Hybrid Materials

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Metal–Organic Frameworks as Efficient Materials for Drug Delivery**

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Great effort is currently being devoted to the development of methods to control drug release to satisfy the ever-growing demand for prolonged and better control of drug administration. Up until now, two routes have been set up: the "organic route", which uses either biocompatible dendritic macromolecules or polymers[1] and the "inorganic route", in which the hosts are inorganic porous solids, such as zeolites[2] or mesoporous silicate materials.[3] In the first case, a wide range of drugs can be encapsulated but a controlled release is difficult to achieve in the absence of a well-defined porosity.[1] In the second case, this release is performed by grafting organic molecules on the pore walls but implies a decrease in the drug-loading capacity.[4,5] Herein, we introduce a third way: the "hybrid" route. Indeed, a combination of high and regular porosity with the presence of organic groups within

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the framework may cumulate the advantages to achieve both a high drug loading and a controlled release. Hybrid inorganic–organic solids with large pores exhibit such characteristics and could represent a valuable alternative in such purposes.

Porous hybrid inorganic–organic solids are indeed very important solids because of their potential applications in gas storage,[6] adsorption, separation,[7] or catalysis.[8] Unfortunately, most of them are microporous (pore diameter < 2 nm), and the small size of their cavities restricts the choice of incorporated species, induces low diffusion rates, and prevents an efficient and controlled drug delivery. To overcome this major problem, we recently developed a method that combines targeted chemistry and structural computer predictions to obtain mesoporous hybrids with large pores. This approach leads to the characterization of two new cubic (*Fd3m)* zeotypic metal carboxylates, denoted MIL-100 and MIL-101 (MIL = Materials of Institut Lavoisier) and built up from trimers of metal octahedra and di- or tricarboxylic acids.[9] The formula of these acids are: $M^{III}_3OX(H_2O)_2L_n$, $p\,H_2O$ (M^{III} = Cr, X = F, OH) where L = 1,3,5-benzene tricarboxylic acid (BTC) or trimesic acid and $n = 2$ for MIL-100 or L = 1,4-benzenedicarboxylic acid (BDC) or terephthalic acid and $n = 3$ for MIL-101 (Figure 1). They are initially hydrated and exhibit giant pores (∅: 25–34 Å) and unprecedented surface areas (3100–5900 $m^2 g^{-1}$) without any loss of crystallinity after water evacuation. Herein, we describe the study of the adsorption and delivery of an model analgesic and anti-inflammatory drug, Ibuprofen, by MIL-100 and MIL-101. Although the toxicity of chromium compounds is well known,[10] their excellent crystallinity allows a better structural control of the insertion, thus illustrating their use as delivery systems.

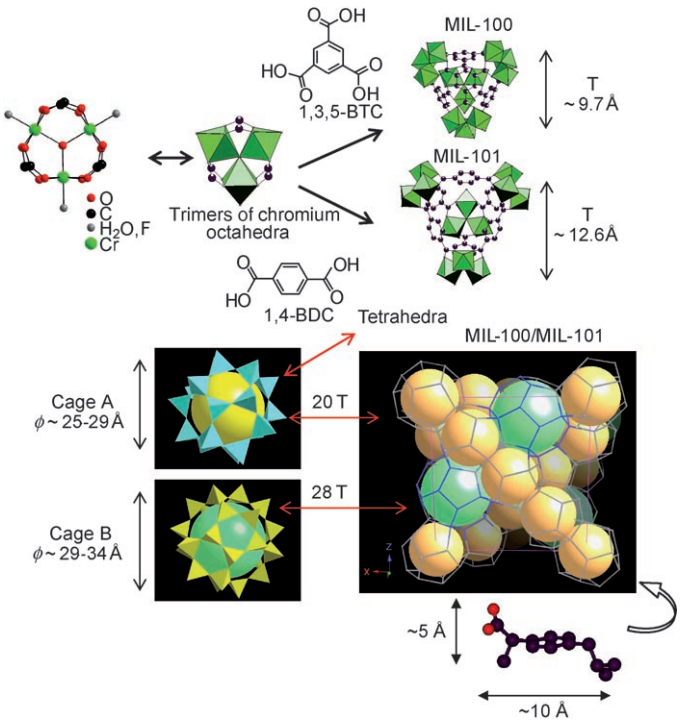

Figure 1. Top: Schematic 3D representation of the tetrahedra (T) built up from trimers of chromium octahedra and 1,4-benzenedicarboxylate moieties or 1,3,5-benzenetricarboxylate groups in MIL-101 and MIL-100, respectively. Bottom: Schematic 3D representation of the mobil-39 (MTN) zeotype architecture of MIL-100 and MIL-101; left: the smaller A cages (yellow spheres with 20 T) and larger B cages (green spheres with 28 T); right: a unit cell (lines connect the T centers).

Ibuprofen was adsorbed by the dehydrated powdered materials from a solution in hexane, and the amount adsorbed was determined by thermogravimetric analysis, UV/Vis spectroscopy, elemental analysis, and X-ray fluorescence; the presence of Ibuprofen was also confirmed by IR spectroscopy. The influence of material dehydration, ratio of Ibuprofen/material, immersion time, and the number of consecutive impregnations on the amount of adsorbed drug was studied (see the Supporting Information).

X-Ray powder diffraction performed on both materials proved that their structures are retained after the drug adsorption. Moreover, N_2 adsorption after the incorporation indicates almost no residual porosity. Therefore, the drug completely fills the pores and/or blocks the windows of the cages, thus leaving approximately no accessible pore volume for nitrogen.

The MIL-100 and MIL-101 materials showed remarkable Ibuprofen adsorption (Table 1). However, both materials, which contain different organic components (BTC in MIL-100 and BDC in MIL-101; Figure 1), adsorb drastically different amounts of Ibuprofen as a result of their different pore sizes. On one hand, the MIL-100 matrix has smaller cages (∅: 25 and 29 Å) than MIL-101 despite relatively large pore volumes (8200 and 12700 $Å^3$) and adsorbs 0.35 g of Ibuprofen/gram of dehydrated MIL-100. On the other hand, MIL-101 with its larger cage sizes (∅: 29 and 34 Å; pore volumes: 12700 and 20600 $Å^3$) shows an unprecedented amount of adsorbed drug, larger than the initial matrix weight (≈ 1.4 grams of Ibuprofen/gram of dehydrated MIL-101). These findings are very important as only very small amounts of material are required for the administration of high dosages. Structural reasons may explain this discrepancy, particularly the dimensions of the windows of the cages relative to those of Ibuprofen. It must be recalled that both solids, built up from large tetrahedra (T; Figure 1), delimit two types of spherical cages. The smaller (A; 16 in the cubic cell), which is limited by 20 T, exhibits exclusively pentagonal windows with a free aperture 4.8×5.8 Å (MIL-100) and 12 Å (MIL-101). The

Table 1: Nitrogen adsorption data and the Ibuprofen content of the materials investigated.

		MIL-100	MIL-101
Starting materials	$S_{langmuir}$ [$m^2 g^{-1}$]	3340	5510
	$V_{meso\text{-}micropore}$ [$cm^3 g^{-1}$]	1.16	2.02
IBU/materials	$S_{langmuir}$ [$m^2 g^{-1}$]	30	6
	$V_{meso\text{-}micropore}$ [$cm^3 g^{-1}$]	0.03	0.02
g IBU/g dehydrated material		0.347	1.376
Kinetic constant		22.9 ± 2	13.0 ± 1
		$[IBU] = Kt$	$[IBU] = Kt^{1/2}$

larger (B; 8 in the cell) with 28 T also possesses hexagonal windows together with the pentagonal ones. The large apertures of the former (8.6 Å and 14.7 × 16 Å for MIL-100 and MIL-101, respectively) allow easy introduction of Ibuprofen, whereas the small dimensions of the pentagonal windows of MIL-100 (close to the Ibuprofen size) are too limited for a valuable introduction of the guest in MIL-100. In other terms, the drastic difference in adsorption between MIL-100 and MIL-101 can be explained by a selective occupation of the larger cages in MIL-100, whereas all the cages are occupied in MIL-101. According to the weight increase, one can estimate that each "small" cage of MIL-101 hosts approximately 56 Ibuprofen molecules and the large cage approximately 92 molecules. This behavior illustrates three facts: 1) the ever-growing need for very large pores, as already claimed by one of us;[11] 2) the hierarchy of mesopores when tunable can act as an internal molecular sieve for a given guest of important dimensions with a selective occupation of the cages—the empty cages remain able to host a different species; and 3) such matrices may provide tools for the study of nanoassemblies of organic compounds and help the development of nano-organic chemistry.

In a second step, solid-state ^{1}H and ^{13}C NMR experiments were performed on Ibuprofen and the anhydrous MIL-100/IBU and MIL-10/IBU (Figure 2). The ^{1}H NMR spectra of

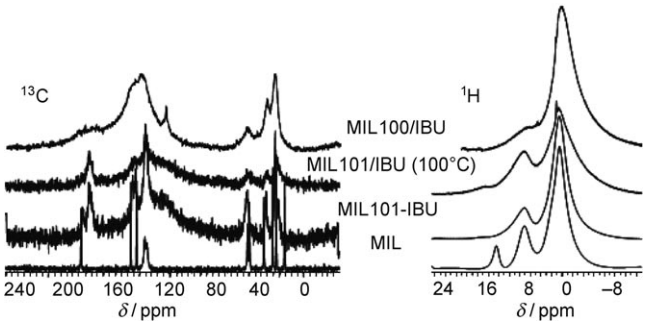

Figure 2. ^{13}C and ^{1}H NMR spectra of Ibuprofen (IBU) and MIL-100 and MIL-101 after the adsorption of Ibuprofen.

Ibuprofen show that it is protonated, whereas ^{13}C NMR data give the expected information on the different sites. A different behavior is observed for MIL-100/IBU and MIL-101/IBU: whereas two contributions were expected from ^{13}C NMR data at approximately $\delta = 175$ and 120 ppm (carboxylic and C–H groups, respectively), only the latter exists. The tight bonding of the carboxylic carbon atom to the chromium centers allows paramagnetic relaxation of this carbon atom, which explains the absence of the a contribution at $\delta = 175$ ppm.

The ^{1}H NMR spectra after insertion shows that the signal at about $\delta = 14$ ppm, which is characteristic of the protonation of Ibuprofen, disappears. Correlatively, the ^{13}C NMR spectra indicate that the CH_3 group on the α-carbon atom of the carboxylic acid is also strongly shifted upon insertion. Both observations are in agreement with the deprotonation of the carboxylic acid group. This result is important as it is indeed a common practice in medicine formulations to prepare the active pharmaceutical ingredient (API) as a salt for better bioavailability.

Other striking aspects of the ^{13}C NMR spectra must be mentioned: Although the signal at $\delta = 175$ ppm from the organic linker from the framework reappears, the signals seen in the spectra of Ibuprofen are indicative of some conformational distribution, at variance with the well-defined crystalline order observed in its pure crystal.

As Ibuprofen is being inserted as an anion, several situations may occur to justify the observed changes: 1) the proton may be fixed on the terminal water molecules of the chromium trimeric units and ensure the interaction with anionic Ibuprofen; 2) the latter could to some extent form a complex with the chromium center, thus replacing the bound terminal water molecules as a result of the Lewis acidic character of these sites;[12] or 3) be strongly located close to a proton in the framework. Finally, the broadening of Ibuprofen signals is consistent with the distribution of the interaction types.

MIL-101 and MIL-100 were compacted as cylindrical pieces to study the kinetics of Ibuprofen delivery. The compacting pressures did not affect the integrity of the structure.

Figure 3 displays the kinetics of Ibuprofen delivery to simulated body fluid (SBF)[13] at 37 °C and with continuous stirring. The delivered Ibuprofen concentration was determined by HPLC. In the Ibuprofen delivery from MIL-100 and MIL-101, three stages related to the drug location within the cages can be distinguished. For each type of cage, two situations occur for the guests: when they are close to the walls, the host–guest interaction is governed both by anion–cation electrostatic interactions and π–π interactions between the aromatic rings of Ibuprofen and the organic part of the skeleton, and are therefore dependent on the size of the cage. Once these interactions are fulfilled, the additional Ibuprofen molecules occupy the leaving space of the cavity, with just Ibuprofen–Ibuprofen interactions. This behavior results in three different regimes during the delivery. The initial release of Ibuprofen concerns only the weakly bonded molecules. The kinetics of Ibuprofen delivery for MIL-100 in the first 2 hours are empirically adjusted with regression factors of > 0.99 to zero-order kinetics ($[IBU] = Kt$; Table 1), drug-concentration independent, and characteristic of pharmaceutical forms that do not disaggregate.[14] The complete release of Ibuprofen is

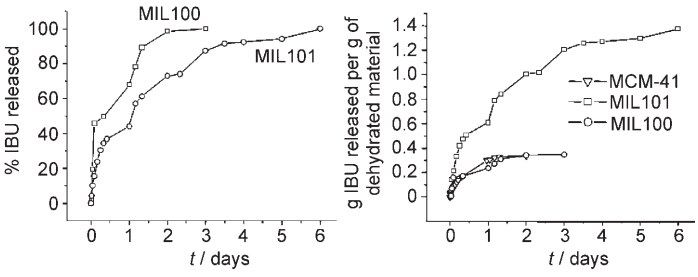

Figure 3. Left: Ibuprofen delivery (% IBU vs *t*) from MIL-101 and MIL-100. Right: Ibuprofen delivery (mg IBU/g dehydrated material vs *t*) from MIL-101 and MIL-100 in comparison with MCM-41.

achieved only after 3 days of assays in vitro, thus illustrating the difference in strength of the two types of interactions.

Ibuprofen delivery for MIL-101 in the first stage (8 h) is mainly governed by a diffusion process, which can be predicted by the Higuchi model ($[IBU] = Kt^{1/2}$; Table 1). Considering that the external diffusion process is avoided by constant agitation during the assays, the diffusion process is only due to the drug movements through the windows of the cages. Besides, because of the very high drug content of MIL-101, the concentration of Ibuprofen in the physiological fluid entering the pores is close to saturation; thus, the delivery rate is limited by the dissolution and diffusion process. In this way, Higuchi[14,15] proposed the following equation for the case in which the drug is dissolved in a saturated solution dispersed in a porous matrix:

$$[IBU] = \sqrt{2\,C_0\,\varepsilon\frac{K\,t}{\tau\pi}}$$

where [IBU] is the amount of drug released in time t by surface unity, C_0 is the saturated solution concentration, ε is the matrix porosity, τ is the tortuosity factor of the capillary system, and K the diffusion constant of the drug molecules in the medium. The ε value was determined from the N_2 adsorption as the accessible surface to the solvent and the τ value was calculated as the relation between the dimensions of bigger and smaller windows when considering both values as constants and including them in the K constant.

Then, the final drug fraction, probably located close to the cage walls, is delivered more slowly as a consequence of the pore diameter and cation–anion and π–π interactions. Therefore, taking into account the difference in window size of the larger and smaller cages, Ibuprofen placed close to the walls of larger cages would be preponderantly released before those hosted into the smaller cages, thus explaining the last two steps of the delivery. Anyhow, the release concerns the anionic form of Ibuprofen, but it might correspond to its exchange and the anions from the SBF.

It took 6 days to the complete drug release with MIL-101, which may be due to the higher proportion of aromatic rings (Ar) in MIL-101 (Ar/Cr = 1.0 [MIL-101]; Ar/Cr = 0.66 [MIL-100]), which increases the number of interactions between the Ibuprofen and the pore surface of MIL-101. Besides, considering the number of metallic centers per formula unit, with only two Lewis acid sites per trimer (the third site is occupied by an OH or F group), one can estimate that approximately 40% of Ibuprofen is bound to the metal sites, in agreement with the slower delivery of approximately 60% of the drug in the two last steps.

Despite being interesting, the performances of the two first hybrid solids for drug delivery must be compared to those of similar materials with comparable cage sizes. MCM-41,[4] with a pore diameter of 36 Å, was chosen for this purpose. MCM-41 and MIL-100 materials showed very similar Ibuprofen dosage and kinetics. Interestingly, the drug content of MIL-101 is four times larger than in MCM-41 and the delivery rate becomes slower, thus taking 6 days for MIL-101 relative to 2 days for MCM-41. Thus, MIL-101 allows a higher dosage of drug and a longer controlled delivery, which supposes advantages for larger pharmacological molecules.

Herein, we have exposed for the first time the remarkable capacity for drug hosting and controlled delivery of porous metal–organic frameworks. One could criticize the fact that this study is based on chromium materials, well known for their toxicity; nevertheless, homologous nontoxic iron carboxylates (rat oral dose: $DL_{50}(Fe) = 30$ g kg, DL_{50}(trimesic acid) = 8.4 g kg, DL_{50}(terephthalic acid) = 5 g kg)[16] exist now in the laboratory as well as several porous hybrid iron(III)-based solids that were reported recently[17] and are being tested to obtain controlled delivery systems. Finally, it is of worth to note the enormous possibilities for the design of new hybrid materials, thus altering compositional modifications and creating new topologies[1] adapted to the structure of the drugs and their dosage requirements. In a more general way, this study provides the first elucidation of the interaction between the active ingredient and its excipient that can be designed by using the carboxylic acid group of the ingredient in a porous metal carboxylate. Knowing that about 80% of the APIs have a carboxylic acid group in their formula, a considerable basis for such a strategy has been created.

Experimental Section

The Supporting Information provides full details of the synthetic methods, Ibuprofen adsorption, and delivery assays, together with the optimization study of Ibuprofen incorporation; determination of the Ibuprofen content by thermogravimetric analysis (TGA), UV/Vis spectroscopy, elemental analysis, and X-ray fluorescence (XRF); and X-ray powder diffraction, N_2 adsorption porosimetric, HPLC, IR spectroscopic, and ^1H and ^{13}C NMR spectroscopic analysis.

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