B(Fe)_IN and EX materials were similarly studied in water and PBS release experiments, as will be discussed below.

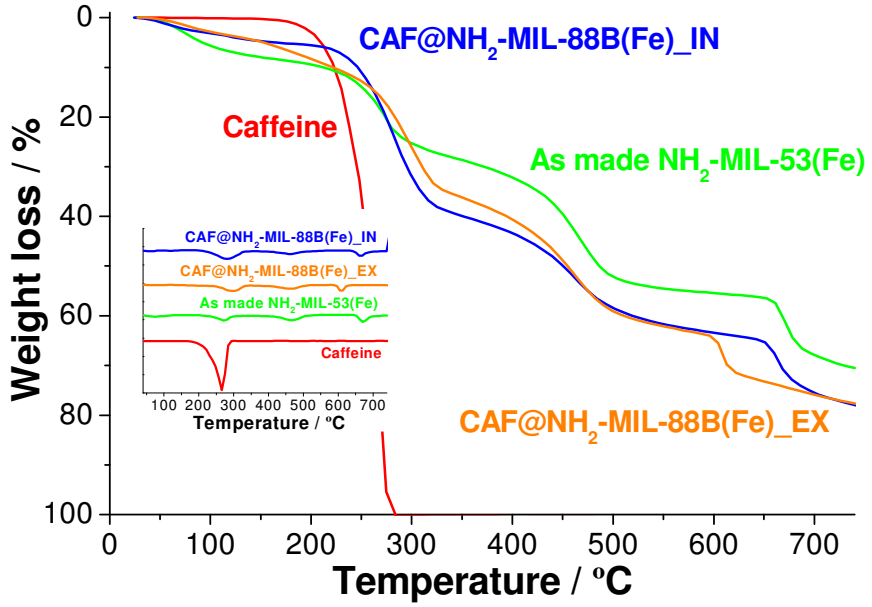


Figure 2. TGA curves (and corresponding derivatives shown in inset) of CAF@$NH_2$-MIL-88B(Fe)_IN, CAF@$NH_2$-MIL-88B(Fe)_EX, caffeine and $NH_2$-MIL-53(Fe).

Caffeine incorporation by the in situ and ex situ (24 h) methods was 38.5 ± 1.2 wt% and 27.7 ± 2.3 wt%, respectively, as determined from the average of TGA analyses carried out with 3 different samples of each (Figure 2). Caffeine weight loss took place for both CAF@$NH_2$-MIL-88B(Fe)_IN and EX materials in the 210-340 ºC range, as shown in Figure 2, i.e. the comparison with the TGA curve of the pure caffeine depicts a thermal enhancement of encapsulated caffeine. The TGA curve corresponding to $NH_2$-MIL-53(Fe) evidences that the organic linker 2-aminoterephthalic acid retained by this material was removed at a similar temperature as caffeine in CAF@$NH_2$-MIL-88B(Fe). This means that the weight loss attributed to caffeine in the sample CAF@$NH_2$-MIL-88B(Fe)_IN may be confused by the presence of the organic linker. The release experiments will clarify whether caffeine or a mixture of caffeine and linker was encapsulated in this sample. Finally, the ex

situ encapsulation was studied at time periods of 8 and 24 h and 3 and 7 days (Figure S2). It was demonstrated that, within the experimental error, no more caffeine was encapsulated after 8 h. In any event, 24 h of contact was used for the ex situ encapsulation.

In the presence of caffeine, swollen $NH_2$-MIL-88B(Fe) phase was directly obtained (CAF@$NH_2$-MIL-88B(Fe)_IN). It has been demonstrated that this MOF is the thermodynamically stable phase among the known Fe-containing $NH_2$-MIL-type crystalline structures.[32] However, the XRD patterns in Figure 3a indicate that the presence of caffeine considerably altered the crystalline structure of $NH_2$-MIL-88B(Fe) with respect to the diffractogram previously reported.[33] The new peak at 6.7 ºC suggests an important swelling effect induced in the MOF by the presence of caffeine, in accordance with the high flexibility of the $NH_2$-MIL-88B structure. Upon chemical extraction of caffeine in ethanol at 80 ºC for 24 h, a $NH_2$-MIL-88B framework was identified. Interestingly, when the synthesis was carried out in the same conditions but without caffeine, $NH_2$-MIL-53(Fe) was obtained, which in turn after an activation process (in the same conditions used to extract caffeine) produced $NH_2$-MIL-88B(Fe). This transformation has also been observed upon heating as-synthesized $NH_2$-MIL-53(Fe) in DMF at 160 °C for 3 days.[33] CAF@$NH_2$-MIL-88B(Fe)_EX presented a very similar diffractogram to CAF@$NH_2$-MIL-88B_IN, although it showed lower crystallinity because the peaks were less clear and defined than in the in situ sample.

An in situ temperature programmed XRD experiment was performed under vacuum atmosphere with sample CAF@$NH_2$-MIL-88B(Fe)_IN. Figure 3b shows that at room temperature, under vacuum, remaining solvent molecules started to be desorbed producing slight modifications in the diffractogram. Peaks at $2\theta$ = 6.7º and 8.6º began to disappear, while two new peaks appeared at $2\theta$ = 9.2º and 9.8º. As discussed in connection with the

TGA curves, caffeine removal started at approximately 200 ºC, so that at about 250 ºC the caffeine desorption was considered ended with a final diffractogram associated to $NH_2$-MIL-88B(Fe) (notice that the XRD patterns were taken after 1 h at each temperature, while the TGA curves correspond to continuous experiments at 10 ºC/min).[34] At temperatures above 250 ºC, the structure collapsed. The comparison of both Figures 2 and 3b suggests that the total removal of caffeine and the structure collapse are coincident phenomena. A last comment must be made about the peak at 12.4º in the case of both the CAF@$NH_2$-MIL-88B(Fe)_IN and EX samples (Figure 3a). This is a structural peak of the MOF, unrelated to caffeine (which has a peak at a similar angle), since it dramatically evolved at temperature values close to room temperature, below those needed to remove caffeine (Figure 3b).

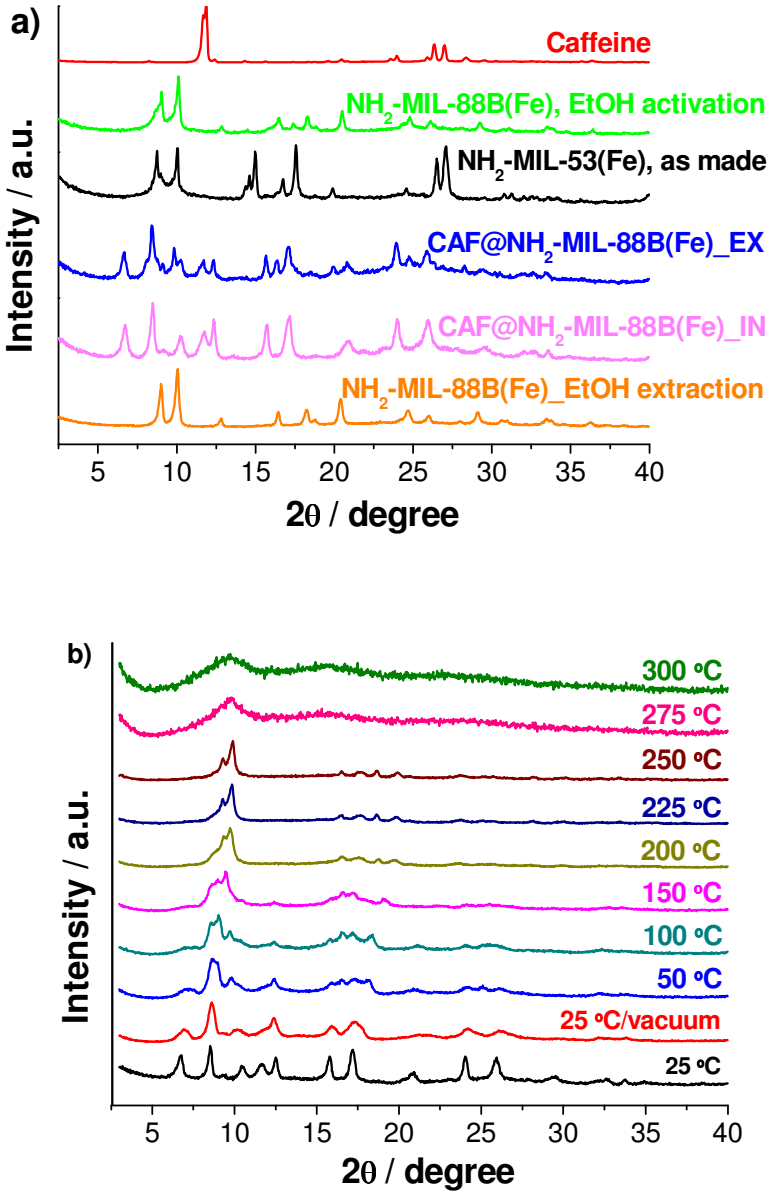


Figure 3. a) XRD patterns of CAF@$NH_2$-MIL-88B(Fe)_IN after ethanol extraction (i.e. $NH_2$-MIL-88B(Fe)), CAF@$NH_2$-MIL-88B(Fe)_IN, CAF@$NH_2$-MIL-88B(Fe)_EX, as made $NH_2$-MIL-53(Fe), $NH_2$-MIL-53(Fe) after ethanol activation (i.e. $NH_2$-MIL-88B(Fe)) and caffeine. b) X-ray thermodiffractograms of CAF@$NH_2$-MIL-88B(Fe)_IN in vacuum from temperatures of 25 ºC to 300 ºC.

Table 1. Parameters corresponding to the resolution of $NH_2$-MIL-53(Fe), CAF@$NH_2$-MIL-88B(Fe)_IN, $NH_2$-MIL-88B(Fe) obtained by ethanol extraction of CAF@$NH_2$-MIL-88B(Fe)_IN and $NH_2$-MIL-88B obtained by treatment at 250 ºC of CAF@$NH_2$-MIL-88B(Fe)_IN. Cif files corresponding to the three $NH_2$-MIL-88B(Fe) samples are available as supporting information.

| **Sample** | **$NH_2$-MIL-53(Fe)** | **CAF@$NH_2$-MIL-88B(Fe)** | **$NH_2$-MIL-88B(Fe) (by ethanol extraction)** | **$NH_2$-MIL-88B(Fe) (by 250 ºC treatment)** |
|---|---|---|---|---|
| **Empirical formula** | $Fe(OH)[(OOC)_2NH_2\text{-}C_6H_3]\cdot 0.3((HOOC)_2NH_2\text{-}C_6H_3)$ | $Fe_3O(OH_2)_3[(OOC)_2NH_2\text{-}C_6H_3]\cdot 2(CAF)$ | $Fe_3O(OH_2)_3[(OOC)_2NH_2\text{-}C_6H_3]$ | $Fe_3O(OH_2)_3[(OOC)_2NH_2\text{-}C_6H_3]$ |
| **Crystal system** | Body-centered orthorhombic | Triclinic | Hexagonal | Hexagonal |
| **Space group** | *IMMA* | *P1* | *P63/MMC* | *P63/MMC* |
| **a / b / c [Å]** | 6.938/17.49/12.23 | 14.89/15.27/16.92 | 11.08/11.08/19.28 | 10.38/10.38/19.14 |
| **α / β / γ [º]** | 90/90/90 | 90 /90/120 | 90/90/120 | 90/90/120 |
| **Volume [$Å^3$]** | 1450 | 3332 | 2050 | 1783 |
| **$R_{wp}$ [%]** | 10.2 | 9.6 | 8.6 | 8.6 |
| **$R_p$ [%]** | 6.3 | 7.5 | 6.5 | 6.7 |

To gain an insight into the different materials obtained, powder XRD patterns were analyzed by means of Materials Studio software (Table 1, Figure S3). As-made $NH_2$-MIL-53(Fe), CAF@$NH_2$-MIL-88B(Fe)_IN and two $NH_2$-MIL-88B(Fe) samples obtained after the removal of caffeine by ethanol extraction or thermal treatment at 250 ºC were submitted

to a Rietveld refinement, similarly to CAF@ZIF-8.[15] Cif files used as an initial estimation were taken from Bauer et al.[33] Rwp parameters for each adjustment were between 8.6% and 10.2%, considering them to be successful structural refinements.

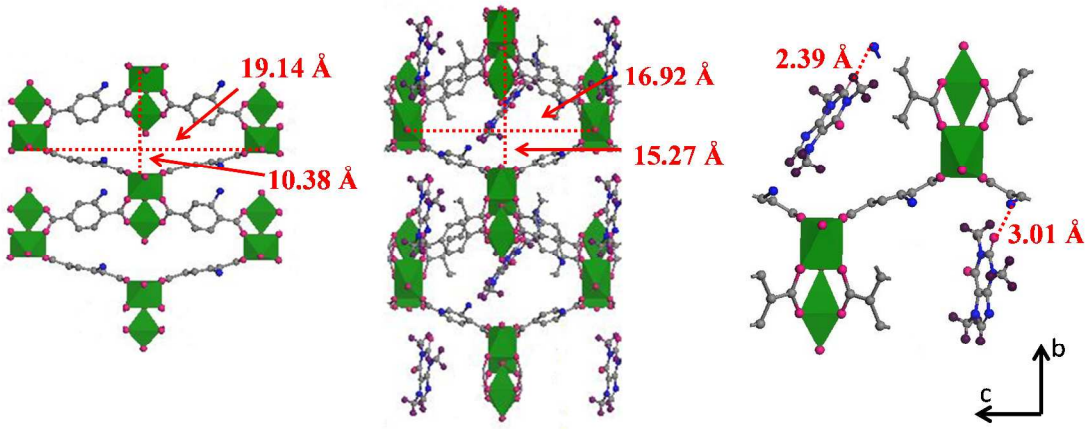


Figure 4. $NH_2$-MIL-88B(Fe) (left) and CAF@$NH_2$-MIL-88B(Fe)_IN (middle) structures along direction [100] and detail of caffeine-MOF interactions (right); gray, carbon; blue, nitrogen; red, oxygen; purple, hydrogen; green, $Fe_3O(OH_2)_3$ octahedron.

The cell volume cell increased in the MOF because of the presence of caffeine molecules in the structure from 1783 $Å^3$ for CAF@$NH_2$-MIL-88B_IN treated at 250 ºC to 3332 $Å^3$ for as-synthesized CAF@$NH_2$-MIL-88B_IN. This increase in the volume cell was attributed to two molecules of caffeine within the structure, where the theoretical value (33.4 wt%) was close to the TGA (38.5 ± 1.2 wt%) and UV-VIS (36.6 ± 0.9 wt%) estimations. Refinement studies showed a preferential caffeine site within the MOF structure. As confirmed below by FTIR, caffeine was oriented with carbonyl groups close to amino groups of the MOF, establishing hydrogen bonds (see Figure 4). When the caffeine was removed by ethanol extraction, the structure presented a higher volume (2050

Å$^3$) with respect to the 250 ºC sample. It is probable that traces of ethanol occupying the pores led to a more open structure than that without any guest in the pores. Thus, the $NH_2$-MIL-88B(Fe) treated at 250 ºC corresponded to its completely closed form. For this reason the structural parameters *a* and *b* showed the lowest values (10.38 Å with a cell volume of 1783 Å$^3$). In contrast, CAF@$NH_2$-MIL-88B(Fe) showed the highest *a* and *b* values (14.89 and 15.27 Å, respectively, with a cell volume of 3332 Å$^3$) in agreement with a very open structure in the presence of caffeine.

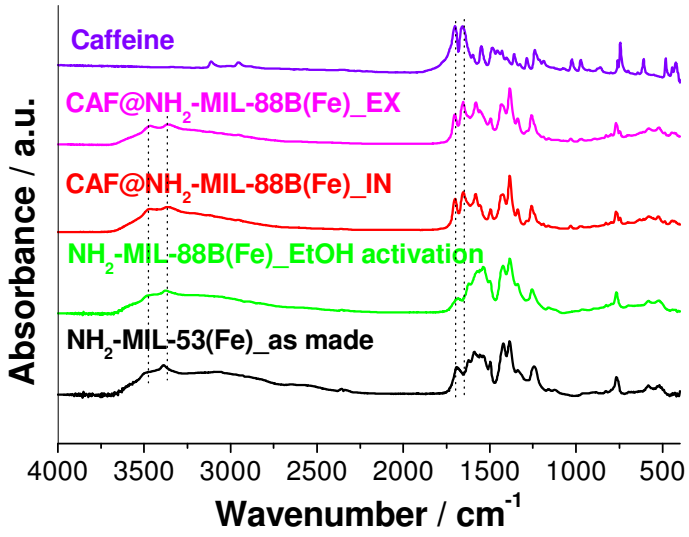


Figure 5. FTIR spectra of as-made $NH_2$-MIL-53(Fe), activated $NH_2$-MIL-53(Fe) (i.e. $NH_2$-MIL-88B(Fe)), CAF@$NH_2$-MIL-88B(Fe)_IN, CAF@$NH_2$-MIL-88B(Fe)_EX and caffeine.

Caffeine was identified by means of FTIR (Figure 5) by the two main bands belonging to carbonyl (C=O) vibrations at 1660 and 1705 cm$^{-1}$.[35] The peak at 1669 cm$^{-1}$ attributed to molecules of free BDC acid encapsulated within the pores of the structure in their protonated form (-$CO_2H$)[36] did not overlap with the caffeine carbonyl bands. Slight

shifts in carbonyl groups from 1660 and 1705 $cm^{-1}$ for caffeine to 1649 and 1699 $cm^{-1}$ for the CAF@$NH_2$-MIL-88B(Fe)_IN and EX samples were detected, as has been observed in the encapsulation of caffeine in other MOFs.[15] The main peaks corresponding to amino N-H bonding were recognized by an absorbance doublet corresponding to symmetric and asymmetric stretching vibrations at around 3390 and 3525 $cm^{-1}$,[32] and wavenumber shifts were appreciated for samples CAF@$NH_2$-MIL-88B(Fe)_EX and IN up to 3360 and 3471 $cm^{-1}$. As demonstrated by the structure refinement of CAF@$NH_2$-MIL-88B(Fe)_IN, caffeine was oriented preferably to the -$NH_2$ groups of the MOF.

The release of caffeine from $NH_2$-CAF@MIL-88B(Fe)_IN was studied as a function of time in both water and PBS media. The water release study was initially made at 37 ºC (Figure 6a). After 3.5 days, a plateau was reached at 19.5 ± 1.1 wt% of caffeine released. This value was too far from the value of caffeine encapsulated estimated by TGA 38.5 ± 1.2 wt% for this sample. Thus, in order to force the caffeine release, the temperature was increased up to 60 ºC and the caffeine release reached a new steady state value in 7.4 days with 26.9 ± 1.2 wt% released. The temperature was increased once more up to 80 ºC with a cumulative caffeine release of 35.2 ± 1.5 wt%, roughly in agreement with the above mentioned TGA value. The discrepancies could be related to a certain amount of linker encapsulated in the MOF synthesis, since the TGA weight losses for caffeine and BDC occurred in a similar temperature range. In summary, we have shown that temperature acted as a kind of activator system for caffeine release, so that the cumulative normalized release of caffeine was 55, 75 and 100% after 37, 60 and 80 ºC, respectively. This control-staggered drug delivery with temperature in water can be attributed to the very strong caffeine-MOF interaction. Similarly, even though the release was carried out at constant

temperature, MIL-53(Fe) and MIL-53(Cr) with encapsulated ibuprofen[37] showed a discontinuous pattern of release.

Simultaneously to the caffeine release, the MOF decomposition was studied by monitoring the time evolution of the organic linker BDC (Figure 6a). It can be seen that the decomposition of the MOF became significant at 80 ºC where the organic linker amount was higher. It can be inferred that in the most dramatic conditions (80 ºC) the caffeine release began to be governed by the MOF degradation, while at 37 ºC or even at 60 ºC caffeine release was considered a diffusion controlled process. At the end of the experiment, a total amount of 19.6 ± 0.8 wt% of BDC was released.

When PBS media was used instead of deionized water for the release experiments, most of the caffeine (36.6 ± 0.9 wt%) was already released at 37 ºC after 2.5 days (Figure 6b), accompanied by an important simultaneous release of BDC (41.2 ± 0.7 wt%). In PBS media, as has been demonstrated for other frameworks,[37] the dissolution of the MOF (phosphates may compete for the metal sites in the MOFs[11]) contributed to the caffeine release from CAF@$NH_2$-MIL-88B(Fe)_IN more than the diffusion process itself, even though the MOF was not completely dissolved. A further insight into the stability of the MOF in PBS at 37 ºC was obtained following the release of BDC from activated (i.e. with no caffeine) $NH_2$-MIL-88B8(Fe). The appropriate comparison (Figure 7) showed a much slower degradation for CAF@$NH_2$-MIL-88B(Fe)_IN, as if the caffeine-MOF interactions contributed to the MOF stability. In fact, while CAF@$NH_2$-MIL-88B(Fe)_IN released 36.6 ± 0.9 wt% of BDC in 2.5 days, $NH_2$-MIL-88B(Fe) released 53.1 wt% of BDC in 0.7 days, which signifies, within the experimental error of the determination, the whole dissolution of the material, according to the empirical formula in Table 1, leaving behind a transparent solution.

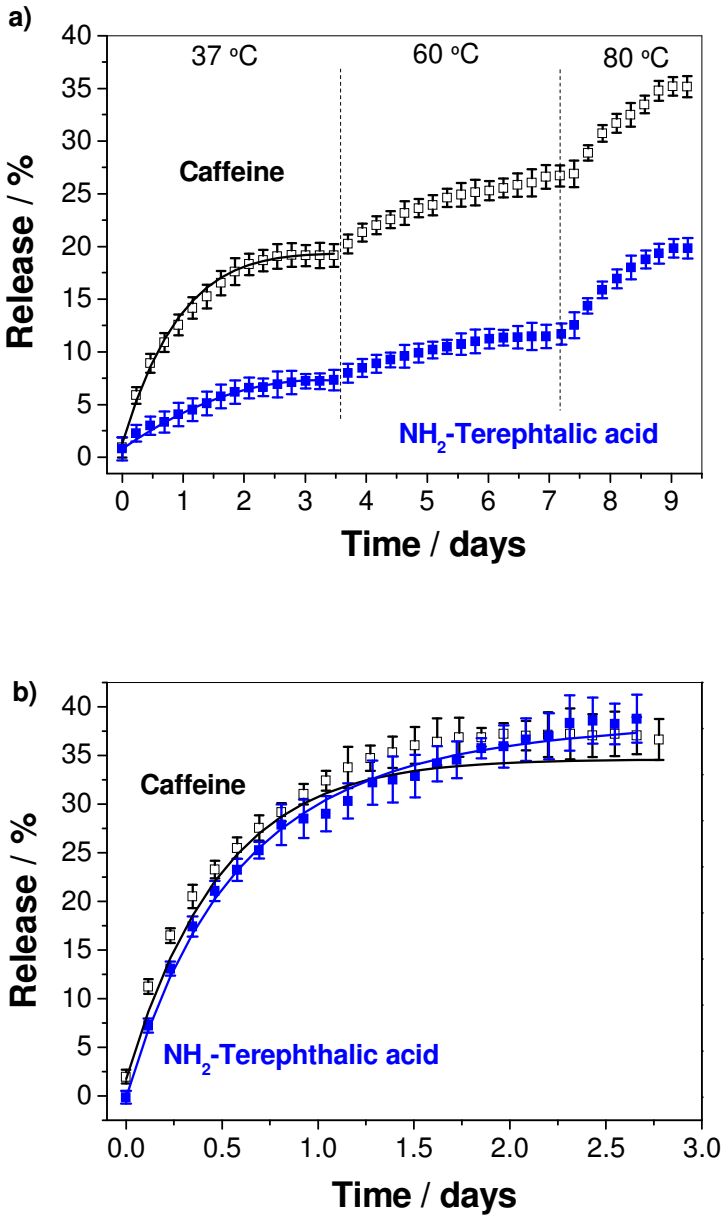


Figure 6. a) Caffeine and 2-aminoterephthalic acid release determined by UV-VIS absorption from CAF@$NH_2$-MIL-88B(Fe) in water at 37, 60 and 80 ºC. b) The same in PBS at 37 ºC. The release was related to the sum of the total amount of dry solid, excluding remaining solvent, i.e. TGA weight loss below 150 ºC, and including encapsulated caffeine.

Caffeine release in water for sample CAF@$NH_2$-MIL-88B(Fe)_EX was 11.3 ± 0.9 wt% at the beginning of the experiment, while CAF@$NH_2$-MIL-88B(Fe)_IN only released 0.9 ± 0.2 wt% of caffeine (Figure S4). In addition, most of the caffeine encapsulated in CAF@$NH_2$-MIL-88B(Fe)_EX was released at 37 ºC (19.2 ± 1.1 wt%), and only a little, 5.4 wt%, was released in the 60 and 80 ºC stages. Total amounts of drug for in situ and ex situ encapsulations as determined by UV-VIS were 35.2 ± 1.5 wt% and 25.2 ± 2.2 wt%, respectively. This means that the one pot, in situ methodology, besides being more simple (only one preparation stage as compared to the traditional synthesis-activation-encapsulation formula), is more efficient than the ex situ methodology.

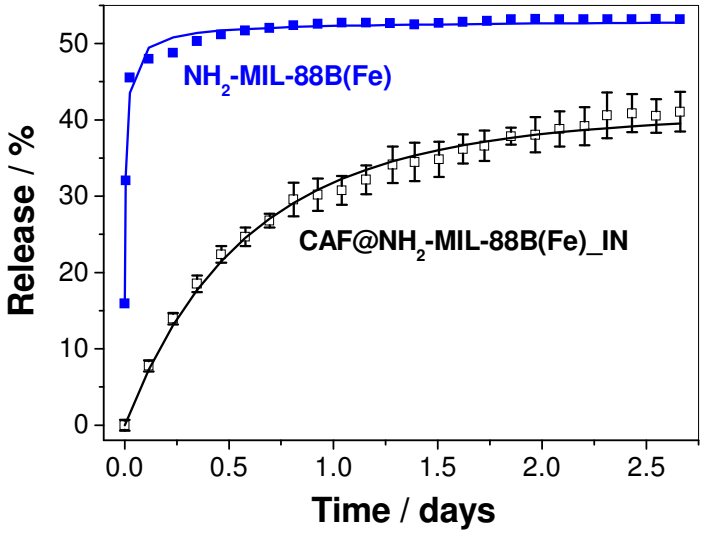


Figure 7. 2-Aminoterephthalic acid release experiments in PBS at 37 ºC determined by UV-VIS absorption from CAF@$NH_2$-MIL-88B(Fe)_IN and $NH_2$-MIL-88B(Fe). The release was related to the sum of the total amount of dry solid, excluding remaining solvent, i.e. TGA weight loss below 150 ºC, and including encapsulated caffeine.

Table 2. Summary of caffeine determinations by TGA, UV-VIS and GC-MS (at 80 ºC in water) and UV-VIS (at 37 ºC in PBS).

| Method | CAF@$NH_2$-MIL-88B(Fe)_IN | CAF@$NH_2$-MIL-88B(Fe)_EX[a] |
|---|---|---|
| TGA | 38.5 ± 1.2 wt% | 27.7 ± 2.3 wt% |
| UV-VIS (water) | 35.2 ± 1.5 wt% | 25.2 ± 2.2 wt% |
| GC-MS (water) | 34.5 wt% | 27.0 wt% |
| UV-VIS (PBS) | 36.6 ± 0.9 wt% | - |

[a]Ex situ encapsulation for 24 h.

To confirm the reliability of caffeine determination made by UV-VIS and by TGA (even though, as mentioned above, a small amount of BDC linker may be confused with caffeine due to their similar removal temperatures), some of the liquid samples coming from the delivery experiments made in water were analyzed by GC-MS. Caffeine contents in CAF@$NH_2$-MIL-88B(Fe)_IN (34.5 wt%) and in CAF@$NH_2$-MIL-88B(Fe)_EX (27.0 wt%) as determined by GC-MS were very similar to those obtained by UV-VIS and TGA - see Table 2 for a summary. In addition, the errors in Figures S4, 6, and 7 were generated from the repetition of the delivery experiments of two different samples of both CAF@$NH_2$-MIL-88B(Fe)_IN and EX materials, evidencing good reproducibility. This parallel checking of the MOF capability favoring the one step or in situ methodology over the traditional synthesis-activation-encapsulation process also suggests that our approach is strong and consistent. If fact, the one step milder conditions (80 ºC) using water as solvent were similar to those used here for the ex situ encapsulation, as described in the

experimental section. We cannot claim general applicability for our methodology, but the conditions applied seem to be resistible by many drugs or additives for other applications of interest. Furthermore, it would seem logical that a process in a single step was easy to scale-up than another three-stage. Thus we believe that this strategy of encapsulation could be applied to other molecules different from caffeine.

## CONCLUSIONS

We have succeeded in the one-step encapsulation of caffeine in $NH_2$-MIL-88B(Fe) by demonstrating high guest loading (ca. 35 wt%) and controlled release. The presence of caffeine (CAF@$NH_2$-MIL-88B(Fe)) produced an important disturbance and swelling in the MOF structure, as demonstrated by the structural determination from powder XRD data. Cell volume increased from 1783-2050 $Å^3$ for empty $NH_2$-MIL-88B(Fe) structures to 3332 $Å^3$ for CAF@$NH_2$-MIL-88B(Fe).

Caffeine release from CAF@$NH_2$-MIL-88B(Fe) reached a constant value after about 3 days in water at 37 ºC, so that the complete release of the drug was only produced by successive working stages at 60 and 80 ºC. The temperature acted as a kind of activator. When the release was performed in PBS, all the caffeine was released in about 2 days at 37 ºC, this being due to the simultaneous degradation of the MOF, as inferred from the direct observation of the MOF ligand release to the liquid medium.

When the synthesis of the MOF was carried out in the absence of caffeine, a $NH_2$-MIL-53(Fe) framework was obtained. In consequence, it can be said that caffeine played the role of structure directing agent or template. A second role of caffeine relates to its contribution to the liquid phase stability of the MOF, as demonstrated through the slower

release of the structural ligand from CAF@$NH_2$-MIL-88B(Fe) than from $NH_2$-MIL-88B(Fe).

Finally, even though the general applicability of the one step or in situ encapsulation was not demonstrated, this approach has clear advantages as compared to the traditional synthesis-activation-encapsulation method. Many MOFs can be synthesized in milder conditions using solvents as water, methanol or water-methanol mixtures. These conditions would be acceptable to preserve the chemical properties of certain guest molecules of interest. Thus excess reactants would be reused giving rise to a simple and scalable process.

## ACKNOWLEDGMENT

Financial support from the Spanish Ministry of Economy and Competitiveness (MAT2010-15870, IPT-2011-0878-420000), the Aragón Government and ESF and Nurel SA (Samca Group) is gratefully acknowledged.

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