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Metal-organic frameworks as stationary phases for chromatography and solid phase extraction: A review

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List of acronyms

ACN – Acetonitrile

mAU – milli-Absorbance units

BET – Brunner-Emmett-Teller

BDA – 2,2'-Dihydroxy-1,1'-binaphthalene-6,6'-dicarboxylic acid

BDC – 1,4-Benzenedicarboxylic acid

BPA – Bisphenol A

BTC – Benzene-1,3,5-tricarboxylic acid

+Cam-S – (*IS*)-(+)-10-Camphorsulfonyl chloride

d-Cam – *d*-Camphorate

CLA – Chloroaniline

CLM – Crosslinking molecule

CUS – Coordinately unsaturated sites

DHM – Dichloromethane

DPHM – Dipentaerythritol hexakis(3-mercaptopropionate)

EDCs – Endocrine disrupting chemicals

EB – Ethylbenzene

Ee – Enantiomeric excess

R-Epo – (*R*)-1,2-Epoxyethylbenzene

EtOH – Ethanol

FAAS – Flame atomic absorption spectrometry

GC – Gas chromatography

HDDMA – 1,6-Hexanediol dimethacrylate

HILIC – Hydrophilic interaction liquid chromatography

L-His – *L*-Histidine

HKUST – Hong Kong University of Science and Technology

HLB – Hydrophilic-Lipophilic Balance

HPLC – High performance liquid chromatography

MeOH – Methanol

MIL – Materials Institute Lavoisier

MOF – Metal-organic framework
MP – Microparticle
MSPE – Magnetic solid-phase extraction
NP – Nanoparticle
OPP – Organophosphorus pesticides
PAA – Phenoxyacetic acid
PAH – Polycyclic aromatic hydrocarbons
PANI – Polyaniline
PEG – Polyethylene glycol
PES – Polyestersulfone
PET - Polyethylene terephthalate
PDMS – Polydimethyl siloxane
PLOT – Porous layer open tubular
POP – *p*-(*tert*-Octyl)phenol
L-Pro – *L*-Proline
PTM – Pentaerythritol tetrakis(3-mercaptopropionate)
RSD – Relative standard deviation
S-2-Ppa – (*S*)-2-Phenylpropionic acid
i-PrOH – *i*-Propanol
SBSE – Stir-bar sorptive extraction
SMA – Stearyl methacrylate
SP – Stationary phase
SPE – Solid-phase extraction
SPME – Solid-phase microextraction
L-Ta – (+)-Diacetyl-*L*-tartaric anhydride
TPA – Terephthalic acid
UV – Ultraviolet
mV – milliVolt
ZIF – Zeolite imidazolate frameworks

Abstract

Analytical chemistry is involved in many areas of human activities for the separation of complex mixtures. One of the most common and popular technique is chromatography, which is based on different affinities of the compounds with the mobile and stationary phases. However, with the progress of chemical industry, modern stationary phases are not always able to solve the upcoming tasks. Thus, there is a demand in the development of new materials possessing advantages over commercial ones. Porous hybrid solids such as Metal-organic frameworks (MOFs) are good candidates to solve this problem due to their unique physico-chemical properties.

This review focuses on the implementation of native and modified MOFs and the comparison of their application in gas, liquid chromatography, and sample preparation (solid-phase extraction). We discuss the progresses and main results obtained until now, summarize the main advantages and current limitations of each application and discuss the possible future developments of these solids.

1. Introduction

Metal-organic frameworks (MOFs) are a class of crystalline porous compounds¹ that was first introduced in the 90's² and became rapidly of increasing interest for a large variety of potential applications^{3,4}, especially in the fields of adsorption and separation. MOFs possess a large chemical and structural flexibility due to the almost infinite possible combinations of inorganic building units and organic linkers. Their chemical or thermal stability is mainly driven by the nature of the metal-ligand bond⁵ and the hydrophobic/hydrophilic character of the solids, among other parameters⁶. These compounds can be easily designed and modified in terms of structural features (pore size, shape...) and functionalities through metal substitution⁷, selection of specific organic ligands⁸ and/or introduction of functional groups⁹. When one considers the use of MOFs in separation sciences, these materials are of interest not only as stationary phases (SP) for chromatography but also as selective extraction supports, due to the presence of multiple specific interactions between analytes and the framework together with the precise control of the porosity¹⁰.

The interest for MOFs in chromatography is increasing steadily, with applications in sample handling e. g. solid phase extraction (SPE)¹¹, solid phase microextraction (SPME)¹², stir bar sorptive extraction (SBSE)¹³, magnetic solid phase extraction (MSPE)¹⁴ for the extraction and identification of unwanted compounds (e.g. Cr(VI) ions¹⁵, herbicides¹⁶, nitrophenols¹⁷) etc. In parallel, other chromatographic applications have been investigated such as MOFs used as stationary phase for high performance liquid chromatography (HPLC)¹⁸ and gas chromatography (GC)¹⁹. In order to be used as stationary phases, materials shall nevertheless fulfill specific requirements such as good chemical and thermal stability along with the ability to interact selectively with targeted analytes. Moreover, the column efficiency (theoretical plate number) must compete with the standards of commercially available SPs. One can expect that MOFs, in comparison with zeolites, inorganic mesoporous solids or porous polymers, can offer a better control of the host-guest interactions with analytes. Indeed, their highly tunable pore size/shape, the variety of acid/basic sites, halogens, the dispersive interactions may enable a separation both per size and through the interactions

with the framework. These features might lead to unique recognition effects and therefore to original chromatographic separations.

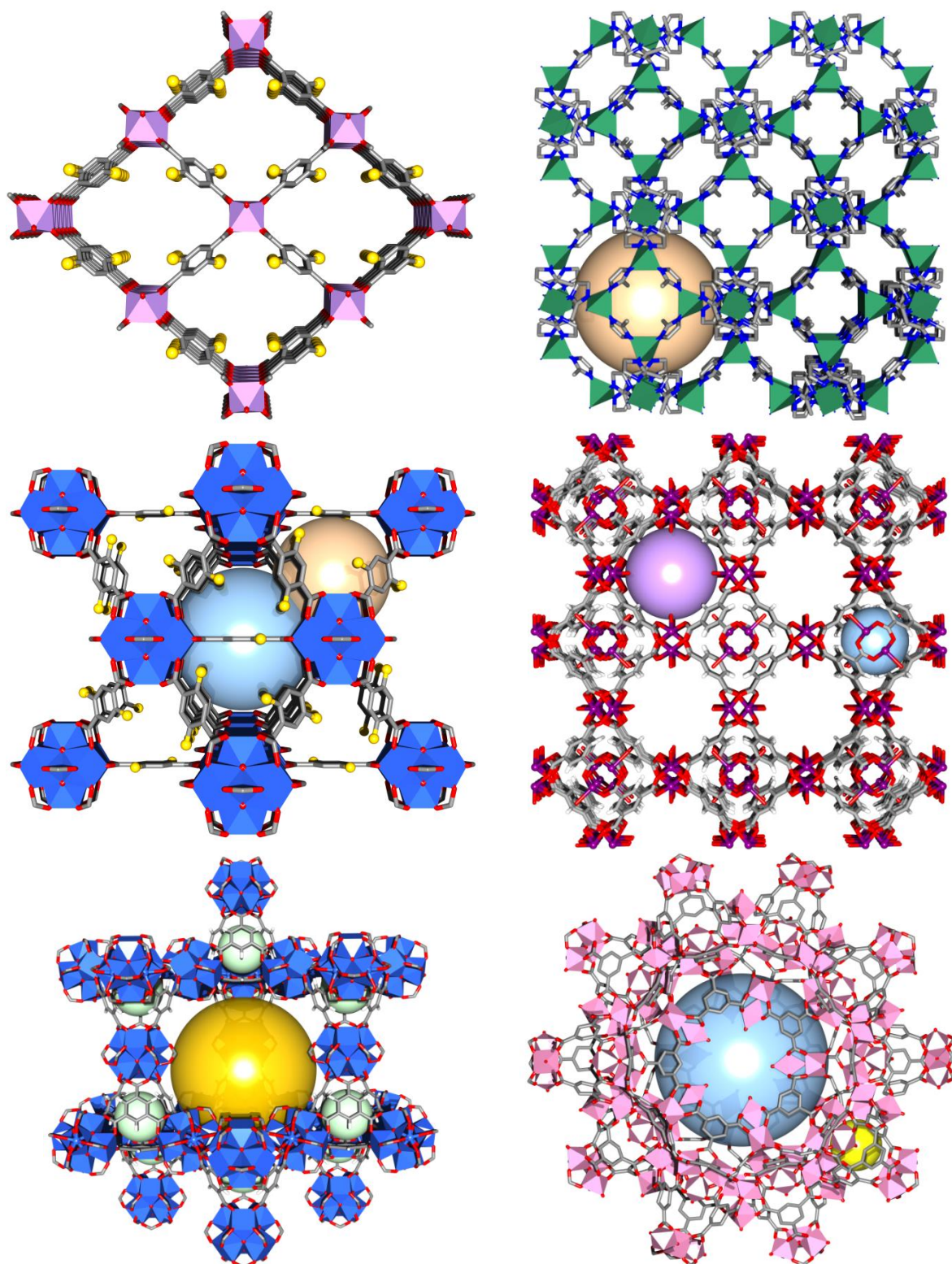


Figure 1. Structure of benchmark MOFs used for chromatographic separation (top left) MIL-53(M), (top right) ZIF-8(Zn), (middle left) UiO-66(Zr), (middle right) HKUST-1(Cu), (bottom left) MOF-808(Zr) and (bottom right) MIL-100(M). Color code: grey = carbon atoms, red = oxygen atoms, yellow spheres = possible functional groups, pink octahedra = trivalent cations, green tetrahedral = Zn(II) cations, blue polyhedra = Zr(IV) cations, purple = Cu(II) cations.

Several reviews have already been published on related topics but they are either focused on a specific kind or separation or not updated anymore²⁰⁻²². Here, we present the different MOFs that have already been used for each kind of application, focusing both on the aspects related to analytical and material chemistry (see Figure 1 for the structure of several benchmark MOFs for chromatography). We report and discuss the plausible mechanisms of MOF-analyte interactions as well as the separation behavior of common analytes. We also highlight the latest tendencies in MOF-based composites materials for stationary phases for different types of chromatography.

2. HPLC

2.1. First attempts

The first use of MOFs for HPLC has been reported in 2007²³. Alaerts et al. investigated the application of the microporous vanadium(IV) terephthalate MIL-47(V) for the separation of C₈ alkylaromatic compounds. The choice of this material was driven by its hydrophobic properties and high porosity as well as its one-dimensional diamond shaped micropores²⁴. The MOF crystals (size of 0.25 to 2.0 μm) were packed into the HPLC column (50 mm (length) x 4 mm (internal diameter, i.d.)). The mixture of ethylbenzene, meta-xylene, and para-xylene was injected and resulted in three well-separated peaks with the strongest retention of para-xylene (Figure 2).

The authors explained the separation as a result of difference between the molecular arrangements of the isomers. Geometry of molecules and their location in MOFs pores played the major role here. For instance, in case of para-xylene, pair of parallel analytes' benzene rings were located in the pores by X-Ray powder diffraction as a result of π - π -interactions between each other without interacting with terephthalic ligands. Therefore, the geometry helped the para-xylenes to be confined in the pore of MIL-47(V), while ethylbenzenes formed non-parallel pairs of molecules, resulting in a less suitable alignment. This explained the lack of retention of ethylbenzene.

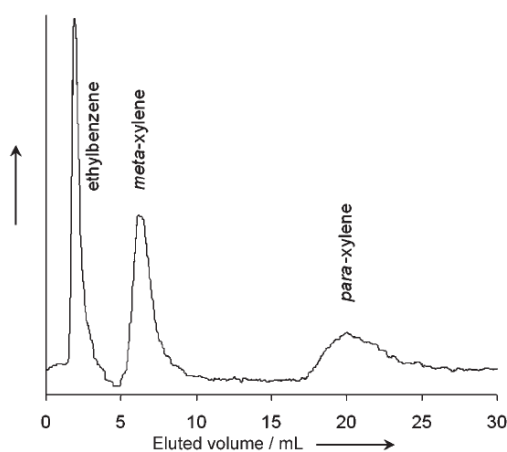


Figure 2. HPLC chromatogram of ethylbenzene, *m*- and *p*-xylenes on the MIL-47 (V) packed column (5 cm x 4 mm i.d.); isocratic elution mode, mobile phase hexane, flow rate 4 mL/min²³.

The results proved that MIL-47 can be used as stationary phase for HPLC. However, at this point, the quality of analysis was still far away from modern chromatography standards. This study was however a starting point for the use of MOFs for chromatographic separations. However, in most cases the use of pure MOF crystals as stationary phase was limited by the fact that despite a good stability and resistance to harsh conditions (high temperature, polar solvents), MOFs particles are often too small ($< 5 \mu\text{m}$) together with a non-regular, polydisperse and anisotropic shape^{25,26}. This leads to strong pressure drops, peak broadening and tailing due to bad quality of packing and blocking of the column frit, ruling out the use of pure MOFs as efficient stationary phases.

In 2010, Ameloot et al²⁷ proposed an alternative solution with the preparation of core-shell MOFs particles. The copper trimesate microporous $\text{Cu}_3(\text{BTC})_2$ was incorporated inside the pores of micrometric silica particles leading to good packing properties and separation abilities (column dimensions: 150 mm x 4.6 mm i.d.). The column backpressure was significantly reduced to 47 bar for the composite against 200 bar for the pure MOF column (heptane, flow rate of 1 mL/min). This led to improved separation of ethylbenzene and styrene, outperforming pure silica with resolution of 7.9 against 1.5. Since then, core-shell particles appears as very promising stationary phases for chromatography and several strategies to synthesize them have been developed and applied to several other MOF structures (see Figure 3).^{28,29}

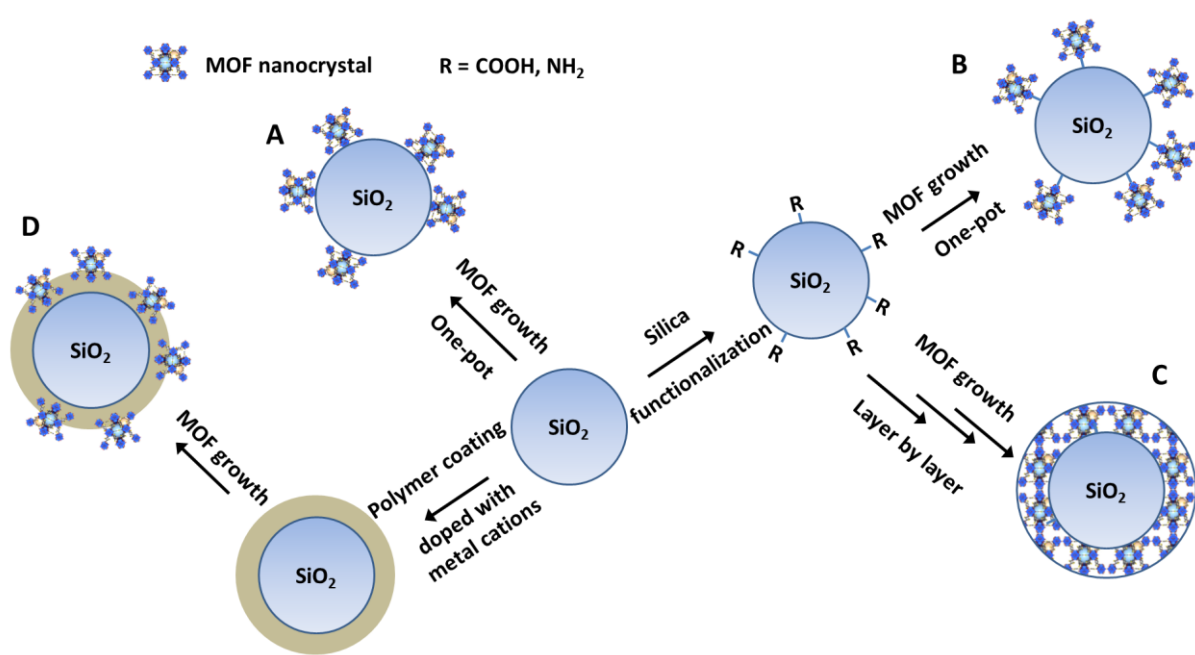


Figure 3. Illustration of the different strategies to prepare silica@MOF core-shell particles through (A) one-pot strategy, (B) silica functionalization followed by one-pot MOF growth, (C) silica functionalization followed by layer-by-layer MOF growth and (D) MOF growth on polymer coated silica particles.

2.2.1. ZIF-8

Zeolite Imidazolate Frameworks (ZIFs) are a sub-class of MOFs that possesses several interesting features due to the structural diversity of zeolites, associated in most cases to a good chemical stability together with a pronounced hydrophobic character³⁰. For example, ZIF-8 exhibits a cubic architecture composed of Zn^{2+} ions and 2-methylimidazole ligands

resulting in a sodalite structure type that possesses 11.6 Å large cages accessible through small apertures of 3.4 Å that are flexible upon guest adsorption³¹. Fu et al³² first proposed a simple and efficient method to prepare ZIF-8@SiO₂ core-shell nanoparticles for HPLC separation. The slurry-packed ZIF-8@SiO₂ column was studied for the separation of endocrine disrupting chemicals (EDCs) (bisphenol A (BPA), β-estradiol (E₂), and *p*-(*tert*-octyl)phenol) (POP)) and different pesticides (thiamethoxam, hexaflumuron, chlorantraniliprole and pymetrozine). The column (5 cm long x 4.6 mm i.d.) demonstrated quite good efficiency for EDCs (23000 plates/m at a flow rate of 0.5 mL/min, 99.5:0.5 acetonitrile/H₂O) with a retention that increased with the amount of MOF anchored on the SiO₂ surface. Despite the fact that the pore windows of ZIF-8 are too small to adsorb the analytes within the pores, the authors explained the separation through external surface interactions with synergic effect of hydrophobic and π-π interactions between the aromatic rings of the analytes and the imidazole rings of the MOF particles as well as with hydrogen bonds with uncovered SiO₂.

Later, ZIF-8-covered silica spheres with dendritic shells (SiO₂@dSiO₂@ZIF-8) particles (2.2 μm in diameter) were considered as a stationary phase for HPLC³³. The separation of basic (aniline derivatives) and acidic (phenol derivatives) analytes was investigated. In both cases, good separation was observed for the SiO₂@dSiO₂-ZIF-8 packed column (50 mm long × 4.6 mm i.d.) using mixtures of acetonitrile and water as the mobile phase (Figure 4), which was attributed to the properties of the ZIF-8 framework combined with the dendritic pore structure of the composite. In this example, MOF nanoparticles were located onto the surface of SiO₂ macropores instead of being grafted onto the external surface of silica. This arrangement made the access of analyte molecules easier, as evidenced by the excellent efficiency of the columns (210-215 kplates/m). In addition, the MOF grafting increased the BET surface area of the material (84-95 m²/g depending on the method of synthesis), which may contribute to the efficiency of the column.

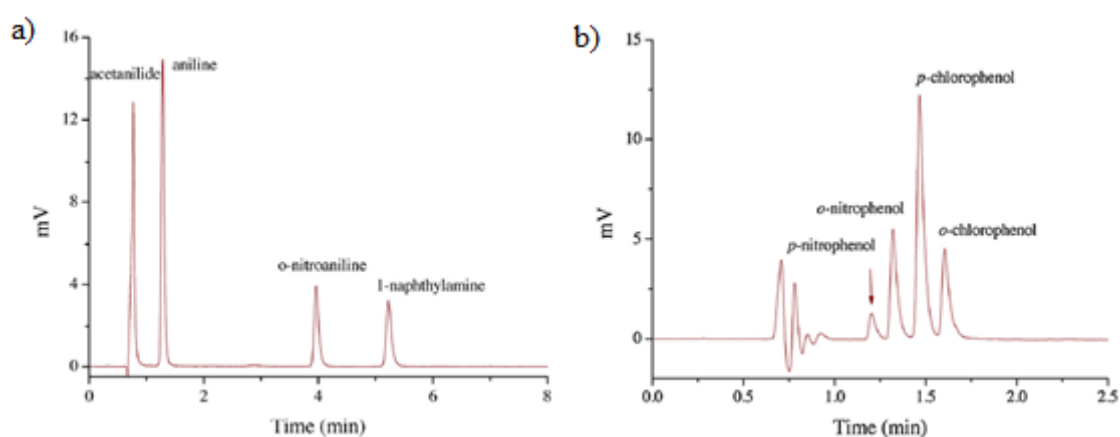


Figure 4. HPLC chromatograms of acetanilide, aniline, *o*-nitroaniline and 1-naphthylamine (a) and *p*-nitrophenol, *o*-nitrophenol, *p*-chlorophenol, *o*-chlorophenol (b) on SiO₂@dSiO₂-ZIF-8 packed column (5 cm x 4.6 mm i.d.); isocratic elution mode, mobile phase 20:80 ACN:H₂O (a) and 35:65 ACN:H₂O (b), flow rate, 1.0 mL/min³³.

2.2.2. UiO-66 and UiO-67

UiO-66 is a robust MOF composed of zirconium oxoclusters Zr₆O₄(OH)₄ and a 1,4-benzene-dicarboxylate (BDC) linker, resulting in a face-centered cubic structure with

microporous octahedral ($\sim 11 \text{ \AA}$) and tetrahedral cages ($\sim 8 \text{ \AA}$), accessible through microporous windows of ca $\sim 5\text{--}7 \text{ \AA}$. UiO-66 presents a large specific surface area ($\sim 1000 \text{ m}^2/\text{g}$)³⁴ and is hydrothermally stable^{35,36}. This MOF is promising as a new stationary phase, as it exhibits a unique reverse-shape selectivity (reverse of molecular dimension, according to the shape of the molecules) and a high affinity for bulkier molecules despite the temperature and pressure due to the difference of rotational freedom of absorbed molecules inside the pores³⁷.

UiO-66(Zr) particles were first grafted on SiO_2 surface (UiO-66@ SiO_2) via pre-synthetic ion anchoring and used as HPLC stationary phase in 2014³⁸ for the separation of a variety of substituted aromatics, chlorobenzene compounds and polycyclic aromatic hydrocarbons (PAHs), using a stainless steel column ($100 \text{ mm} \times 2.1 \text{ mm i.d.}$) packed with $5\mu\text{m}$ core-shell particles. For chloro-substituted benzenes, elution occurred according to their polarity, which is related to the number of chlorine groups. Hence, the properties of separation were mainly attributed to the interactions between analyte atoms and the MOF linker (C—H—Cl). Benzene, naphthalene, phenanthrene and pyrene could also be separated on UiO-66@ SiO_2 column with the following retention order (according the increasing number of aromatic rings): benzene < naphthalene < phenanthrene < pyrene (Figure 5). It was attributed to a retention mechanism involving π - π -stacking interactions between aromatic rings of the PAHs and the ligands of UiO-66. However, the efficiency was poor and only partial separation between naphthalene and phenanthrene occurred. In addition, when looking at the separation of a mixture of styrene and ethylbenzene, styrene had a stronger retention than ethylbenzene, possibly due to strong interactions between the unsaturated double bond of styrene and open metal sites of the MOF.

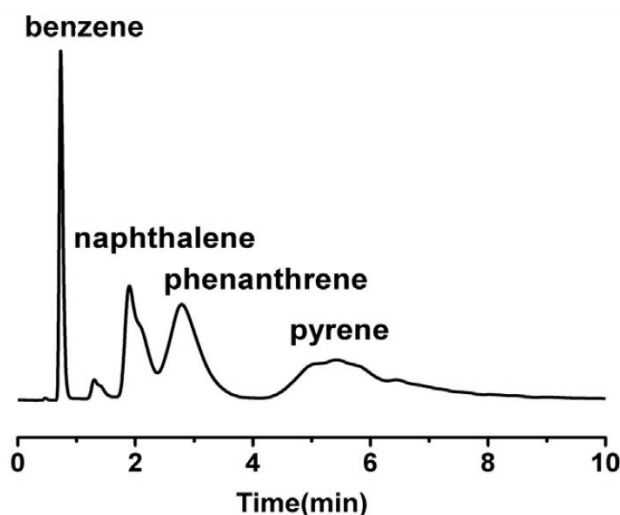


Figure 5. HPLC chromatogram of PAHs on the UiO-66@ SiO_2 packed column ($100 \text{ mm} \times 2.1 \text{ mm i.d.}$); isocratic elution mode, mobile phase hexane, flow rate 0.4 mL/min ³⁸.

Concerning positional isomers, ethylbenzene was less retained than xylenes, their elution order being p-xylene < m-xylene < o-xylene (Figure 6). This highlighted the better affinity of UiO-66 for bulkier molecules due to its reverse shape selectivity³⁷, while these substances are not easily separated even using conventional gas chromatography³⁹.

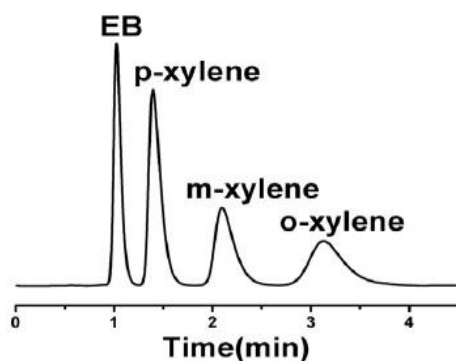


Figure 6. HPLC chromatogram of ethylbenzene (EB), *p*-, *m*- and *o*-xylenes on the UiO-66@SiO₂ packed column (100 mm × 2.1 mm i.d.); isocratic elution mode, mobile phase 98:2 hexane:DCM, flow rate 0.6 mL/min³⁸.

The effect of quantity of anchored UiO-66 on silica particles has then been studied⁴⁰. Three different composites, with different amounts of UiO-66 grafted on amino-terminated silica (corresponding to 0.16, 0.32 and 0.64 g of ZrCl₄ for 0.5 g of SiO₂), have been tested with aniline derivatives as analytes (Figure 7). In this case, the retention was based on a “symbiosis” between the hydrogen bond between the analytes and the basic groups of amino-functionalized silica as well as π - π -stacking interactions between compounds and the MOF shell. By increasing of the amount of UiO-66, the strength of the hydrogen bond between anilines and amino groups of the bonded silica decreased but at the same time, hydrophobic and π - π -interactions increased (Figure 7). Hence, the retention of compounds equally grew leading to the better separation despite larger peak tailing observed in some cases that are probably related to mixed separation mechanisms.

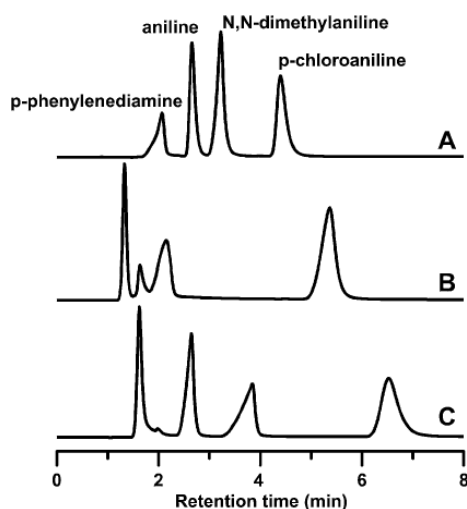


Figure 7. HPLC chromatogram of anilines on the UiO-66@SiO₂-0.16 (A), UiO-66@SiO₂-0.32 (B) and UiO-66@SiO₂-0.64 (C) packed columns (150 mm × 4.6 mm i.d.); isocratic elution mode, mobile phase 17.5% ACN in H₂O, flow rate 1.0 mL/min⁴⁰.

Due to the small window size of UiO-66, although the organic spacer can rotate enabling the adsorption of larger molecules, this MOF is not always able to demonstrate its reverse-shape selectivity⁴¹. This might result in unpredictable separations and could limit the practical use of this material. However, as this MOF is easy to synthesize and functionalize, leading to tunable host guest interactions with the analytes as well as first promising

separation properties, UiO-66 can be considered as a good model for future investigations of MOFs in the field of chromatography⁴². When one considers the core material, SiO₂ is widely used nowadays. However, there is still a need to develop new robust core systems that could replace the SiO₂ particles. The new core particles should better anchor MOF and lead to a better control of the thickness of MOF layer, as these are the most common problems encountered with SiO₂³³. Some studies have already demonstrated advantages of other core materials and will be discussed below.

UiO-67 consists of Zr₆O₄(OH)₄ oxoclusters linked through 4,4'-biphenyldicarboxylate (BPDC²⁻) and is an upper isorecticular analogue of UiO-66 with, as a consequence, a much larger pore size. It was anchored on 3 μm silica non-porous particles to obtain a core-shell material using a layer by layer deposition procedure (18 cycles). MIL-101(Fe)NH₂ and UiO-67 were investigated using the same silica core particles. Columns were packed using the core shell materials and performances were compared to those obtained with bare silica. Using dimethyl phthalate and diethyl phthalate as test molecules, the UiO-67@SiO₂ was found to provide much better efficiency compared to the MIL-101 modified silica and very competitive efficiency compared to the bare silica column. Despite the selectivity was higher using the MIL-101 derived support, the resolution was better using the UiO-67 derived material owing to the better efficiency (Figure 8). The pictures of modified particles obtained by electronic microscopy provided in the paper showed good coverage of particles by the MOFs and spherical shape of the material.⁴³

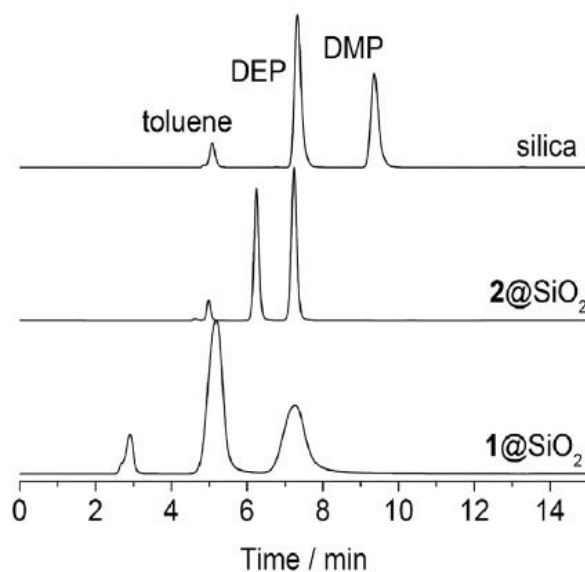


Figure 8. HPLC chromatogram of toluene, dimethyl phthalate (DMP) and diethylphthalate (DEP) on the core particles of silica (silica), UiO-67@SiO₂-0.16 (2@SiO₂), MIL-101(Fe)NH₂@SiO₂- (1@SiO₂) packed columns (250 mm x 3 mm i.d.); isocratic elution mode, different hexane/ethyl acetate mobile phase composition (from bottom to top: 80:20, 50:50, 70:30) ; flow rate 0.5 mL/min.

2.2.3. HKUST-1

HKUST-1 (Cu₃(BTC)₂(H₂O)₃) is a cubic-centered MOF, whose structure is built from Cu₂(OAc)₄ paddlewheel-type secondary building units connected by trimesate ligands resulting into large square shaped pores of 9 x 9 Å⁴⁴. The applications of HKUST-1 for liquid phase separation are however limited due to its poor stability in water, but remain promising

for use in normal-phase conditions (e.g. with non-polar solvents like hexane)²². For example, Weiwei et al. synthesized well-defined core-shell particles consisting of an HKUST-1 layer on the surface of magnetic silica microparticles (MPs) through a liquid phase epitaxial process⁴⁵. This technique allows the control of the thickness and orientation of the shell as well as the minimization of the agglomeration of the particles that typically ruled out any uniform column packing. As a result, an homogenous film of HKUST-1 particles, that was formed onto the carboxyl functionalized magnetic microparticles (narrow size $3.55 \pm 0.17 \mu\text{m}$), has been considered for HPLC (column size $50 \text{ mm} \times 2.0 \text{ mm i.d.}$) with the aim to demonstrate specific MOF affinities⁴⁶. Authors have first studied the separation of pyridine and 4,4'-bipyridine. Despite both analytes demonstrated a strong interaction between Cu(II) open metal sites and nitrogen atoms from the heterocycles via both σ -donating and π -accepting interaction, 4,4'-bipyridine was eluted immediately while pyridine showed a much longer retention (Figure 9), evidencing the size exclusion effect of the MOF.

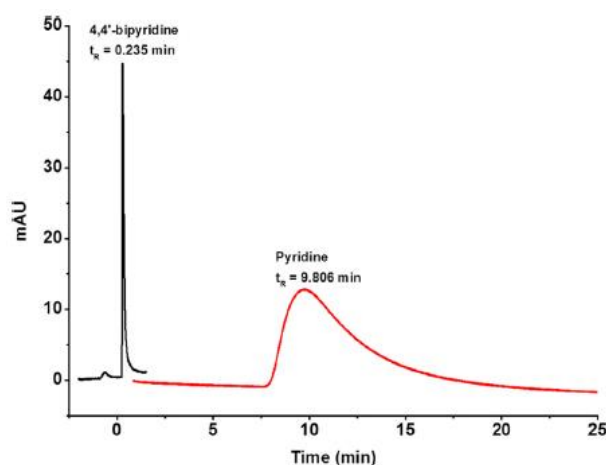


Figure 9. HPLC chromatogram of pyridine and 4,4'-bipyridine on the HKUST-1 magnetic silica MPs packed column ($50 \text{ mm} \times 2.0 \text{ mm i.d.}$); isocratic elution mode, mobile phase MeOH, flow rate 0.3 mL/min ⁴⁶.

Further investigations showed that the choice of the mobile phase has an impact not only on the strength of the retention of analytes, but also on the selectivity of the MOF-MPs packed column. For example, a mixture of three chloroanilines has been considered: when MeOH was used as the mobile phase it led to a very poor separation (low retention), while acetonitrile could improve the results thanks to its aprotic nature (Figure 10).

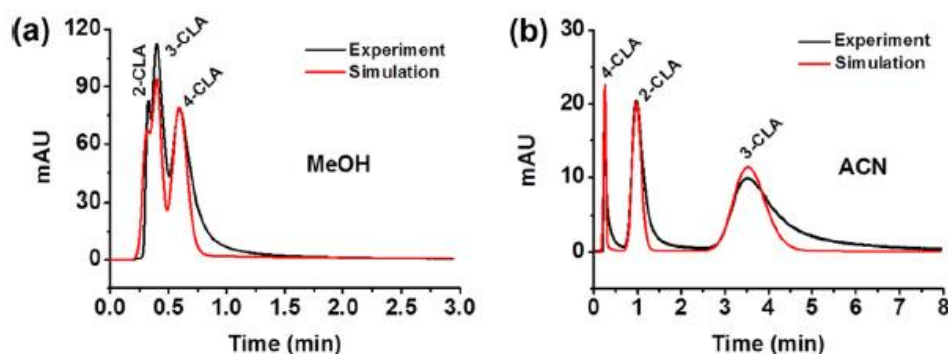


Figure 10. HPLC chromatograms of chloroaniline isomers on the HKUST-1 magnetic silica MPs packed column (50 mm × 2.0 mm i.d.); isocratic elution mode, mobile phase MeOH (a), ACN (b), flow rate 0.3 mL/min⁴⁶.

Moreover, the elution order was also changed from 2- < 3- < 4-chloroaniline, corresponding to an increasing distance between the amino and the chlorine substituent, to 4- < 2- < 3-chloroaniline. Authors suggested this was due to the analytes interactions between the NH₂-group of chloroanilines and MOF's Cu(II) open metal sites that were less active due to the presence of the nitrile groups of the solvent. In addition, molecular modelling (ChromX simulations) demonstrated that the calculated behavior of HKUST-1 was in very good agreement with the experimental data in line with the mechanism of retention proposed⁴⁰.

2.2.4. MOF-808

MOF-808 is a Zr(IV)-based MOF based on Zr₆ oxoclusters connected to six 1,3,5-benzenetricarboxylic linkers and six formate anions. The obtained structure consists of tetrahedral cages with internal pore diameters of 4.8 Å and octahedral cages of 18.4 Å⁴⁷. In a recent study, MOF-808@SiO₂ core-shell particles have been applied as a hydrophilic interaction liquid chromatography (HILIC) stationary phase⁴⁸. In comparison with UiO-66@SiO₂ developed earlier⁴⁹, MOF-808@SiO₂ material demonstrated better stability and separation toward hydrophilic substances such as sulfonamides, alkaloids, nucleosides, nucleobases, antibiotic compounds, and multiple carbohydrate and amino acid compounds. For example, the separation of sulfonamides (sulfadimoxine, sulfadiazine, sulfaguanidine and sulfasalazine) has been studied with MOF-808@SiO₂ packed column (Figure 11) and compared with bare and amino-modified silicas SPs. These compounds were not able to be effectively separated neither on the bare silica, nor on amino-modified columns under the same chromatographic conditions. Moreover, the retention times of sulfonamides were increased by increasing the acetonitrile concentration in the area between 60% and 95%, which confirmed that the mechanism of interactions of MOF-808@SiO₂ with the analytes is conditioned by hydrophilic interactions.

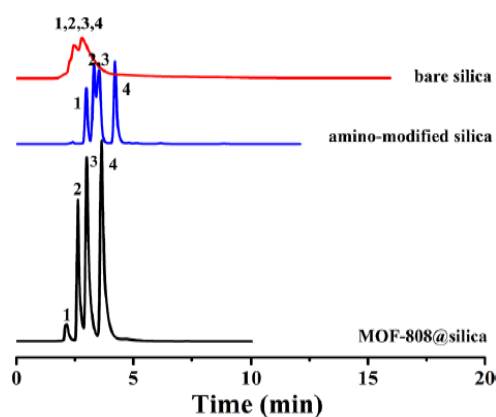


Figure 11. HPLC chromatograms of sulfadimoxine (1), sulfadiazine (2), sulfaguanidine (3), sulfasalazine (4) on the bare, amino-modified and MOF-808@SiO₂ packed columns (150 mm × 4.6 mm i.d.); isocratic elution mode, mobile phase 90% ACN and 10% 100 mmol/L ammonium acetate, flow rate 0.8 mL/min⁴⁸.

2.2.5. NH₂-UiO-66

Recently, MOFs were used as independent monomers covalently organized by crosslinking molecules (CLMs) into an orderly hybrid monolithic stationary phase⁵⁰. In this

study UiO-66-NH₂ was used as a model, since the amino group does not participate in coordination and can be chemically modified (linked by CLMs to form the monolith). Here, pentaerythritol tetrakis(3-mercaptopropionate) (PTM), dipentaerythritol hexakis(3-mercaptopropionate) (DPHM), 1,6-hexanediol dimethacrylate (HDDMA), and stearyl methacrylate (SMA) were applied as CLMs. Obtained materials were packed in a 200 mm × 75 μm i.d. stainless steel nano-HPLC column and tested. Alkylbenzenes (benzene, toluene, ethylbenzene, propylbenzene, butylbenzene and pentylbenzene) could be eluted in order of their polarity on all the prepared monoliths under isocratic elution using a 50% ACN mobile phase (Figure 12).

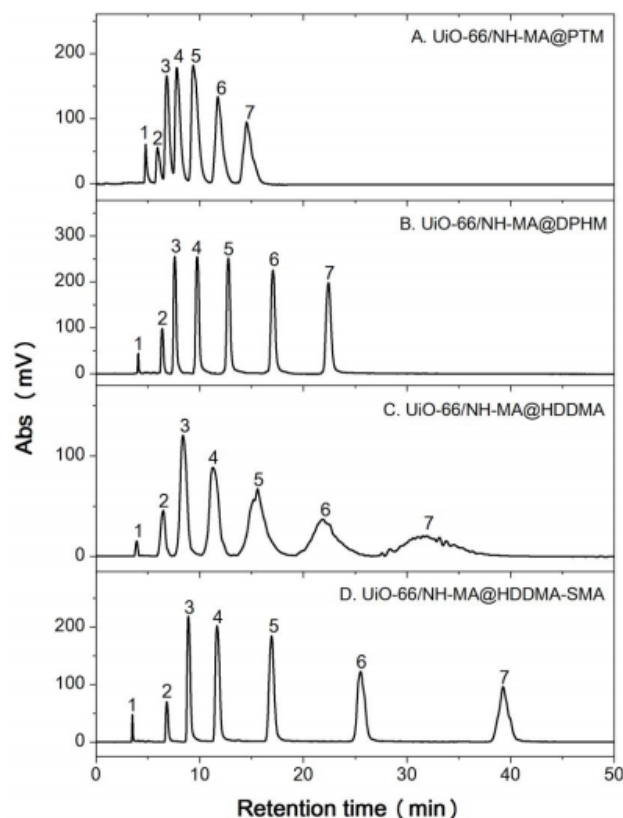


Figure 12. HPLC chromatograms on the UiO-66/NH-MA@CLMs hybrid monolithic columns (200 mm × 75 μm i.d.) for the separation of alkylbenzenes (1, thiourea; 2, benzene, 3, toluene; 4, ethylbenzene; 5, propylbenzene; 6, butylbenzene; 7, pentylbenzene); isocratic elution mode, mobile phase 50:50 ACN:H₂O, flow rate 200 nL/min⁵⁰.

The authors explained chromatographic behavior by typical reversed-phase HPLC mechanism. The surface area consisted mostly of the MOF, while the mesopore size significantly depended on the CLMs used. In all the carried experiments the separation sequence was in accordance with the hydrophobicity, but the contributions of pore sieving and electrostatic repulsion effects cannot be discarded, especially with diphenol isomers, amino acids, and proteins separation.

2.2.6. MOF-235

Core-shell particles using MOF-235 have also been proposed for HILIC⁵¹. MOF-235 is a Fe(III)-based MOF formed with terephthalic acid as ligand. Having the formula [Fe₃O(1,4-BDC)₃(DMF)₃][FeCl₄](DMF)₃, this MOF is an example of a hexagonal net of aligned, corner-sharing octahedral iron trimers connected by BDC linkers resulting in

hexagonal micropores⁵². In this study the surface of silica spheres was covered by MOF-235 particles and PEG (polyethylene glycol). The obtained material has been tested as a HILIC stationary phase on a variety of compounds. The successful separation of alkaloids was achieved (Figure 13a). In addition, the separation results of sanguinarine, caffeine, theophylline, theobromine, chelerythrine, and berberine was improved in comparison with the results obtained by the team with other MOF-based stationary phases.

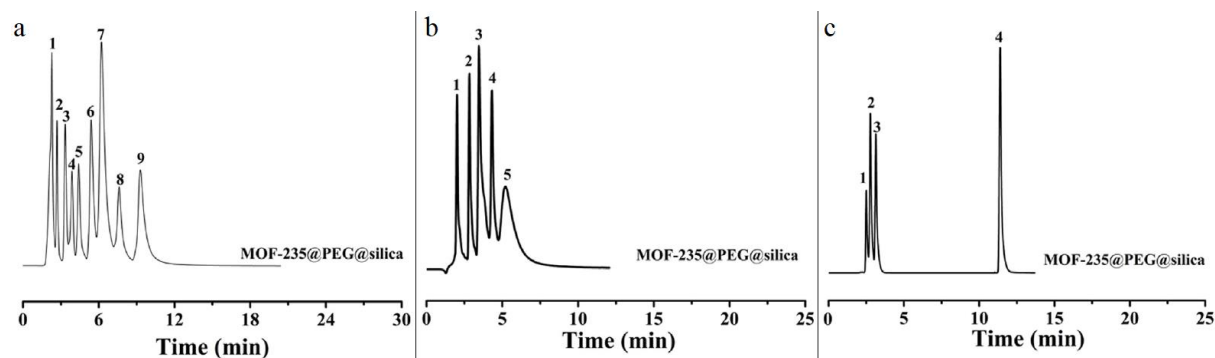


Figure 13. HPLC chromatograms of alkaloids (a), nucleobases (b) and sulfonamides (c) on the MOF-235@PEG@silica column (150 mm x 4.6 mm i. d.):

(a) (1, sanguinarine, 2, caffeine, 3, theophylline, 4, theobromine, 5, chelerythrine, 6, berberine, 7, palmatine chloride, 8, jatrorrhizine, 9, coptisine) isocratic mode, mobile phase 80% ACN and 20% 100 mmol/L ammonium acetate; flow rate 0.8 mL/min;

(b) (1, 6-Chlorouracil, 2, thymine, 3, xanthine, 4, cytosine, 5, cytidine), mobile phase: 80% ACN 20% 100 mmol/L ammonium acetate; flow rate 0.8 mL/min;

(c) sulfonamides (1, sulfadumoxine, 2, sulfadiazine, 3, sulfaguanidine, 4, succinylsulfathiazole, gradient mode, mobile phase: 0→5 min 90% ACN, 10% 100 mmol/L ammonium acetate, 5→6 min 80% ACN, 20% 100 mmol/L ammonium acetate, flow rate 0.8 mL/min⁵¹).

Nucleosides and nucleobases were also separated on the obtained material packed column (Figure 13b). In addition, the mixture of four sulfonamides was also tested on the composite (Figure 13c) but unlike the other groups of analytes, the separation was achieved only in gradient elution mode in that case. The experimental data were compared with the results of the amino-modified silica packed columns (150 mm x 4.6 mm i. d.). In that case, the different groups of analytes were not successfully separated (only partly and with lower efficiency). One can therefore say that the synergy of MOF-235 and PEG plays a significant role in the mechanism of retention. Overall, the data confirmed the potential of MOF-235@PEG@silica for HILIC separation, as the composite demonstrated acceptable efficiency in all the cases (up to 2629.4 plates/m). The results showed significantly improved separation abilities in comparison with the ordinary core-shell MOF@silica composites. Hence, introducing a functional polymer like PEG seems to be able to enhance the chromatographic performance. However, a comparison with a PEG bonded silica would have been of major interest to clarify the effect of PEG on the separation.

2.2.7. MIL-53 (Al)

MIL-53(Al) is another widely studied MOF for HPLC^{53,54}. It exhibits a nanoporous flexible framework constructed with infinite chains of corner-sharing $\text{AlO}_4(\text{OH})_2$ octahedra, connected by 4 BDC linkers, resulting in 8.5 Å large 1D rhombic-shaped pores⁵⁵. MIL-53(Al) was synthesized using recycled waste PET bottle according to the principles of green chemistry and applied for HPLC separation⁵⁶. Particles sized from 5 to 10 μm were obtained and packed into the columns (100 and 150 mm × 4.6 mm i.d.). For all the investigated

mixtures authors reported the detailed optimum conditions and evaluation parameters for separation. For example, a mixture of seven alkyl benzenes (benzene, toluene, ethylbenzene, n-propylbenzene, n-butylbenzene, n-pentylbenzene and n-hexylbenzene) was baseline separated on a 100 mm \times 4.6 mm i.d. column packed with the obtained material (isocratic mode, mobile phase: ACN/H₂O 60:40, flow rate: 0.30 mL/min). Here, the retention increased with alkyl chain length. The best column efficiency was exhibited for 1-phenylhexane (62.4 kplates/m at 0.30 mL/min). Successful separation was also obtained for PAHs (column efficiency 63.2 kplates/m for anthracene) (gradient mode, mobile phase: ACN/H₂O, gradient elution program 0 \rightarrow 8 min (45% ACN), 8 \rightarrow 20 min (linear gradient 45 \rightarrow 80% ACN), 20 \rightarrow 22 min (80% ACN), flow rate: 0.35 mL/min). The green-synthesized MIL-53 was also used for a mixture of acetone, acetophenone, and butyrophenone separation (isocratic elution mode, mobile phase: 80:20 ACN/H₂O, flow rate: 0.20 mL/min). Butyrophenone demonstrated the highest performance among the other analytes in this series (14.3 kplates/m). The column itself showed a good equilibrium between run time and resolution as well as low peak tailing for all the ketones.

Phenolic compounds were also separated using the described material. Two series of compounds were tested under different experimental conditions. Phenol, resorcinol and phloroglucinol were fully separated with a chromatographic resolution higher than of 2.92 (isocratic elution mode, 85:15 ACN:H₂O, flow rate of 0.25 mL/min). As for substituted phenols (4-aminophenol, *p*-cresol, 4- nitrophenol, 4-chlorophenol, and 2-naphthol), they were totally separated (resolution $>$ 1.70) under isocratic elution conditions (ACN:H₂O 60:40, flow rate 0.30 mL/min). All the previously discussed compounds were normally separated on a 100 mm \times 4.6 mm i.d. column but separation of xylenes and methylxanthines needed in a longer (150 mm long) column, since on the 100 mm one only partial separation was achieved. The same column perfectly separated *o*-, *m*- and *p*-xylenes (65:35 ACN/H₂O at flow rate 0.35 mL/min). Here, the *o*-xylene demonstrated the highest affinity to MIL-53. Authors explained it by the polarity and the interaction between the methyl groups and the terephthalate pore walls of the MOF. High-resolution separation for a mixture of theobromine, theophylline, and caffeine confirmed the possibility of MIL-53(AI) to distinguish the structural isomers (Figure 14).

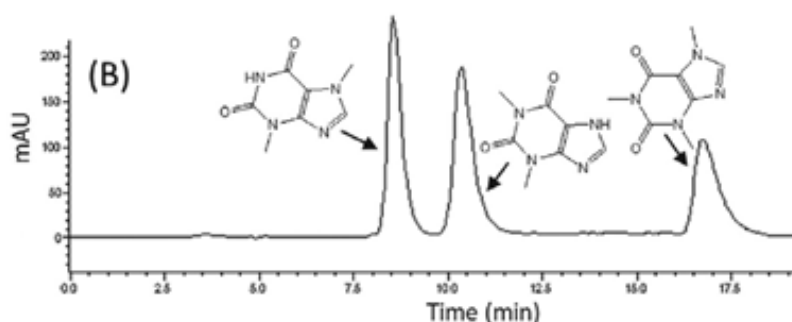


Figure 14. HPLC chromatogram on the MIL-53(AI) column (150 mm \times 4.6 mm i.d.) for the separation of theobromine, theophylline, and caffeine, isocratic elution mode, mobile phase 70:30 ACN:H₂O, flow rate 0.25 mL/min⁵⁶.

In case of xylenes, the best efficiency was only 7 kplates/m (*p*-xylene), when among methylxanthines, theobromine had 30.2 kplates/m at optimum conditions. As for retention factors, the highest were 2.39 for *o*-xylene and 4.06 for caffeine relatively, while the chromatographic resolution reached more than 2.59. Concerning the retention mechanism, as

in cases of previously discussed materials, it can be explained by π - π -interactions between the benzene ring of ligand and the analytes. In addition, the experiments demonstrated high reproducibility (RSD were $\leq 0.57\%$ for retention time, $\leq 3.77\%$ for half peak width, $\leq 3.05\%$ for peak height, and $\leq 3.88\%$ for peak area in all cases).

Compared to the previously cited MOFs packed columns, the described MIL-53(Al) columns gave competitive selectivity and quite good efficiency for the discussed analytes at the given conditions, demonstrating the potential of MIL-53(Al) as a stationary phase for HPLC applications. It is worth mentioning that despite of using a pure MOF (not a composite or core-shell form), researchers still achieved satisfying results. One advantage of this material is the possibility to synthesize relatively large crystals between 5 and 10 μm . Indeed, using this particle size range prevents from a high column backpressure while testing. In addition, the direct use of MOF prevents from non-specific interactions occurring between the silica support bearing the MOF.

2.3. Conclusion

Among the various MOFs considered so far as potential stationary phases for liquid chromatography, we have presented here the most promising ones. The use of pure MOF columns is interesting despite it still requires further investigations in order to compete with the performances of HPLC and UltraHPLC. Many researchers focus on particles functionalized by MOFs, based mostly on dense or porous silica core combined with promising MOFs for separation. As evidenced in the review, the grafting of MOF particles on silica cores certainly minimizes the problem of excessive backpressure and improves the peak resolution, but this is far from being sufficient. Despite repeatability of separations reaches the standards of HPLC, reproducibility of supports synthesis must however still be demonstrated for separations in normal phase and reverse phase chromatography.⁵⁷

Indeed, this approach requires a thorough selection of material testing conditions, mainly due to the weak interaction between the MOF particle and the SiO_2 surface. In addition, MOF@ SiO_2 particles can result into irregular shaped agglomerates that are not compatible with a good column packing due to too large column backpressure and low definition of separation⁴⁰. The MOF-covered magnetic silica microparticles usually allowed a better separation in comparison with the applications of pure MOF and MOF grafted on SiO_2 ^{46,58}. Though, the application as an HPLC stationary phase might be limited due to the lack of variates of the constitutive ligand, the core-shell particle synthesis might still be modified to obtain other MOF based composites.

3. Gas Chromatography

According to previous reviews^{59,60} gas chromatography (GC) might be the most promising area among analytical techniques for application of MOFs as stationary phases. Within last years, various MOF materials and column structures have been evaluated for gas chromatography. In GC, the mobile phase consists of a gas flowing through a glass or a metal column. Most of the time, the inner surface of the column is coated by a thin film of a stationary phase. The separation is based on both volatility and interaction with the stationary phase.

In 2006, the microporous zinc-based MOF-508 [Zn(BDC)-(4,4'-bpy)_{0.5}] was considered as a stationary phase for gas chromatography. Its framework is catenated with 2 similar forms – MOF-508a and MOF-508b – built with paddle-wheel dinuclear {Zn₂(COO)₄} oxoclusters supported by the BDC ligands forming a distorted 2D square net. This framework is pillared by 4,4'-bipyridine, resulting in a 3D cubic lattice with 4.0 Å large 1D pores. The column (120 cm x 0.125 inch) packed with single crystals of MOF-508b with sizes of 25–100 μm showed perfect separation of natural gas components and, moreover, of linear and branched isomers of alkanes such as pentane and hexane due to van der Waals interactions of analytes with the microporous MOF-508⁶¹. More recently, other MOFs have been considered for application as stationary GC phase. Their properties are described in the following sections.

3.1.1. MIL-101

MIL-101(Cr) is a mesoporous chromium terephthalate MOF with accessible coordinately unsaturated sites (CUS) that possesses an exceptional chemical and thermal stability. A MIL-101(Cr) coated capillary column was prepared in 2010 in order to improve the separation of xylene isomers and ethylbenzene by GC⁶². The coating of the capillary column was obtained by a dynamic coating method⁶³ in order to decrease the needed amount of MIL-101. The columns filled using this technique (15 m long x 0.53 mm i.d., MOF film thickness 0.4 μm) led to a high resolution separation (Figure 15). For *p*-xylene, the number of theoretical plates was up to 3800 m⁻¹, which was much higher than that of the ordinary silica PLOT (porous layer open tubular) columns. The present MIL-101 coated capillary column separated *p*-xylene and *m*-xylene, even though such separation is still challenging (as mentioned earlier) due to the similarity of their boiling points. Moreover, it has been shown that resolution and selectivity could be improved by choosing the right temperature. As expected, the observed selectivity decreased when the temperature increased, but the column efficiency was improved at the same time. In addition, increasing the injected analyte mass linearly increased only the peak area, without any change in retention time (retention factor remained stable) in the range investigated.

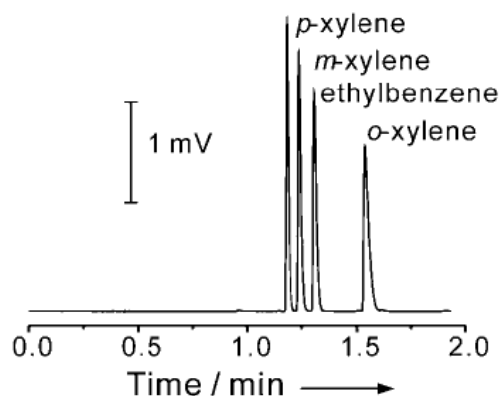


Figure 15. GC chromatogram of xylene isomers and ethylbenzene on the MIL-101 coated capillary column (15 m x 0.53 mm i.d.) at 160°C under a N₂ flow rate of 3ml/min⁶².

It is worth mentioning that, as previously reported, increasing the analyte mass led to larger asymmetry factors, suggesting a column overloading and, as a result, a decrease of column efficiency (up to 2000 theoretical plates/m)⁶⁴. Here, significantly improved separation results were explained by large MOF pore window diameter (1.4 and 1.6 nm) as well as the polarity of MIL-101 and its coordinately unsaturated sites.

3.1.2. MIL-100

MIL-100(Fe, Cr), a rigid mesoporous MOF based on trivalent cations and trimesic acid possessing 2.4 and 2.7 nm mesoporous cages accessible through microporous windows (≈ 0.5 and 0.9 nm, respectively), has been studied as a stationary phase for GC^{65,66}. MIL-100(Fe, Cr) coated capillary columns (20 m long x 0.25 mm i.d.), produced by dynamic coating method, have been evaluated for the separation of alkane isomers: the MIL-100(Fe) one demonstrated better results for the separation of alkane isomers in comparison with the chromium analogue.⁶⁵ For hexane (Figure 16a) and heptane (figure 16b) isotherms, the MOF exhibit a selectivity according to the shape of the molecule (linear, branched or cyclic). This effect is certainly related to size exclusion effect of the pore windows that have already been observed with other MOF derived materials.^{67,68}

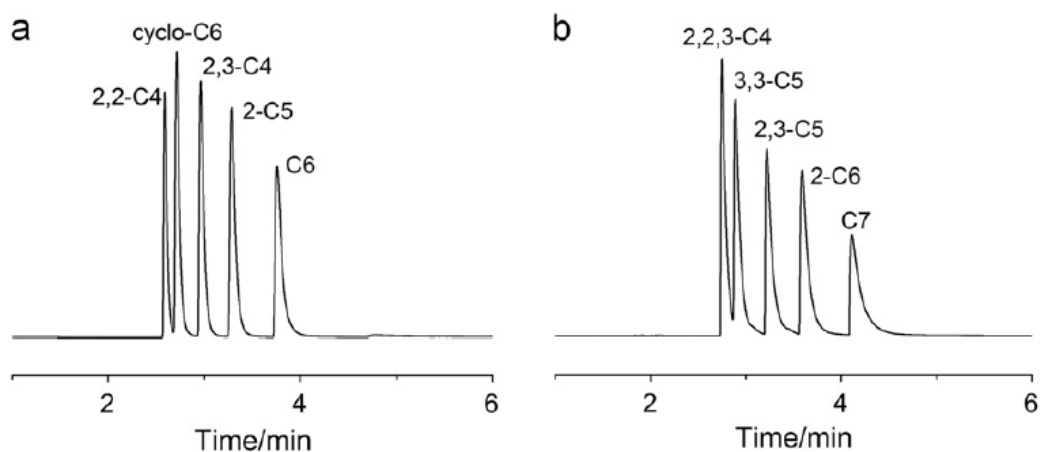


Figure 16. GC chromatograms on MIL-100 (Fe) coated capillary column (20 m x 0.25 mm i.d.) for the separation of alkanes: 2,2-dimethylbutane (2,2-C4), cyclohexane (cyclo-C6), 2,3-dimethylbutane (2,3-C4), 2-methylpentane (2-C5) and hexane (C6) at 80°C under a N_2 flow rate of 1.0 mL/min (a), 2,2,3-trimethylbutane (2,2,3-C4), 3,3-dimethylpentane (3,3-C5), 2,3-dimethylpentane (2,3-C5), 2-methylhexane (2-C6) and heptane (C7) at 110°C under a N_2 flow rate of 1.0 mL/min (b)⁶⁵.

In case of the MIL-100(Cr) column, increasing the temperature from 70°C to 110°C improved the peak shape to some extent, but reduced the selectivity and resolution (Figure 17). Therefore, the alkane isomers were not baseline separated and the peaks were broad and presented a strong tailing.

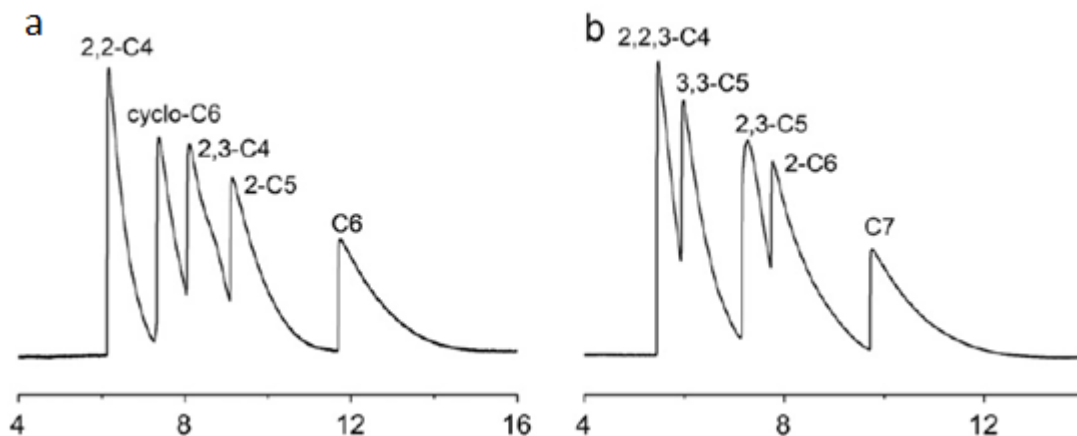


Figure 17. GC chromatograms on MIL-100(Cr) coated capillary columns (20m x 0.25 mm i.d.) for the separation of the alkanes: 2,2-dimethylbutane (2,2-C4), cyclohexane (cyclo-C6), 2,3-dimethylbutane (2,3-C4), 2-methylpentane (2-C5) and hexane (C6) at 80°C under a N_2 flow rate of 1.0 mL/min (a),

2,2,3-trimethylbutane (2,2,3-C4), 3,3-dimethylpentane (3,3-C5), 2,3-dimethylpentane (2,3-C5), 2-methylhexane (2-C6) and heptane (C7) at 110°C under a N₂ flow rate of 1.0 mL/min (b)⁶⁵.

The authors⁶⁵ explained lower column efficiency, along with a severe peak tailing of MIL-100(Cr) coated capillary column in comparison with the iron analogue, by the nature of the metal and differences in polarity. Precisely, the radius of Fe(III) is smaller and electrostatic interactions with the oxygen from the framework are stronger. It results into less partial negative charges and weaker C-H-O bonding between alkyl groups of analytes and the oxygen atoms from the framework.

3.1.3. UiO-66

In addition to HPLC, UiO-66 can be applied for GC applications, mainly thanks to its thermal and chemical stability and its high degree of chemical tunability. Chang et al. have checked the possibility of using UiO-66 coated capillary columns to separate alkane isomers and benzene homologues⁶⁹. Here, authors used 20 m long x 0.25 mm i.d. column, coated by the MOF onto the pre-treated capillary column by a dynamic coating method. They revealed that the peak area increased linearly with the mass injected within the studied range, without any change in retention time, peak shape and efficiency. The selectivity of the separation of hydrocarbons on the UiO-66 coated capillary column decreased when increasing the temperature, except for propylbenzene and 1,3,5-trimethylbenzene where an increase of selectivity was observed (Figure 18). In any case, the high thermal stability of UiO-66 allows performing GC experiments up to 200°C, which meets the requirements of most potential applications.

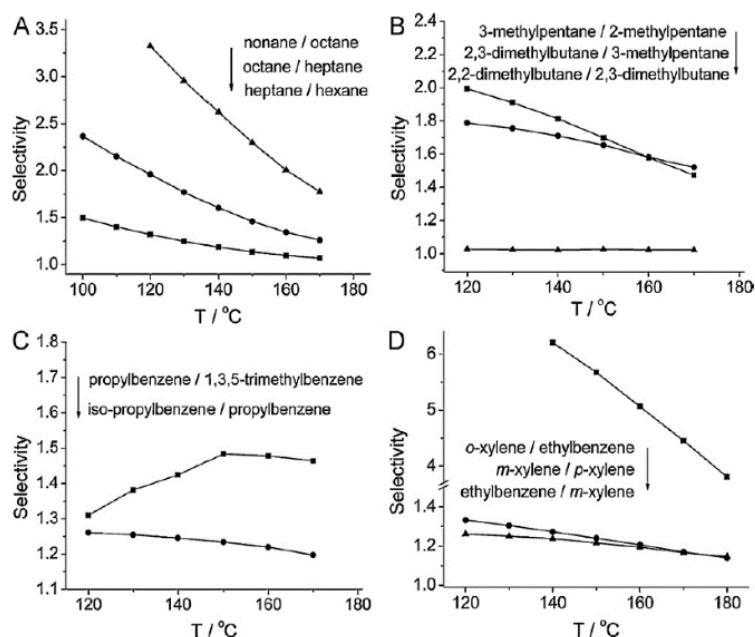


Figure 18. Selectivity of *n*-alkanes, hexane isomers, propylbenzene isomers, xylene and ethylbenzene on UiO-66 coated capillary column in the temperature range of 100–180°C at a N₂ flow rate of 1 mL/min⁶⁹.

3.2. Conclusion

MOF-coated columns present several advantages in gas chromatography. Firstly, their preparation is easy and so is the fabrication of capillary columns (especially using a dynamic coating method). Secondly, the columns themselves need only a small amount of MOFs to be

covered by. Thirdly, the diverse structures and unique properties may allow MOFs to overcome the existing barriers due to the new analytes-stationary phase interactions. Therefore, thermally stable MOFs are very attractive and cost-effective candidates as novel stationary phases in capillary gas chromatography. However, the strength of the MOF-column interaction still needs to be optimized in order to obtain columns presenting long term stability.

4. Chiral separation

This application deserves a separate chapter of this review since chiral separation involves dedicated SPs bearing enantioselective sites. Chiral recognition is an increasingly significant research topic in stereochemistry and biologically active compounds as well as in the pharmaceutical industry⁷⁰. Due to various chemical and physical properties, MOFs might help solving upcoming problems. Indeed, MOFs can exhibit chiral properties either when their organic linker is chiral itself or when the compounds trapped inside the pores are enantioactive⁷¹. Very recently, a review was published on this topic²⁰.

4.1. HPLC

4.1.1. $(\text{Me}_2\text{NH}_2)_2\text{Mn}_4\text{O}(\text{d-cam})_4 \cdot (\text{H}_2\text{O})_5$

When one considers chiral MOFs, a representative example is the planar Mn_4O -based homochiral MOF $(\text{Me}_2\text{NH}_2)_2\text{Mn}_4\text{O}(\text{d-cam})_4 \cdot (\text{H}_2\text{O})_5$ (d-cam = d-camphorate). This solid possesses coordinately unsaturated sites (CUS) and was considered for the separation of ibuprofen enantiomers in HPLC⁷². This MOF crystallizes in an orthorhombic chiral space group I222, featuring a planar tetracoordinated oxygen containing a Mn_4O cluster-based homochiral MOF. The asymmetric unit consists of two crystallographically independent Mn atoms, one O atom, and one d-cam ligand. The chirality of MOF was explained not only by the d-cam ligand, but also by planar Mn_4O clusters having 222 symmetry. The pore size of the compound is located within the 5-10 Å range (Figure 19).

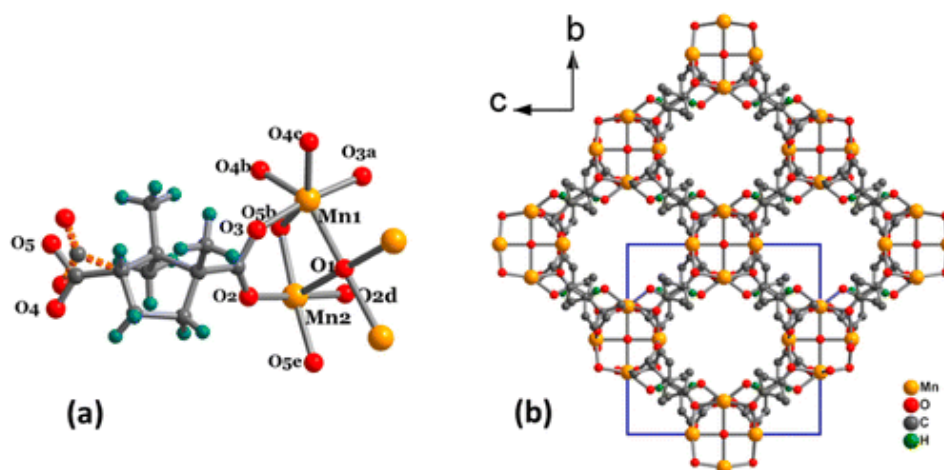


Figure 19. View of (a) the building unit and (b) the Mn_4O cluster-based body-centered-cubic framework of $[\text{Mn}_4\text{O}(\text{D-cam})_4]^{2-}$ ⁷².

This MOF crystallizes as 5-10 μm uniform cubic particles. Thus, the material could be packed into 10 cm long × 4.6 mm i.d. column for the separation of (±)-ibuprofen and (±)-1-

phenyl-1, 2-ethanediol. In the first case, the (+)-isomer was almost unretained, while the (-) isomer was retained and exhibited a strong tailing associated to strong interactions with the chiral stationary phase (Figure 20). The chiral recognition mechanism was explained by hydrogen-bonding and electrostatic interactions.

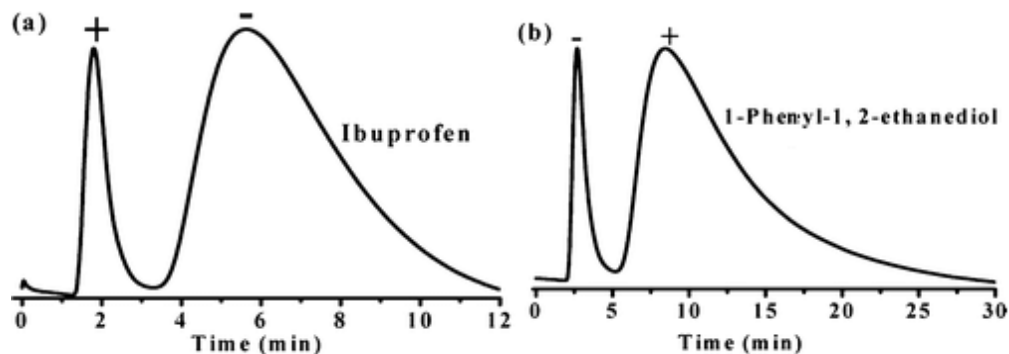


Figure 20. HPLC chromatogram on the Mn_4O -based homochiral MOF column ($10\text{ cm} \times 4.6\text{ mm i.d.}$) for the enantioseparation of (\pm)-ibuprofen (a) and (\pm)-1-phenyl-1,2-ethanediol (b) racemates, isocratic elution mode, mobile phase 96:4 hexane:isopropyl alcohol, flow rate 0.2 mL/min^{72} .

4.1.2. (R)-CuMOF-1@silica

A core-shell composite (R)-CuMOF-1@silica has also been proposed for chiral separations⁷³. The MOF itself contains an H-bonded chiral framework made of BDA-bridged $\text{Cu}_2(\text{carboxylate})_4$ paddle-wheels that crystalizes in the chiral space group I222. Each $\text{Cu}_4(\text{BDA})_2$ macrocycle forms cavities having a diameter of 6.2 \AA each⁷⁴. The material was tested as HPLC stationary phase for the enantioseparation of various sulfoxide enantiomers. Very high selectivity between the two enantiomers of phenyl methyl sulfoxide was obtained as evidenced on Figure 21.

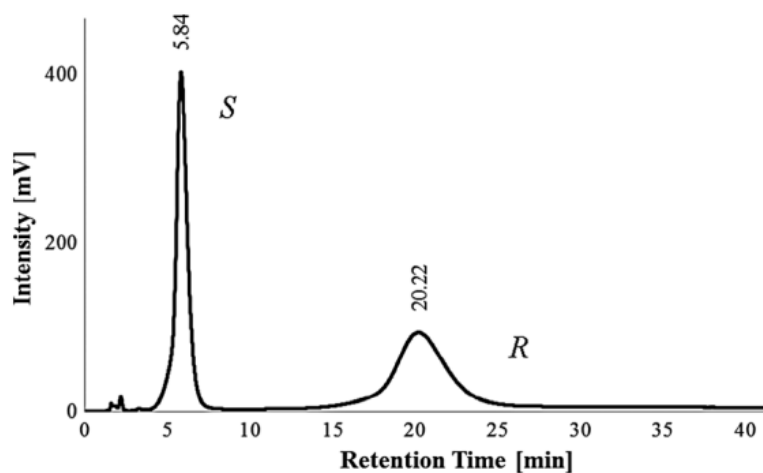


Figure 21. Enantiomer resolution of phenyl methyl sulfoxide on (R)-CuMOF-1@silica composite column ($15\text{ cm} \times 4.6\text{ mm i.d.}$), isocratic elution mode, mobile phase 50:50 hexane: EtOH, flow rate: 1.0 mL/min^{73} .

The separation factors were larger for unsubstituted and *p*-substituted phenyl methyl sulfoxides than for their *o*- and *m*-substituted isomers. Interestingly, in all cases (S)-isomer

was eluted first, followed by the peak of (R)-isomer that is much more retained. This separation behavior was explained by the inclusion of the (R)-enantiomer in the pores of (R)-CuMOF-1, supported by hydrogen bonding interactions between the phenolic OH group of (R)-CuMOF-1 and the SO group of the sulfoxide (Figure 22). In addition, polar and or big substituents (Cl and OMe) at the ortho-position of the phenyl group weakened this hydrogen bond formation explaining the poor enantioselectivity observed.

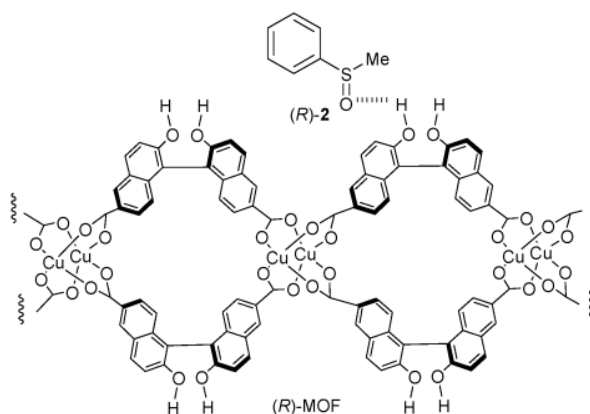


Figure 22. Proposed chiral recognition mechanism of methyl phenyl sulfoxide enantiomers⁷³.

4.2. GC

Though the number of studies is significantly less than those dealing with HPLC, chiral MOFs have also been investigated for GC chiral separations. Hence, a series of chiral MOFs were first prepared by adding different chiral recognition sites onto the mesoporous MIL-101-NH₂ material through a post-synthetic covalent binding of ligands such as (*S*)-2-Phenylpropionic acid (*S*-2-Ppa), (*R*)-1,2-epoxyethylbenzene (*R*-Epo), (+)-diacetyl-*L*-tartaric anhydride (*L*-Ta), *L*-proline (*L*-Pro) and (1*S*)-(+)-10-camphorsulfonyl chloride (+-Cam-S)⁷⁵. Their chiral separation abilities were then checked on 12 racemic mixtures using a capillary column (30 m long × 0.25 mm. i.d.).

MIL-101-*S*-2-Ppa column separated the racemates of 2-methyl-2,4-pentanediol, 1,2-pentanediol. However, its application does not look universal as hydroxyl groups play significant role in the mechanism (single-OH alcohols were not separated). Apparently, the separation relied on the chiral matching of diols interacting with the chiral center of the ligand and the O...H...O=C hydrogen-bonding interactions between diols and the MOF.

Citronellal racemates were separated using MIL-101-*S*-2-Ppa and MIL-101-*R*-Epo driven by π - π -interactions. All racemates were separated on the MIL-101-(+)-Ac-*L*-Ta due to hydrogen-bond sites (-NH₂ and/or -OH groups), giving strong hydrogen-bonding interactions between MIL-101-(+)-Ac-*L*-Ta and the compounds and peak tailing. However, nothing was separated on MIL-101-1*S*-(+)-Cam-S due to the lack of π - π and hydrogen-bonding interactions sites in this MOF. The authors did not propose any detailed separation mechanism. But since the kinetic diameter of analytes is significantly less than the pore size of MIL-101 (~14 Å), adsorption of the molecules in the MOF pore should be a key step here. For further investigations, one would ideally consider using a mesoporous stable MOF material with a functionalize linker in order to make a chiral ligand and study any possible interesting properties without changing systematically the framework.

4.3. Conclusion

Although the discussed MOF-packed chiral columns showed high chiral recognition ability, the peak shape and column efficiency are still not satisfactory, probably due to non-specific interactions and inhomogeneous packing material. The ideal material for chiral separation should not only present adequate chiral selectivity of MOF but also be synthesized following the requirements for chromatography (uniform microcrystals with narrow particle size distribution), which remain highly challenging.

5. Solid-phase extraction

The application of enrichment techniques, especially SPE, before the step of analysis is essential when traces are looked for. The trapping material needs to be selective to simplify the following chromatographic separation but the efficiency requirements for cartridges used in SPE are much lower than those of HPLC or even GC. Hence, in case of non-possibility of using the MOFs as stationary phases for chromatography, it could be successfully applied for the extraction of molecules from complex mixture followed by conventional GC- or LC-analysis.

Basically, the mechanism of SPE is similar to the one of chromatography: the solid material used can be considered as a stationary phase and the solvents used for rinsing and removing the target compound as a mobile phase. Using MOFs in solid-phase extraction could have a big impact on improvement of the quality of trace enrichment. Indeed, a few studies demonstrated that MOF enabled both holding the targeted analyte and the removal of unwanted compounds. This was tentatively explained by the unique properties of this class of materials such as molecular size exclusion in case of MIL-101⁷⁶. MOFs could be used as single crystals, but composites with other materials can increase the adsorption efficiency and selectivity for targeted molecules. To our knowledge, the first study of using MOFs as SPE material has been published in 2012 by Sohrabi et al.⁷⁷ [(Fe₃O₄-Pyridine)/Cu₃(BTC)₂] has been applied for preconcentration of Pd(II) and its quantification using flame atomic absorption spectrometry (FAAS). The magnetic properties of the sorbent contributed to a rapid and easy extraction of the target ions from the solution (up to 96.8%).

5.1.1. MIL-101(Cr)

MIL-101(Cr)/Polyaniline (PANI)/SiO₂ has been exploited as sorbent for extraction and enrichment of carvacrol and thymol in plant and food samples⁷⁸. In this study, aniline was polymerized inside pores of the MIL-101(Cr) and distributed on the surface of the composite using silica microparticles. The obtained material was packed into a 1 mL cartridge (l = 50 mm, i.d. = 7 mm) supported by 2 frits. Sorption performances of the MIL-101(Cr)/PANI/SiO₂ composite have been compared with widely used in SPE polydimethyl siloxane (PDMS) and PANI/SiO₂. For extraction of carvacrol and thymol, MIL-101(Cr)/Polyaniline (PANI)/SiO₂ demonstrated about 11.5- and 22.5-times better efficiency. The ratio “surface-to-volume” as well as the interactions with analytes increased due to the presence of MIL-101(Cr) in the sorbent. The composite also demonstrated good pH stability, which was important because the analytes extraction efficiency depends on its tautomeric form.

The application of MIL-101 as SPE sorbent for the analysis of multiclass organic UV filters in water was proposed recently by Nurerk et al.⁷⁹. The extraction efficiency of the MOF sorbent used as pure crystals was compared to commercial cartridges of C₁₈-SiO₂ and a proprietary Hydrophilic- Lipophilic Balance (HLB) adsorbent. The recoveries obtained using MIL-101 were much higher (6-52%) compared to the C₁₈-SiO₂ sorbent due to a synergic effect of π - π and hydrophobic interactions. The MOF exhibited a much higher recovery in comparison with HLB sorbent and also improved the extraction ability of UV filters due to the larger surface area.

5.1.2. UiO-67

UiO-67 is an upper analogue of UiO-66 that exhibits a reasonable chemical stability, although not as good as UiO-66 under humid conditions⁸⁰. UiO-67 pure crystals were used as SPE sorbent for trace enrichment of phenoxyacetic acid (PAA) herbicides in vegetables¹⁶. Analytes were captured due to hydrophobic interactions, π - π -stacking and hydrogen bond interactions with Zr-OH groups. The extraction efficiency depended on acidity level and the optimum results (up to 95% of recovery) were obtained at pH=3, while increasing pH from 3 to 5 decreased strongly the extraction recovery, which was explained by stronger attraction of hydroxyl-anions than PAAs at neutral or deprotonated form despite the high affinity to Zr-OH. In case of pH < 3, a decrease of adsorption was observed, explained by the large repulsive force between Zr-O-H⁺ and protonated PAAs. Therefore, this MOF demonstrated as a whole a good recovery that strongly depends on the observed conditions, which limits its application.

5.1.3. Zinc-based MOF with histamine

A Zn-based MOF synthesized from zinc and histamine was described by Amiri et al.⁸¹ as a highly efficient material used in estimation of organophosphorus pesticides (OPPs) in commercial grocery products. The structure of the obtained material is close to ZIF-8 and the selectivities of these two MOFs were compared, as well as to an activated carbon and C-18 bonded silica. The Zn-MOF predominance over standard sorbents was explained by the higher porosity of the MOF combined with adsorption sites having a high affinity for phosphorus. The higher extraction efficiency compared to ZIF-8 was account for the increase of hydrophobic interaction and π - π -stacking between the aromatic rings of pesticides and MOF ligand, leading to recoveries of target compounds between 91.9 and 99.5%. All the results were repeatable, which proved the good stability of the MOF under testing conditions.

5.1.4. MIL-53(Al)-NH₂ modified with histidine

A novel application of MOFs in the chiral separation field has been proposed by Lu et al.⁸² Instead of the fabrication of high-quality homochiral MOF columns, authors used mixed-matrix membranes. This alternative material gathered the advantages of a pure polymer matrix such as its mechanical stability and easy processing with the one of the MOFs, which terminal organic ligands resulted in a good interfacial compatibility and separation properties. As an example, the microporous flexible Al terephthalate MIL-53(Al) (non-chiral MOF) grafted on a polyestersulfone has been subjected to a cross-reaction with L-His, the amino acid giving the enantiomeric properties to the material. The average pore diameter of the obtained MIL-53-NH-L-His (5.4±0.1 Å) is lower than that of pristine MIL-53-NH₂ in its open form (6.9±0.5 Å). The chiral separation was performed in liquid phase, but authors used the gas chromatography to monitor if the separation proceeded. The results proved that the MIL-

53-NH-L-His nanocrystals act as an enantioselective sorbent for *R*-(+)-1-phenylethanol over *S*-(-)-1-phenylethanol (ee=71%) since the peak of the *S*-enantiomer was almost not detected (Figure 23). It gave evidences that the MIL-53-NH-L-His exhibits promises for separating enantiomers, although the pore size of this MOF does not allow separating larger chiral molecules of interest.

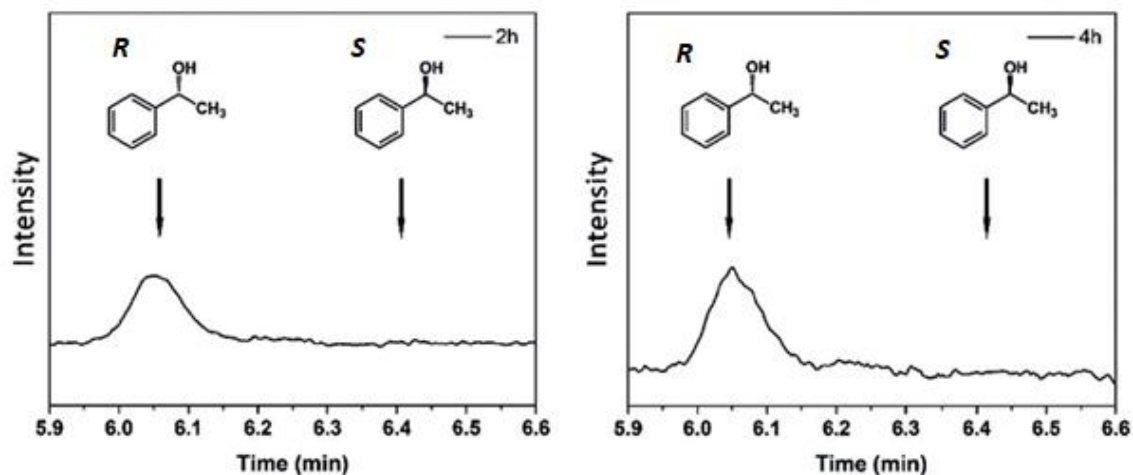


Figure 23. GC chromatograms of resolved 1-phenylethanol enantiomers after separation for 2 h (left) and 4h (right) under conditions of 0.01 mol/L racemic 1-phenylethanol as feed⁸².

5.1.5. Towards implementation of size exclusion effects of MOFs

As MOFs exhibit controlled pore size and shape, one can take advantage from the size exclusion effect (SEE) for the separation and extraction of macromolecules including biomolecules, as described in a recent review.⁸³ In addition, SEE could allow original sample preparation capabilities for peptides enrichment and later for phosphopeptides, glycopeptides, glycans, proteins and nucleic acids.⁷⁶ Thus, the contribution of MOFs for biomolecules analysis from sample preparation to separation could be of major interest if their stability in water is high enough.

Remark *Stricto Sensu*, in size exclusion chromatography, interactions with the SP are prohibited for the determination of the Mw of polymers. For that purpose, MOFs that could interact with the molecules of interest would be useless in a regular SEC separation mode.

5.2. Conclusion

With time, MOFs have been widely considered in different fields of separation applications and SPE is a very promising one using both pure MOF crystals^{16,79,82}, and composites of MOFs with other sorbents⁸¹. High extraction efficiency, selectivity and specificity together with reproducibility and reusability have been reported. In comparison with commercially available sorbents, MOFs predominantly demonstrated better results^{81,82}, evidencing their potential for application in SPE. In addition to SPE applications, MOFs have been investigated in Solid Phase Micro Extraction (SPME), stir bar and dispersive and microdispersive SPE.⁸⁴

6. Conclusion

As shown in this review, MOFs have been to date investigated as new materials for different kinds of chromatography and sample treatment methods based on compound trapping due to their interesting properties including a high-modular ordered structure, a tunable porosity, a large surface area, and an ability to establish selective interactions with target analytes according to their composition. The first results have been obtained using GC but this technique presents some limits such as the fact that not all the compounds can be studied, especially nonvolatile and thermally labile ones due to the relatively high temperature required. Therefore, researchers nowadays pay more attention to investigations in area of LC as it is more universal. The area of extraction and preparative separations must be mentioned too.

However, the topic still requires more thorough investigations. Several problems have already been overcome such as decreasing the column backpressure in HPLC by developing synthesis methods in order to get micrometric homogeneous particles. Still further studies and testing are required using more complex but promising MOFs, especially for chiral separations. The chemical and thermal stability of the MOFs in working condition as well as their possible high cost and, sometimes, the degree of complexity of their synthetic conditions and/or the lack of monodisperse microparticles still inhibit their practical use. Therefore, future studies should focus mainly on thermally and chemically robust MOFs, like for example Zr(IV) and Ti(IV) carboxylates, and should consider the shaping step required prior to the MOF use.⁸⁵ One can also think at varying the nature of core particles for the composite materials: it can change the stability and add specific properties missed by the MOFs. At the same time, there is a niche for the development of future stationary phase materials for high-added values applications, such as chiral selective membranes. Last but not least, for valorization of the developed materials, the increase of performances, i.e. selectivity and resolution, provided by the modification of a support by grafting MOFs must be fully demonstrated.

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