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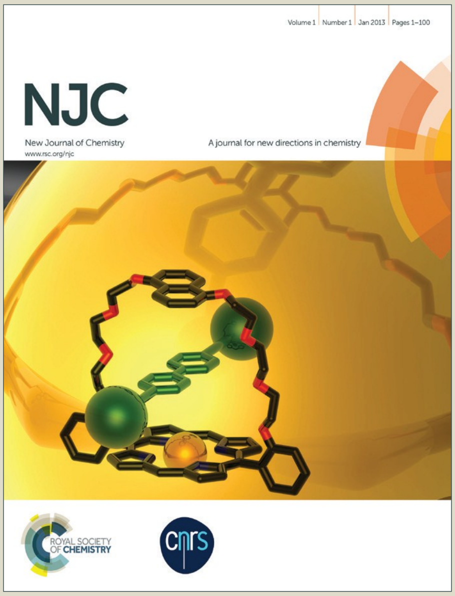

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PERSPECTIVE

Surface molecular engineering in the confined space of templated porous silica

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Advanced materials for molecular sensing, selective adsorption and heterogeneous catalysis require a fine control at the surface-fluid interface. To reach this objective several aspects of the material have to be considered: i) the molecular structure of the active sites, ii) their vicinity at the nanometer scale of length, iii) their distribution in the solid and iv) the confinement controlled by the size and shape of the porosity. The approaches developed to synthesise such materials are reviewed here considering mainly mesoporous templated silicas such as MCM-41, SBA-15 and related materials. In addition, a new nomenclature (**InGASE**) is proposed to classify hybrid or non hybrid materials depending on the location of the function in the porous solid support and the nature of the linker. Special attention is devoted to the different strategies described in the literature to control the grafting or anchoring of organic functions and metal complexes. The challenge is to obtain isolated and well-defined unique sites in a confined nanometric space with an appropriate environment. Applications in the fields of catalysis, adsorption, sensing and drug delivery are breifly surveyed.

For you François and for "la joie de vivre", the friendship and the devotion to the community that you brought to us during your outstanding career.

1. Introduction

Biological systems are often considered as models when developing materials for catalysis or separation. Indeed, such systems behave as receptors or enzymes that have been optimised by natural selection to operate at relative low temperatures and at a quasi-neutral pH in aqueous solution. Confinement and molecular recognition are two key factors of their high selectivity and efficiency. Among them, metalloproteins are good examples of such systems.[1] Indeed, their active sites are well-defined mononuclear or oligomeric metallic centres located in nanometric cavities. Furthermore, their structure consists of a folded protein allowing specific molecular interactions and selective catalytic transformations. Accordingly, two aspects need to be treated for the design of bio-inspired advanced materials: the structure of the active site and its local environment for confinement control.

Bioinorganic molecular models of the active site of metalloproteins are widely covered in the literature. These molecular analogues have been developed mainly for structural determination of the active site, using spectroscopic techniques.[2] However, their success is limited when reactivity is at stake, since the confinement is absent. Grafting bio-mimetic complexes into the pore of a solid support can correct for the absence of confinement. In addition, the loss of mobility prevents the dimerisation of the metal complex, often observed in solution for the molecular analogues. For that purpose, polymers and inorganic oxides are the most used supports. The latter possess more defined porosities and exhibit higher mechanical and thermal stabilities, which is preferable for applications in catalysis, adsorption and sensing.

For instance, zeolites combine both active sites and confinement. These microporous solids are crystalline aluminosilicates synthesised in the presence of molecular templates (hydrated inorganic cations or organic molecules such as NR_4^+, R = Me, Et, Pr, etc) that define the shape and size of the subnanometric pores. The high surface area, ordered micropores, tuneable acidity (Brønsted and Lewis), ion-exchange capacity and shape-selective control allow their use for different processes involving separation and catalysis.[3-6] For example, zeolite ZSM-5 is active in shape selective and acid catalysed reactions used in the industrial production of ethylbenzene from benzene and ethylene, and xylenes from toluene.[7] Titanosilicalite-1 (TS-1) is another example of a zeolite used in industry as a heterogeneous oxidation catalyst. It combines confinement and redox active sites (Ti^{IV} species).[8, 9]

To broaden the analogy with bio-systems, it is important ~~to~~ to access to a large variety of active sites and move towards more organic environments. Despite some attempts to introduce organic functions in zeolites, their small pore size (<1.2 nm) precludes most of the possibilities, as it affects both the zeolite structure and the site accessibility.[5, 10] Indeed, the

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use of porous solid matter brings additional problems such as accessibility and diffusion.[11, 12] For instance, an organic molecular layer is about 0.5 to 1.0 nm thick while accessibility requires a clearance of at least 1 nm. Therefore, pores having a diameter larger than 3 nm are required. This pore size falls within the range of the so-called mesoporous solids (2-50 nm, IUPAC definition), where templated mesostructured porous oxides can be found. By contrast with zeolites, the pores of these solids are templated by auto-assembled surfactants (micelles) and the pore walls are amorphous.[13, 14] Among them, MCM-41[13, 14] and SBA-15[15] are the most studied systems for internal pore organic functionalisation. We will treat these systems extensively here.

The organic functionality can be introduced in a porous oxide either during the synthesis of the porous support or as a modification of the porous support. This is often called co-condensation (or direct synthesis) and post-functionalisation in soft chemistry.[16-18] In the latter case, three main techniques are applied: 1) impregnation of molecules in the emptied porous volume, 2) incorporation of charged species by ion-exchange of cations or anions located in the porosity, and 3) covalent grafting on the surface of the pore, usually called post-grafting.[19, 20] The function can be located: i) in the pore without any covalent bond to the internal surface (***I*** = **in**ternal), ii) fixed via direct bonds to the support (***G*** = **g**rafted) or tethered via an organic linker (***A*** = **a**nchored), or iii) in the solid framework either surfacing (***S*** = **s**urfacing) or inside the bulk (***E*** = **e**mbedded) (Fig. 1, see ***InGASE*** nomenclature, section 2). The application of the material will determine the location of the function in the solid. For instance, optical applications require that the active species be protected inside the matrix, whereas catalysis requires their accessibility and implies specific location at the surface of the pore.

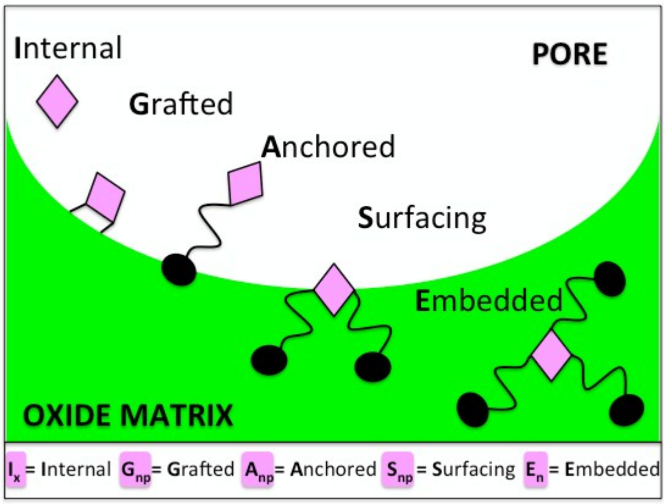


Fig. 1 ***InGASE*** nomenclature for the location of a function in a porous solid: I_x for internal functions (molecules or ions) of the fluid phase (x = ***l*** or ***g*** for liquid or gas) located in the pore without any covalent link to the surface, G_{np}/A_{np} for grafted/anchored functions on the surface of the pore wall, S_{np} for species surfacing at the interface, and E_{np} for functions embedded in the solid matrix (n = coordination number and p = *podality, i.e.,* number of links with the inorganic matrix).

In this review, we will first introduce a new nomenclature in order to rationalise the different functionalisation possibilities encountered in porous materials. Then, we will focus on the different post-grafting approaches described for molecular engineering on the surface of a soft-templated oxide, and in particular on silica and alumina-based mesostructured porous materials. Indeed, post-grafting/anchoring approaches offer more molecular flexibility and chemical combinations with a better control of the porous network than co-condensation techniques (Fig. 2).

These approaches will be described mainly on 2D hexagonal silicas such as MCM-41 and SBA-15, though they can be applied to other mesostructured porous oxides and in most of the cases to non-porous oxides. Impregnation and ion-exchange techniques are not reviewed here, since most of the applications (catalysis, adsorption, separation, etc) require strong fixation of the molecule to avoid leaching during the application. We will outline the recent strategies developed to design multifunctional materials. We are specifically interested in the strategies that can be controlled at a molecular level and that overcome the problem of heterogeneous site distribution inherent to post-synthetic syntheses. Some recent applications of these materials in the field of catalysis, adsorption, sensors and nanomedicine will be described.

2. Nomenclature

In relation to accessibility, reactivity and stability, the denomination of any organic or inorganic function in a porous material should contain information on its location at the solid-fluid (gas or liquid) interface and its binding mode to the solid rather than on the synthesis route or any precursors used as it has been specifically introduced for transition metal ions.[21] Along this line of thought, surface oxygen ions in reactive oxides like MgO are denoted as O^{n-}_{mC} where *n*-provides the oxidation state of oxygen anions and m the coordination number: O^{2-}_{5c} stands for an oxide ion (O^{2-}) surfacing in the 100 plan.[22] For surface transition metal ions similar descriptors are applied, $M^{n+}_{mC,}$ with for instance Ni^{2+}_{4C} for a tetracoordinated Ni(II) ion that is located on the edge of cubic nickel oxide, NiO.[23] This nomenclature may also apply for an ion that does not pertain to the lattice, *i. e.,* being an adatome or a dopant when the coordination does not necessarily correspond to the number of linkages to the host solid. For example, for a monopodal hexacoordinated complex such as $[Co(en)_2(OH)(\equiv SiO)]^+$ (en = ethylenediamine) grafted to silica, the single inorganic Si-O-Co link is not described with the Co^{3+}_{6C} nomenclature.[24] Therefore, podality, often used in surface organometallic chemistry, has to be added as a quantitative descriptor.[25] In fact, a descriptor giving the number of bonds with the surface or "legs" of a function has an equivalent in ^{29}Si NMR spectroscopy, describing resonance of this nucleus in silicate and organosilicate compounds. These species are usually reported as Q_n, T_m, D_p, M_q species. *Q* indicates that Si^{4+} binds four oxide ions, while *T* binds only three O^{2-} ions with a fourth bond with one carbon. Then, D type of silicon binds two O^{2-} ions for two other Si-C bonds, etc. In fact the podality is provided by *n, m, p* and *q* that defines how many of the O^{2-} ions are involved in a Si-O-Si bridges.[26, 27] Accordingly, a Q_2 stands for a $[(\equiv Si0)_2(\equiv SiOH)_2Si]$ moieties and a D_1 for $[(R)_2(\equiv SiOH)(\equiv SiO)Si]$ species. When surface species are transition metal ions, Averseng *et al.* propose to introduce a supplementary information concerning the type of linkage to the support, referring to grafting or anchoring.[29] The former dealing with metal ions directly linked to the oxide support via one or several M-O bond(s) while the latter referring to metal ions linked to the support via a tether. The tether is usually an organic linker that is grafted on one side to the support and on the other to the metal via a ligand to metal type of bond. In this nomenclature, a grafted species is noted (*aM/x,y,z,…*) where *a* is the number of metal centers of the species considered, and *x*, *y* , *z* , … are the numbers of chemical bonds between each metal centre and the surface. For instance, a grafted pair of metal centres would be noted (*2M/1,1*) when each of the metal have a single link to the support (podality = 1). For anchoring, the number is preceded by L so that in the previous example for each metal sharing a single bond with the support, the name becomes (*2M/L1,L1*).

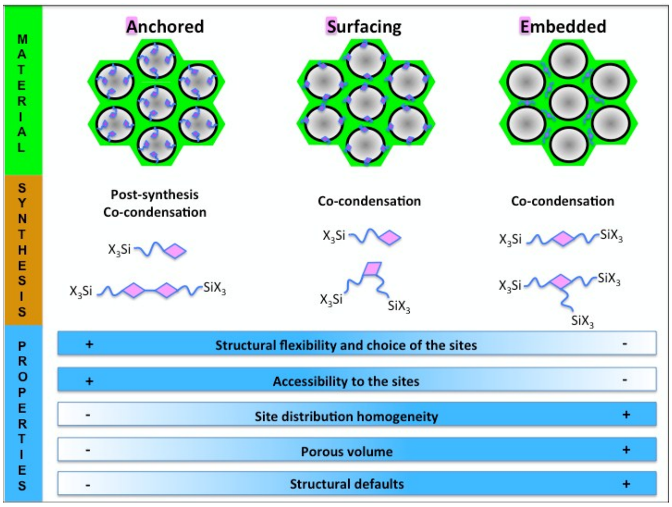


Fig. 2 Post-grafting *vs* co-condensation synthetic approaches and location of the functions in the porous solid support.

In the nomenclature proposed below, we try to conciliate information on location, coordination number, podality and nature of the linkage with the support. In this so-called "***InGASE***" nomenclature, the five letters stand for the location and type of binding of the species on the surface: $\boldsymbol{I_{nx}}$ for internal functions (molecules or ions) of the fluid phase (***n*** = coordination number, ***x*** = ***l*** or ***g*** for liquid or gas) located in the pore without any covalent link to the surface, $\boldsymbol{G_{np}}$ for grafted or $\boldsymbol{A_{np}}$ for anchored functions on the surface of the pore wall, $\boldsymbol{S_{np}}$ for species surfacing at the interface, and $\boldsymbol{E_{np}}$ for functions embedded in the solid phase (***n*** = coordination number, and ***p*** = *podality, i.e.,* number of links with the inorganic matrix, Figure 1).[28] Note that the use of letters ***G*** or ***A*** for grafting or anchoring takes into account the distinction made by Averseng *et al.* when binding of transition metal complexes to inorganic oxides is at stake.[29] The present nomenclature incudes coordination number used by nomenclatures mentioned above for describing surface oxide species or transition metal ions.[21, 22, 23] Note also that a surface metal ion such as Ni^{2+}_{4C} Located on a edge of a step in a bulk oxide is a surfacing species of $\boldsymbol{S_{n4}}$ type where ***n*** = *4* under vacuum and *5* or *6* when one or two molecules are adsorbed on it, like water or other Lewis bases in non-inert atmospheres.

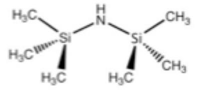
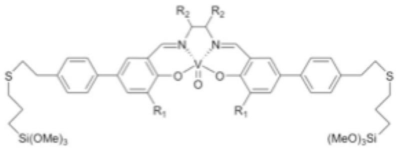
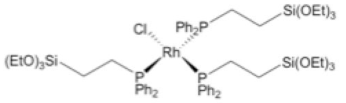
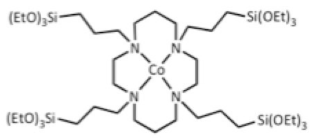
Internal species that occupies more or less freely the pore volume; $\boldsymbol{I_{nl}}$ and $\boldsymbol{I_{ng}}$ may conveniently designate functionalities in the liquid (***l***) and gas (***g***) phases entrapped in the pore. Impregnation methods that consist in introducing solvated species into the pores without any covalent nor electrostatic interaction with the solid phase leads to $\boldsymbol{I_{nls}}$ species where s stands for solvated species. In contrast, ion-exchanged materials would implies $\boldsymbol{I_{nle}}$ type of species where (e) indicates that electrostatic interactions are at stake.[19, 21]

In the case of organic species, the linkage to the support often occurs via one or several organic chain(s) and it is therefore an anchoring. An anchored amine using propylaminetriethoxysilane can generate three different species $\boldsymbol{A_{11}}$, $\boldsymbol{A_{12}}$ and $\boldsymbol{A_{13}}$ describing an amine fixed via a single propyl tether via a mono, di or tripodal silicon atom. These species are usually characterized by their grafted silicon moieties known as *T_1*, *T_2* and *T_3* species, respectively, from solid ^{29}Si-NMR spectroscopy, the utility of the new nomenclature will appear in more complex situations, as we shall see below. In the case of metal complexes, some examples will reveal the advantages of the *InGASE* nomenclature. For example, the monopodal cobalt complex cited above $[Co(en)_2(OH)(\equiv SiO)]^+$, which is six fold coordinated with a single direct link to the support is noted *Co^{3+}-**G_{61}*** or more descriptively *$[Co(en)_2(OH)(\equiv SiO)]^+$-**$G_{61}$***. This nomenclature is particularly adapted when the number of ligands, the coordination state as well as the podality can vary concomitantly.[21] This is the case of grafted carbonyl-Ni(I) complexes on silica $[Ni(CO)_m(\equiv SiO)(SiOH)_{p-1}]$, where *m* may increase from 0 to 4, *p* can decrease from 3 to 1 and the coordination number varies from 3 to 5 concomitantly.[30] In this series of species, one moves from *Ni^+-**G_{33}*** in vacuum, to *Ni^+-G_{43}* in low CO pressure, and *Ni^+-**G_{42}*** (square-planar), *Ni^+-**G_{52}*** (trigonal bipyramidal), and *Ni^+-**G_{51}*** (trigonal bipyramidal), upon increasing CO pressure.[30]

The first functions identified as surfacing species were Ni(II) and Cu(II) species with the bidentate N-salicylaldimine-propylamine-trimethoxysilane (L_B) as organic precursor for surface linkage into a mesoprous silica.[28] The synthesis of the material was designed to afford mainly *$[Cu(L_B)_2]$-**S_{4a2}*** characterized by only two anchoring specified by the indice “a2”. However, it was found that some of the copper complexes possess a mixed organic-inorganic linkage within the same coordination sphere. The proposed notations *$[Cu(L_B)(\equiv SiO)_{2-x}(H_2O)_x]$-**$S_{4a2g(2-x)}$*** or *$Cu^{2+}$-**$Aa_{42g(2-x)}$*** (x = 1,0) take into account such a complexity where the letter “a” and “g” are added to specified the nature of the linkage (anchored or grafted). Note that such surfacing metal ions were accessible to any reactant or ligand from the fluid phase, and the metal could be even exchanged by another metal ion such as Ni^{2+}.[28]

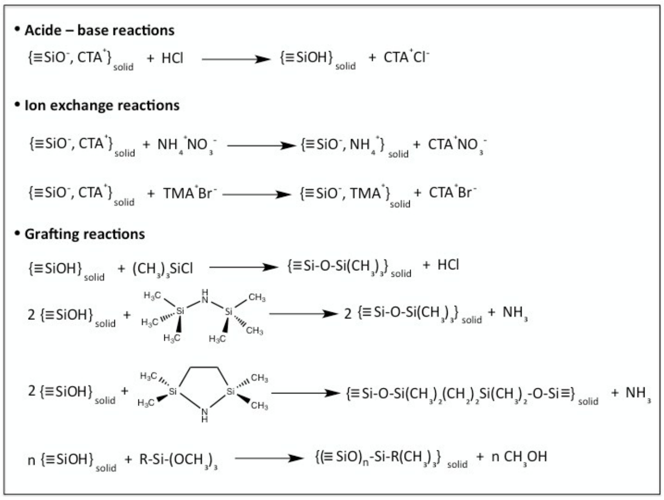
In some cases, the function is fully incorporated in the bulk of the host matrix (embedded) and presents some peculiar properties such as inaccessibility to molecules from the gas or liquid phase. As example, the use of N-(2-aminoethyl)-3-aminopropyltrimethoxysilane (L_A) with Ni^{2+} ions to synthesise a hybrid mesoprous material, generates *$[Ni(L_A)_2(\equiv SiO)_2]$-**$E_{6a2g2}$*** species, with a mixed type of linkage.[28] Note that the new nomenclature allows a description of complex cases where different types of coordination states and different linkages coexist all together as illustrated in both examples given above for ***S*** and ***E*** species.

The location of the function in the material depends on both synthesis procedure and type of molecular precursors. A post-synthesis treatment leads exclusively to ***G*** or ***A*** types of species with a drawback coming from the distribution of functions due to diffusion limitation inside the pore network during grafting. In the case of syntheses by co-condensation, the location of the function in ***G***, ***A***, ***S*** or ***E*** positions may coexist and depends on the nature of the organosilane (OS) precursor (Fig. 1). Useful OS molecules possess at least one or several polycondensable $-SiX_3$, $-SiRX_2$ or $-SiRR'X$ surface attaching functions to react with the hydroxyl groups (X^- = MeO^-, EtO^-, Cl^-, etc and R, R’ = alkyl, aryl, etc) present at the silica surface. One of the key parameters that determines the location of the specific function is the number of polycondensable attaching groups. In the present work, organosilane with *n* polycondensable attaching functions will be designated as *OS_n* (Scheme 1).

Type of Organosilane	Exemple of Organosilane	Ref.
OS_1		**63**
$(OS_1)_2$		**137**
OS_2		**169**
OS_3		**39**
OS_4		**43**

Scheme 1 Examples of organosilanes of OS_x type, x being the number of anchoring functions potentially leading to ***A_{nx}*** types of species .

Since co-condensation is based on statistical distribution of functions in the solid, a mixture of ***G***, ***A***, ***S*** and ***E*** species is expected in the case of OS_1.[31, 32] The type of function (polarity, charge, H-bonding capacity, etc) and the experimental conditions (pH, solvent, temperature, etc) can favour one or the other type.[28, 33, 34] In the case of OS_2 and OS_3, by contrast, ***E*** species will be favoured.[34-39] Furthermore, the presence of the organic function inside the pore wall may generate a loss of structural control compared to the pure silica analogue.[33, 40, 41]



Scheme 2 Exemples of reactions involved in the functionalisation of a mesoporous silica leading to $\boldsymbol{I_{1ie}}$ (top) or $\boldsymbol{G_{41}}$ or $\boldsymbol{G_{42}}$ species.

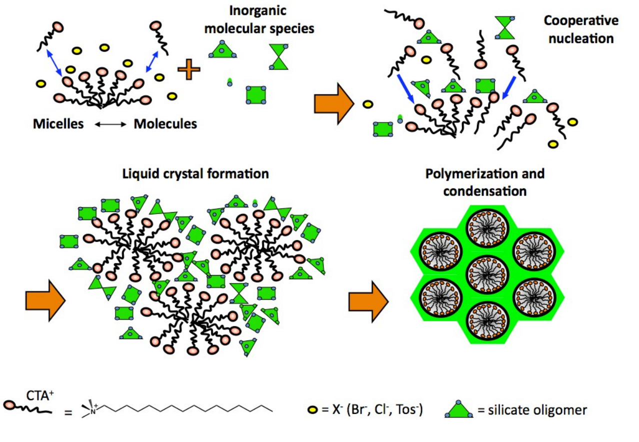


Fig. 3 Formation mechanism of 2D hexagonal mesostructured porous silica using a cationic template of the type CTA^+X^- in basic conditions. CTA^+ = cetyltrimethylammonium, X^- = Br^-, Cl^-, Tos^- ; Tos^- = tosylate $CH_3C_6H_4SO_2^-$.[48, 49]

Finally, materials containing only one type of function will be denoted using the single letter of that function (***I***, ***G***, ***A***, ***S*** or ***E*** materials). ***E*** materials with high content of organic functions are usually called periodic mesoporous organosilicas (PMOS).[35-38, 42] If several types of site functions coexist, several letters will be used, *e.g.,* if both ***A*** and ***E*** functions are present, the material will be denoted ***AE***. For example, Corriu *et al.* developed multifunctional materials with one metal-cyclam complex inside of the framework (***E*** species) and another metal-cyclam complex tethered on the internal surface of the pore of the silica support (***A*** species), using different metal ions such as Cu^{II} or Co^{II}.[43, 32]

3. Mesoporous support: Choice and synthesis approach

The 2D hexagonal MCM-41 is the first and the most frequently used mesostructured porous support. [44 13, 14] Its synthesis has been widely reported, reproduced and optimised.[16] The time of synthesis has also been reduced using specific counterions of the surfactant (e.g. tosylate) or microwave thermal treatments.[45-47] The synthesis is performed in an aqueous solution under basic conditions (pH = 10 - 13). The electrostatic interactions between the solvated oligomeric silicate precursors and the cationic quaternary ammonium heads of the surfactant molecules combined with the hydrophobic interactions between the non-polar surfactant tails drives the formation of the mesostructured solid. [48] The structure is, in fact, generated by the “cooperative” molecular assembly of the surfactant molecules, which are called templates or structure-directing agents (SDA), with the inorganic precursors into ordered nanostructures through non-covalent interactions (Fig. 3).[48, 49] The size of the pore is directly related to the length of the organic chain of the templating surfactant affording pore size diameters from 2.4 to 4.5 nm for C_{12} to C_{22} for the length of the surfactant tail.[50] This size can be measured from nitrogen chemisorption at 77 K using various models. Among them, the most popular is the one proposed by Barrett-Joyner-Halenda (BJH),[51] that unfortunately provides an underestimated value of about 0.7 nm in the above range of sizes.[52-54] At this point in time, the two best methods are the BdB (Broekhoff and de Boer)[55] and the DFT methods, which give similar values (± 0.2 nm). The above range of values was determined using these methods.

Stucky *et al.* demonstrated that these kinds of solids could also be formed below the isoelectric point of silica (pH < 2). In this case, the molecular assembly of cationic silica species with cationic quaternary ammonium species requires that the assembly takes place through bridging anions.[48, 50] Using silica precursors in acidic conditions and cationic surfactants or triblock co-polymers such as P123 as organic template, the SBA series of mesostructured materials can be obtained. The SBA-15, which presents a similar 2D hexagonal structure to MCM-41, is one of the most commonly used mesoporous supports for incorporating functionalities to design materials for different applications. One of the advantages of SBA-15 relies on its superior stability in comparison to MCM-41, though for the latter type of structures much effort has been made using either classic or microwave autoclaving.[48]

The advantage of using the 2D hexagonal MCM-41 is that there is a large range of phase stability contrary to cubic (MCM-48) and lamellar (MCM-50) solids, which can be obtained in similar conditions for higher surfactant/silica ratios.[13, 14] The synthesis, structure and characterisation of mesostructured porous materials and the strategies for synthesising hybrid materials have been summarised in several review articles.[16, 17, 34, 56-65] Some of the reactions involved in the synthesis of these hybrid materials in basic conditions such as for MCM-41 type of silica, are presented in Scheme 2.

Surfactants and block co-polymers are *soft templates*, which allow for the creation of the material mesostructure. The interactions between the template and the framework source lead to a strong ability to control material properties, such as particle size, morphology and porosity. An alternative for creating mesoporosity is to use *hard templates*, which are structured solids. The mesostructured material is built by filling the pores of the hard template (carbon, resin, etc) with the framework precursors followed by the dissolution or decomposition of the solid template.[66-72] This approach, also called *nanocasting*, allows tuneable composition and controllable structure and morphology, although small long-range ordering is observed in the pore walls. In addition, the shape and size of the container can influence the crystallinity and mesostructure of the final material.[73]

4. Design of a multifunctional material

In order to design multifunctional materials starting from a templated oxide and by post-grafting the functions, four main questions arise straightaway:

- Are the functions isolated one from the other in order to afford unique specific sites?
- Is the environment equivalent throughout the solid for each function?
- How are the functions distributed on the surface
- When two different functions (F_1 and F_2) are grafted or anchored what is the location relative to one another?

In order to answer these questions, we have to control the environment both at the short and long distances during the synthesis of the material. The simplest strategy to obtain site isolation is by diluting the function on the surface. A high specific surface is therefore required, which is available for mesoporous materials (~ 600-1200 $m^2.g^{-1}$). Then two options arise: either to incorporate a small amount of guest molecules, or to reduce the number of host sites available for grafting. The first approach is the most widely used, but no control of the distance between functions is at stake. The second one has been effectively used to control the grafting of organometallic complexes. This approach, which is called surface organometallic chemistry (SMOC),[25, 74-77] considers the support as a rigid ligand, and has been mainly applied to the design of heterogeneous catalysts with control at a molecular level. In addition, by using this technique, the vicinity of the metallic active site can be determined by controlled degradation of a heteroleptic organometallic precursor (Fig. 4).[78]An alternative strategy to afford control at short distance is to prepare a dismountable molecular platform containing two or three functions at a designated distance. These functions are left on the surface after grafting (Fig. 5). This approach is derived from the so-called molecular imprinting technique, which has been largely developed in the field of polymers.[79-82] Finally, in order to control the distribution of the functions at both short and long distance with a high concentration of functions on the surface, two approaches can be used: either by steric hindrance using a bulky patterning group that protects the desired function and that is removed after grafting (Fig. 6),[83, 84] or to choose as a molecular pattern a charged molecule that is homogeneously distributed on the surface of the solid, and then graft the desired molecules in the remaining space (Fig. 7).[52, 85, 86] The latter approach, though more complicated from a synthetic point of view, is more versatile and can be adapted to synthesise multifunctional materials.

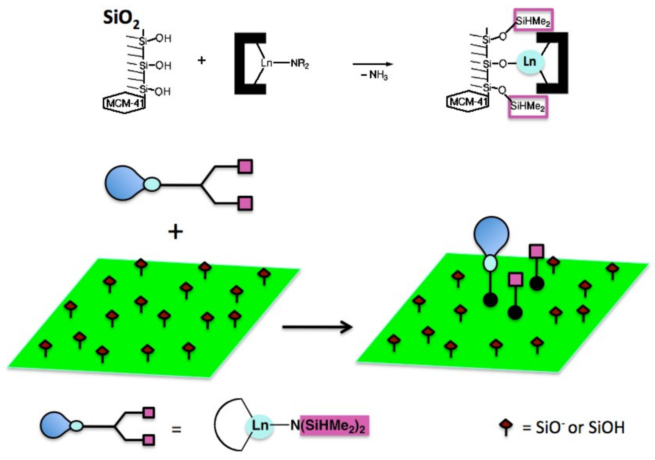


Fig. 4 Controlled degradation of a heteroleptic organometallic precursor to afford site isolation with a defined environment of a $\boldsymbol{G_{n1}}$ grafted function.[78]

5. Dilution for site isolation

Dilution of the guest molecules on the surface of an inorganic support is the easiest way to obtain isolated species. However, low amounts of the targeted function are incorporated, and this does not facilitate the characterisation of the grafted species. If moderated amounts of guest molecules are incorporated, the dispersion of the functions can be further tuned by choosing an appropriate solvent for the grafting. Asefa and his co-workers have demonstrated that the solvent used during the functionalisation of the silica to design acid-base bifunctional heterogeneous catalysts for Henry and aldol reactions (C-C bond coupling) has an influence on both density and spacing between functions.[87-89] They proved that MCM-41 mesoporous silica can be functionalised with a series of amines (basic) leaving some silanol groups (acidic) available for reactivity. The amount of amine incorporated ranges between 1 and 2 $mmol.g^{-1}$. The use of a polar-protic solvent such as ethanol or isopropanol generates isolated basic sites compared to the use of a non-polar solvent like toluene that affords closely spaced basic sites. Indeed, during the grafting reaction in ethanol, ethoxy groups are formed on the silica surface preventing the grafting of additional amine functions.[88] Therefore, the material prepared in ethanol contains a lower amount of basic functions that are better dispersed and characterised by a higher specific surface compared to the material prepared in toluene. The catalytic activity depends on the degree of site isolation, surface area, and relative spacing between both functions. The cooperative efficiency between acidic and basic sites was found to be better in the materials prepared in ethanol or isopropanol.[88, 89] Using this solvent-assisted post-grafting method, Sharma et al. studied a tandem C-C forming reaction (Sonogashira and Henry reactions) using a multifunctional material with grafted Pd(II) diamine complexes, amine groups and residual silanol functions distributed on the surface of a mesostructured porous silica (MCM-41 and SBA-15).[90] Salmio and Brühwiler observed a similar solvent effect for the grafting of a series of amines in MCM-41 in THF and toluene.[20, 91] They suggested that a more polar solvent such as THF generates a more uniform distribution of the functions by increasing their mobility, this effect being more important in the case of strongly interacting amines. The advantage of this approach is that it is simple,versatile, and not too time-consuming. However, there is control neither at close vicinity of the function nor at long distance, thus affording a heterogeneous distribution of acidic and basic functions on the surface.

The choice of the molecular precursor is also important. Tilley and co-workers have developed the so-called “thermolytic molecular precursor” method to generate multicomponent oxide materials that can be used as supports in the design of heterogeneous catalysts.[92] This approach can also be used to generate isolated metal sites by grafting a metal complex containing oxygen-rich ligands such as $L_nM[OSi(O^tBu)_3]_m$ (L = alkoxide, amide, alkyl, etc) onto the inorganic support (MCM-41 or SBA-15) in a non-polar solvent such as hexane. The grafting occurs via a protonolysis reaction, which results in the elimination of HO^tBu and/or $HOSi(O^tBu)_3$.[92] Both M-O-surface and Si-O-surface linkages may form during the grafting procedure, and quantification of the species released by these reactions provides information about the type of sites that are present and the approximate quantities of each.

Another strategy to obtain relatively isolated sites is to use a mixture of the target silane diluted with a “spacer” silane (for example an alkyl group). This approach, termed “cooperative dilution” was developed by Hicks et al.[93] It offers the possibility of introducing hydrophobicity or hydrophilicity by choosing an adequate “spacer” silane. However, a random distribution of the functions is commonly observed, but this distribution is tuned by the physico-chemical differences between both functions. Depending on the nature of the function, several behaviours can be observed: aggregation, interaction with the surface of the support, and different diffusion speeds throughout the channels of the silica. These parameters may influence the distribution and the relative amount of the functions within the solid.

An alternate, elegant approach is to diminish the density of the host sites in the solid by thermal treatment in order to provide a support with isolated host sites. This technique has been largely applied in the design of single-site organometallic heterogeneous catalysts on non-porous silica and it is often called Surface Organo Metallic Chemistry (SOMC).[25, 94] Spectroscopic and reactivity studies have demonstrated that silica treated at 700°C under vacuum is an ideal support to prepare single-site heterogeneous catalysts.[76] Using this treatment, only *ca.* 0.7 $OH.nm^{-2}$ remain in the case of Aerosil® silica. The silanol groups are isolated and statistically distributed at the surface of the solid, with an average distance of *ca.* 1.3 nm between each silanol group.[76, 94] By comparison, a conventional treatment at 200-300 °C would lead to a coverage of 1.5-2.8 $OH.nm^{-2}$.[78, 94] Organometallic complexes of the $[MX_xL_n]$ type (X and L defined from Green formalism)[95] can react with surface silanols ≡SiOH to yield $\equiv SiOMX_{(x-1)}L_n$ along with XH. This reaction corresponds to the replacement of one X ligand by a siloxy ligand, and this occurs without major changes in terms of structure and geometry of the grafted species.[76, 94] Copéret and Basset have extensively developed this approach in the design of single site heterogeneous catalysts for alkene metathesis.[76, 96-98] A detailed spectroscopic characterisation of the grafted species has allowed them to establish structure-activity correlations for these materials.[94] However, in some cases a heterogeneous surface is revealed, because the isolated sites (≡SiOH) are affected by different environments that depend on the number and type of the siloxane neighbouring bridges. This effect is more obvious for metal complexes directly linked to the silica surface.[94] To cope with this problem, Anwander and co-workers have demonstrated that the vicinity of the metallic active site can be determined by controlled degradation of a heteroleptic organometallic precursor (Fig. 4).[78] Tailor-made molecular precursors exhibiting reactive docking positions (a silylamide moiety, for example) and strongly chelating ancillary ligands (eg. Salen type) complexed to a lanthanide ion, *i.e.,* $Ln(L)(NR_2)$, with H_2L = *N,N′*-bis(3,5-di-*tert*-butylsalicylidene)-ethane-1,2-diamine), R = $SiHMe_2$ and Ln = Y, have been designed to allow grafting of LnL complexes surrounded by R functions.[99] The grafting sequence involves silylamine elimination and subsequent lanthanide dioxide bond formation and concomitant surface silylation due to the released silylamine. The vicinity of the grafted metal complex is therefore hydrophobised, which can affect the catalytic activity. These materials show higher activity in the Diels-Alder reaction than the corresponding molecular analogues, since grafting avoids dimer formation, which competes with substrate coordination during the catalytic reaction.[99]

6. Control at short distance: molecular imprinting

The technique of molecular imprinting (MI) allows material design for specific recognition, with the formation of specific sites by the use of templates based on the « lock-and-key » principle. At the end of the 1940s Dickey prepared specific adsorbents based on molecular recognition.[100]-[101] His pioneering method consisted in building the structure of the adsorbent in the presence of the compound for which the adsorbent was sought. As a proof of concept, he used methyl orange as an adsorption target and the adsorbent was prepared by imprinting the molecule in a nanostructured silica gel. Subsequent removal of the imprint molecule yielded a gel capable of specific adsorption. In this example the adsorbent holds the molecule by van der Waals’ forces, hydrogen bonds, inter-ionic attraction or other non-covalent interactions.[100] This type of approach was extensively developed some decades later and continues to be a fruitful

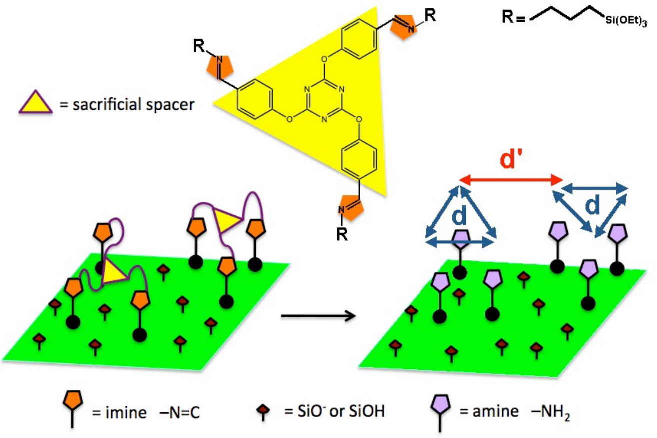


Fig. 5 Use of a dismountable anchored platform (***A$_{33}$*** type) to control the distance between the grafted ***A$_{1x}$*** amines, based on the molecular imprinting principle. [102-104]

strategy to synthesise functionalised materials both on silica gel[105-107] and on cross-linked polymers. [80, 108-112]

Molecularly imprinted polymers (MIPs) have been applied in an increasing number of fields where molecular bonds are at stake. These include the use of MIPs as (i) tailor-made separation materials,[110] (ii) mimics of antibody and receptor binding sites in recognition systems,[111, 113] (iii) enzyme mimics for applications in bio-inspired catalysis,[112] and (iv) recognition elements in bio-sensors.[79-81, 114] The stability and low cost of MIPs make them advantageous for analysis and industrial applications. A key step in the synthesis design is the selection of the functional monomers, which are the building blocks to form the material. The polymer's specificity and affinity are directly related to the strength of the complex formed between the template and the monomers. The fixation of the binding groups can be achieved by various chemical reactions (e.g. condensation and addition polymerisations) as long as these reactions do not disrupt the preformed template-building block complex.[111] Two main approaches –covalent and non-covalent— have been developed for obtaining MIPs. These depend on the interaction between the template and the building blocks during the imprinting step. In the covalent approach, reversible chemical bonds are established between the template and the functional monomers, thus allowing for accurate control during the introduction of the functional groups at certain vicinity. However, cleavage of the template from the polymer is sometimes problematic and prior modification of the template is required. [111, 112,115] Metal-coordination has also been studied to orient different functional groups during imprinting.[112] In the non-covalent approach, hydrogen bonds, ionic interactions, van der Waals forces and hydrophobic effects are involved. Therefore, excess of the functional monomer is used to stabilize the template-monomer entity during polymerisation, which can afford heterogeneous sites. Despite this drawback, this method has been largely employed because of the ease of preparation and the large number of available functional monomers.[111, 112]

Wulff was the first to extend molecular imprinting to silica using the covalent approach.[116, 117] Using an elegant approach, he demonstrated that it is possible to graft two amine groups at a specific distance by connecting them through a spacer that is removed after grafting by hydrolysis under mild conditions. Sasaki *et al.* used a similar approach to position three amines using different types of tripodal spacers on a silica-gel surface (Fig. 5).[102, 103]

Moriahra et al. developed molecular imprinting in silica and aluminium-doped silica for heterogeneous catalyst design by using chiral amines as templates to form "molecular footprint" cavities in the solid and induce chiral recognition. [118-120] These materials were tested as catalysts of acyl transfer reactions, condensations, racemisations and reductions. Their studies show that the configuration of the template bound during imprinting predetermines the structure of the cavity and the catalytic reactivity through molecular recognition. Molecularly imprinted silicas were further developed by Davies, Katz and co-workers for applications in catalysis [105, 106, 112, 121] As in the previous studies, they used a "sacrificial spacer" such as an aromatic ring carrying up to three *3*-aminopropyltrialkoxysilane side groups. This system generates and occupies microporosity and attaches functional organic groups to the pore walls with a controlled distance between the amine functions. The trialkoxysilane part of the molecule's arms is incorporated into the silica framework during the sol-gel synthesis. After removal of the aromatic core, a cavity is generated with spatially organised amine functions covalently linked to the pore walls.[106] This technique was applied by Shin et al. to position two or three amines by post-grafting a platform carrying the amine groups on mesostructured porous silica (SBA-15) under diluted conditions.[104] The surface was then covered with long-chain functions (C_{18}) in order to isolate the template molecules and therefore create microporous cavities on the coated surface of the mesoporous silica after removal of the template molecules under mild conditions. This strategy has even been applied to incorporate a mixture of different chemical functionalities that are locally organised relative to one another. Bass et al. have synthesised bifunctional thiol-amine sites on mesoporous silica by using a xanthate-protected imprint that reacts thermolytically to generate both thiol and amine functions in the final solid.[122]

The local organisation of chemical functionalities is demonstrated by using molecular probes based on orthogonal coupling strategies for thiols, amines and thiol-amine pairs. This molecular imprinting technique has been extended to the use of a thermodynamically stable metal complex to introduce two ligands that are near each other.[123, 124] This method called "metal-template / metal-exchange", used at low surface loadings ensures correlated pairs of covalently attached ligands. Stack and co-workers have demonstrated that a stable $Cu^{I}L_2$ (L = phenanathroline derivative) complex can be first grafted onto a mesoporous silica such as SBA-15, and then the templating metal is exchanged by the desired ion –such as Fe^{II} or Mn^{II} — to afford a catalyst for epoxydation.[123, 124]

The main advantage of the molecular imprinting approach is the easy control of the distance between the grafted functions, which are, in the majority of the cases, within a ~ 1 nm length cavity. However, a low amount of functions is incorporated (< 1 molecule.nm^{-2}) and the synthesis of the organosilane precursors is not always straightforward, which limits the use of this technique.

7. Controls at short and long distance

In order to control the distance between grafted functions at short and long distance, Jones & McKittrick have developed a simple molecular patterning/spacing approach that can be used to create site-isolated molecular catalysts at a high loading of functions. The authors called this approach the “protection-deprotection” method (Fig. 6).[93] They have applied this method to isolate aminosilicas from each other on the surface of a mesoporous SBA-15 silica, that possesses an average pore diameter of ~ 5 nm. These amines can be further complexed to a metal ion to allow the fixation of the metal complex within the solid support. For that purpose, a bulky molecule possessing a tritylamine function was designed and synthesised.[83, 84] Indeed, a bulky group is used to protect the amino group of the tether that is later deprotected once the tether is covalently grafted onto the silica surface. An N=C bound is formed, that can be easily hydrolysed under mild conditions. By varying the size of the protecting group, the amine spacing and loading can be controlled. This approach presents three advantages: i) a high amount of the function (up to 1.3 mmol NH_2/g of solid) can be incorporated, ii) the protected amines are homogeneously spaced due to steric interactions between the phenyl groups of the protecting group, iii) the protecting group limits both amine-amine as well as amine-silanol interactions.[83, 125, 126] Therefore, the distribution of the functions on the surface is more homogenous than in the traditional dilution grafting methods. The utility of this scaffold technique in the design of supported metal complex catalysts with single-site characteristics has been demonstrated in creating well-defined constrained-geometry Ti and Zr catalysts for ethylene polymerisation.[93, 127-130] This method has been used by other research groups to tailor organic functions on both SBA-15 and MCM-41.[131]

This technique presents the advantage of incorporating a high number of functions using few synthesis steps. However, a limited number of functions can be incorporated. For the time being, researchers have only used amines. The distance between the functions cannot be greatly varied, since this approach depends on the protecting group used. In addition, during the first step of the synthesis, the protected functions are statistically distributed on the surface, even if the steric are statistically distributed on the surface, even if the steric hindrance also governs the arrangement of the functions on the silica surface (Fig. 6).

Ariga and co-workers have reported a pioneering study on bio-inorganic hybrid materials using organosilane cationic surfactants carrying a peptide or an amino acid residue as a structure-directing agent. After forming the mesostructured porous silica using a direct synthesis, hydrolysis of the linkage between the surfactant and the peptide (or amino acid) leads to regular mesopores with immobilised amino acid residues.[132, 133] The functions are homogeneously spaced on the surface of the mesoporous silica due to electrostatic repulsion between the cationic surfactant molecules during the synthesis of the solid. In the case of alanine, the hybrid material obtained using this approach catalyzes acetalisation of ketones in ethanol under mild conditions.[133]

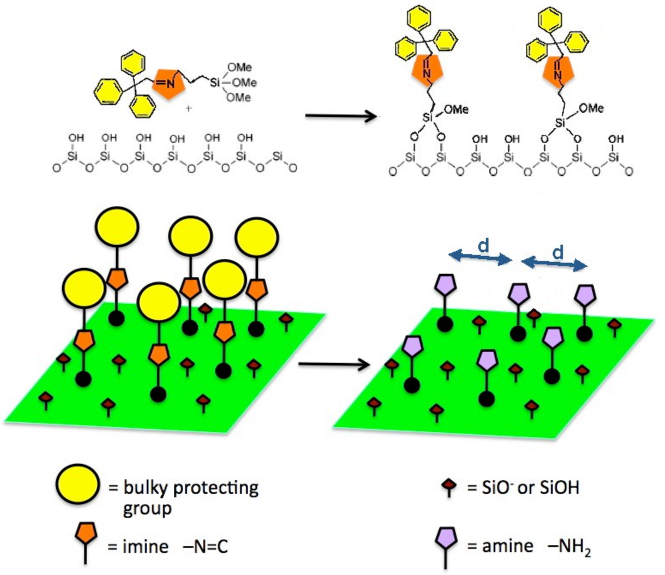


Fig. 6 Protection-deprotection method using a bulky protecting group moving from a ***A₂₁*** amide to a ***A₁₁*** amine. [93]

8. Molecular patterning

The surface of a mesoporous silica can be modified by using the structure template –*e.g.* cetyltrimethylammonium (CTA$^+$)— as a molecular stencil. Indeed, the electrostatic self-repulsion between the cationic heads of CTA$^+$ generates a regularly patterned surface. This is the basis of the “molecular stencil patterning” (MSP) approach developed in our group and which will be detailed in the following. Mechanical patterning is a technique that has been largely developed in the design of mesoporous films.[134-137] If molecules are used as stencils, this technique can also be applied to distribute functions in 3D mesoporous oxides.

In the case of 2D hexagonal templated silicas, it has been demonstrated that there is a cooperative assembly mechanism during hydrothermal synthesis (Fig. 3).[48, 49] First, the surfactant molecules interact in the solution electrostatically with the charged silica precursors. For example, in the case of MCM-41, there is charge-matching between the negatively charged silicate clusters SiO$^-$ and the organic surfactant molecules CTA$^+$, which is necessary to bind tightly both components together.

The formation of Si-O-Si covalent bonds, as well as the interaction between the “inorganic-modified” surfactant molecules –including hydrophobic forces— leads to the final

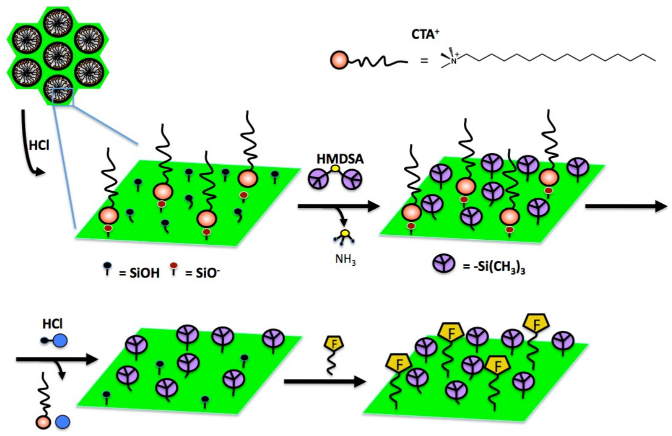


Fig. 7 Molecular stencil pattering technique designed for homogeneous distribution of two functions: function **F** is isolated by hydrophobic groups (**TMS** = trimethylsilyl $(CH_3)_3Si$, $\boldsymbol{G}_{41}$ species). Both CTA$^+$ and TMA$^+$ can act as protecting function to afford a patterned surface. CTA$^+$ = cetyltrimethylammonium $[(C_{16}H_{33})N(CH_3)_3]^+)$; TMA$^+$ = tetramethylammonium $[N(CH_3)_4]^+)$.[52, 85, 138]

ordered mesostructure. Since the Si-O-Si covalent bond enthalpies are more than one order of magnitude larger than those of the non-covalent interactions –hydrogen bonds, electrostatic or Van der Waals—, the formation of the silica-surfactant hybrid precursor is crucial for the mesostructure of the final material. The formation of this hybrid precursor is kinetically controlled by using basic or acidic conditions, as demonstrated in the synthesis of MCM-41 (pH ~ 11) and SBA-15 (pH < 2).[48] This mechanism is favoured when the concentration of the surfactant is not very high, which is particularly the case for the LUS mesoporous silica.[45, 46]

This electrostatic interaction between CTA$^+$ molecules and SiO$^-$ groups is used in the "molecular stencil patterning" (MSP) technique to incorporate homogeneously one or more functions in the silica (Fig. 7). In an as-made mesoporous silica such as LUS or MCM-41, there are ~1.6 CTA$^+$ / nm^2. This corresponds to about 45 % of the surface covered by trimethyl ammonium (TMA) head groups of CTA$^+$ surfactant molecules; this estimate is based on Van der Waals radium of a TMA$^+$ moiety of 0.334 nm.[138] These quaternary ammonium groups can be used as "masking functions" and they are, as we mentioned above, homogeneously distributed on the surface owing to their electrostatic self-repulsions.

As a proof of concept, trimethylsilyl (TMS) moieties were grafted onto the available surface without displacing the masking functions.[85, 138] The use of hexamethyldisilazane (HMDSA) as silylating agent allows grafting TMS moieties around the CTA$^+$ molecules with a minimal displacement of the latter (Scheme 3). Indeed, the reaction between HMDSA and the silica generates ammonia as a by-product, which does not displace CTA$^+$ molecules whereas chlorotrimethylsilane (CTMS) generates HCl, which displaces the CTA$^+$ molecules, and[138] therefore a fully silylated surface is formed instead (Scheme 2).

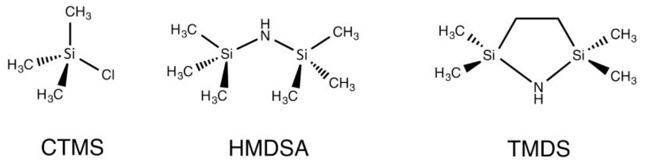
Badiei *et al.* have shown that the ^{13}C and ^{29}Si NMR signal corresponding to the TMS group is shifted depending upon the local environment.[138] Indeed, in the presence of CTA$^+$ molecules, the Si-O-Si angle is smaller than for a fully TMS functionalised surface and this angle can even be greater for a partially TMS functionalised surface without the CTA$^+$ masking functions (Fig. 8). This angle modification explains the shift of the NMR signal, which is an indirect indication of a homogeneous distribution of the TMS groups around the masking functions.

(TMA$^+$) ions can also be used as a masking agent (Fig. 7).[139] This molecule allows avoiding the hydrophobic interactions between the alkyl chains present in CTA$^+$ molecules. The CTA$^+$ / TMA$^+$ exchange can be performed prior to the MSP synthesis. Then, the incorporation of the first function (F$_1$) using the MSP technique is favoured in the presence of TMA$^+$ groups due to steric considerations. The different types of reactions involved in MSP technique are summarised in Scheme 2.

We now come to the second step of the MSP technique. Once the first function is grafted (F$_1$ = TMS), we remove the "masking agent" to reveal the "latent image", rather like in a classical photograph developing (Fig. 7). The solid is treated with 1.1 equivalents of HCl in an ethanol solution at low temperature to avoid TMS leaching.[86]

Then the third step: given the interest in creating multifunctional materials, we can obtain a surface where the second function (F$_2$) is surrounded by the first one (F$_1$ = TMS). This function is often an organic molecule such as a ligand, which can be further complexed to a metal ion.[53, 86, 139-141] It can also be a tether to link the desired molecule or complex.[52, 141, 142] These isolated metal complexes may offer good opportunity to generate highly dispersed metallic nanoparticles, as for example for palladium supported on mesoporous silica.[143]

In order to prove the homogeneous distribution of this technique, we designed a material where F$_1$ was trimethylsilyl (TMS) and F$_2$, an europium (III) complex with 1,10-phenanthroline.[52] The europium complex was used in order to analyse the functions' distribution in the solid. Indeed, the Eu content in a silica fibre was measured by EDX analysis coupled to transmission electron microscopy (TEM). The Eu content is constant along the fibre and in agreement with the chemical analyses of the bulk material. A slight metal enrichment is observed at the external surface of the fibre and at the



Scheme 3 Examples of organosilanes that allow grafting of hydrophobic functions on silica. CTMS = chlorotrimethylsilane; HMDSA = hexamethyldisilazane; TMDS = 2,2,5,5-tetramethyl-2,5-disila-1-azacyclopentane.

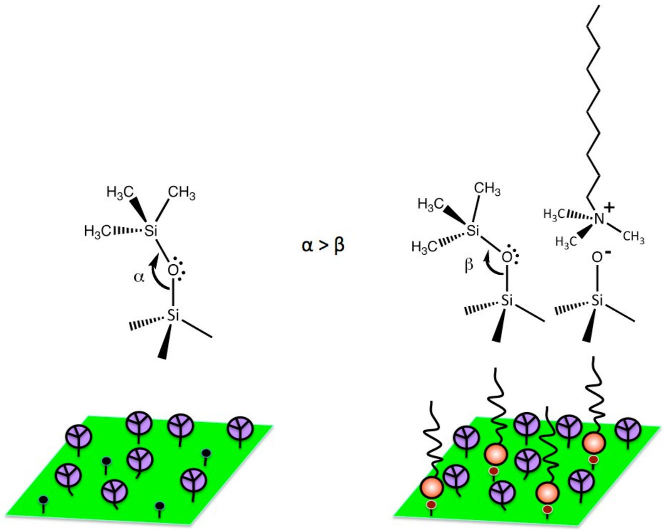


Fig. 8 Si-O-Si angle for the grafted TMS moieties in the absence and in the presence of CTA$^+$ molecules (TMS = trimethylsilyl $(CH_3)_3Si$, ***G*$_{41}$** species; CTA$^+$ = cetyltrimethylammonium $[(C_{16}H_{33})N(CH_3)_3]^+$, ***I*$_{1ie}$** species).[138]

entrance of the channels. This is a consequence of a higher displacement of the masking agent in the more accessible parts of the fibre. Indeed, a less covered surface will lead to an increased number of grafted metal complexes. In addition, the luminescence properties of the material are consistent with single site type. This would appear to validate our MSP technique as an efficient tool to generate isolated sites homogeneously distributed in a mesostructured porous material.[52]

As TMS functions are only linked to the surface through a single Si-O-Si bond, some experimental conditions such as the presence of an amine or an acid, can lead to partial leaching of the hydrophobic TMS functions through Si-O-Si cleavage.[53] Indeed, once an amine function is grafted on the surface, a partial displacement of the surrounded TMS groups can be observed. In that case, a capping of the surface using HMDSA can be performed to full cover the surface. This step is required when an amine is grafted as F_2 function and complexation to a metal ion is desired. A fully covered surface will prevent direct reaction of the metal ion with the silica surface.[53] The distribution of the desired functions is not altered since the spacing functions (F_1) are displaced after the grafting of the function (F_2). This surface reparation can be compared to a retouch of a damaged picture.

A hydrophobic dipoldal function can be used instead of TMS in the MSP technique, *i. e.,* ethyl-1,2-bis(dimethylsilane), using 2,2,5,5-tetramethyl-2,5-disila-1-azacyclopentane (TMDS) as reactant (Scheme 2).[139, 144] This dipodal silane is more robust than TMS and no leaching is observed during the MSP synthesis. This homogeneous hydrophobation of the mesoporous silica using MSP can also be performed for nanoparticles of a size comprised between 50 and 100 nm of diameter.[144]

9. Applications and perspectives

The above overview deals mainly with silica surface chemistry and put emphasis on function linkers, location and distribution. The new nomenclature and the synthesis strategies to control function distribution at the fluid-solid interface can be applied to other types of matrices such as:

- Non-silica oxides such as Al_2O_3, TiO_2, Cr_2O_3, Mn_3O_4, Fe_2O_3, NiO, Co_3O_4, CuO, ZrO_2, Nb_2O_5, In_2O_3, SnO_2, Sb_2O_5, HfO_2, Ta_2O_5, WO_3 and CeO_2.[68, 73, 145, 146]
- Mixed oxides such as Si-Al, Si-Ti, Al-Ti, Zr-W, Ni-Al, Nb-W, Nb-Ta.[145 147, 148 149-154]
- Non-oxide materials such as metals, carbides, sulphides, selenides, phosphates, nitrides, carbons and organic polymers.[155-157,158,159, 71]

The nature of the framework can confer additional properties to the material such as electronic conductivity, magnetic interactions, acidity and redox behaviour. In the case of mesoporous metallic oxides, nanocrystalline domains can be observed within the amorphous walls. Furthermore, hierarchical structures starting from zeolites have been developed in the last years, often called mesoporous zeolites.[160-162] Such materials combine the confinement and specific properties –shape, acidic and metallic sites— of the micropores. They also provide facilitated access to the sites and improved transport within the mesoporous network, which are key parameters for applications such as catalysis and separation. Finally, in addition to silanes, other types of tether functions can be used, such as phosphonates.[163-166]

9.1. Heterogeneous Catalysis

Heterogeneous catalysis is one of the most explored applications of materials so designed. The immobilisation of catalytically active species on inorganic supports enables not only the generation of recyclable catalysts but also comparable ore even higher catalytic activities compared with their homogeneous analogues, owing to the unique environments of the surface.[25, 39, 64, 75, 76, 167-170] Catalytic performance may be increased by: i) the creation of new geometries and arrangements by surface, ii) the increasing stability of active structures by site isolation, iii) a heightened multifunctionality of the surface, iv) the modification of electronic states by surface, and v) the enhancement of substrate density around active sites.[171-174]

There are two general routes to prepare a supported catalyst on a mesoporous silica: (i) stepwise building the ligand and the metal complex at the surface of the material, and (ii) immobilizing a presynthesised catalyst precursor containing an anchorable functionality.[143] The first route is a multi-step approach whereby the intended complex is assembled on the solid support as in a homogeneous solution and likely leads to multisited materials in most of the cases. The second one results in a more well-defined system. However, if the catalyst precursor is bulky, obstruction of the pore entrance is often

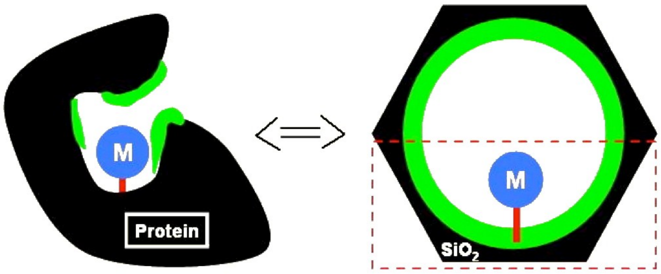


Fig. 9 Bioinspired analogy between the structural principal of metalloenzymes and the design of a supported metal ion in the organically modified pore of a MCM-41.[52]

observed, leading to a non homogeneous distribution of the functions in the silica channels.[175] In addition, depending on the ligand, during the incorporation of the metal complex, some of the anchorable ligands can be decomplexed, leading again to some ill-defined sites on the support.[175] The presence of such ill-defined sites on the surface of the heterogeneous catalyst makes them often less reactive and selective than their homogeneous analogues.

Heterogeneous catalysts supported on mesoporous silica often show improved catalytic activities. Both local environment and pore confinement can affect the reactivity of the grafted species for low pore size materials such as MCM-41 with a bulky function or a metal complex inside the pores. By contrast, the local environment of the grafted metal complex may have a more significant influence than the pore confinement, especially in the case of relative large pores such as in SBA-15 mesoporous silica, where no diffusion restriction of substrates and products is at stake.[176] In the latter case, fine-tuning of the steric hindrance around the metal centre may control the rate and selectivity of the catalytic reaction. Going further in the environment control of an active site, one may take enzymes as a model (Fig. 9). This approach has been particularly developed combining confinement, hydrophobicity and metal-ion based catalytic sites such as Cu^{II}, Fe^{II}, Ru^{II}, Rh^{I} and Mn^{III}.[39, 53, 86, 141, 177-180]

As in the enzymes, one material can combine both acid and basic functions, hydrophobic and redox sites or even acid, hydrophobic and redox functions. Such complex systems could optimise the selectivity in fine chemical production and therefore lower both the cost of the process and the amount of side-products. In particular, much attention has been paid to the double catalytic activation of electrophiles and nucleophiles by acidic and basic functions and tandem reactions. An increasing number of studies are devoted to cooperative catalysis, which functions by grafting different catalysts on the same support.[90, 181]

9.2. Adsorption

Fryxell and co-workers developed a pioneering work in the design and use of selective mesoporous metal adsorbents to treat contaminated water. The incorporation of thiol functions in a mesoporous silica allows absorption of toxic ions such as Hg^{2+}, Pb^{2+} and Cd^{2+}.[182-185] Other ligands such as diamides, sulphonate, iminodiacetate or 3,4-hydroxypyridinone (HOPO) can be incorporated to adsorb lanthanides and actinides.[185-187]

Here again, the design of a multifunctional material can influence the properties of the final adsorbent. As an example, Lam *et al.* have shown that the distribution of the adsorbent function on the surface of a mesoporous silica can have a strong effect on the adsorption properties of the material. They compared two MCM-41 materials with a different distribution of aminopropyl (AP) moieties in the Ag^{+}/Cu^{2+} separation, the aim of the study being the recovery of precious and commodity metals from industrial effluent and waste water.[131] The two materials present a similar AP loading (1.0 – 1.2 $mmol.g^{-1}$) but a different AP distribution: in the first one the functions are randomly distributed by refluxing the AP precursor in toluene in the presence of the silica support, and in the second, the "protection-deprotection" technique developed by Jones *et al.* is used to space the AP functions.[126] In the first case Cu^{2+} is preferentially adsorbed, whereas the second material is 100 % Ag^{+} selective.[131] Indeed, as demonstrated by the Yoshitake group, classical grafting of a relatively high amount of functions (1-2 mmol per gram of solid), results in a broad distribution of distances between the organic functions for MCM-41 and SBA-15 mesoporous silicas.[188] However, the "protection-deprotection" method of Jones *et al.* (Fig. 6) renders a more homogenous spacing between the organic functions. Therefore, the variation in site density affects the distance and interactions between neighbouring sites and, consequently, the site availability for metal adsorption will differ, as observed for an Ag^{+}/Cu^{2+} mixture.

9.3. Sensors

Mesoporous oxides are ideal platforms in the design of chemosensors and biosensors.[189, 190] The modification of the solid surface by organic functions such as -SH, -COOH, $-NH_2$, $-(CH_2)_nCH_3$, and -Ph can confer the material specific recognition of a molecule or a function. The controlled grafting of one or more of such functions and their environment may affect the selectivity in the recognition process of these systems. In addition, due to the high specific surface and volume, many active functions can be incorporated, therefore minimizing the size of the final dispositive. These materials present potential applications in the detection of toxic metals in water,[191] gas sensing,[192, 193] food quality control[194] and optical detection.[190]

Due to the relatively large cavities present in the mesoporous materials (2-50 nm), these solids can host biological species to develop biosensors.[189, 195-197] The main advantages of the inorganic matrix are the increased stability of the system, since the solid prevents denaturing the biological species, and the possibility of recovery and reuse of the active species. The immobilisation of the biomolecule involves chimi- and/or physisorption, which can be tuned by the nature and relative position of the functionalities present in the silica as well as the pore size of the cavities.

9.4. Drug Delivery

The strategies here reviewed were initially developed for bulk mesoporous silica, with particle sizes higher than 200 nm in most of the cases. When the particle size diminishes, the external surface becomes more important, as compared to the internal one (600-1000 m^2.g^{-1}). In that case, the location of the function outside or inside the particle becomes an important issue.[20, 198, 199]

In the past few years, much effort has been devoted to the design of functionalised mesoporous silica nanoparticles as drug nanocargo.[200-207] The internal surface can be functionalised to optimise the internalisation of the drug, whereas the external surface can be modified to allow furtivity in the biological medium. A targeting group, such an antibody, can be incorporated in order to aim the drug at the desired part of the body. In addition, the delivery can be controlled by the incorporation of a nanogate or a nanovalve that can respond to stimuli such as light, pH, a redox activation, or an enzymatic reaction.[208-213]

The controlled incorporation of two or more functions inside the nanoparticles could favour the adsorption and further release of a specific drug. In addition, for some specific cancer treatments, dual drug therapy is required, which implies the incorporation of both drugs in the same nanocargo. The control of both size, surface functionalisation and stabilisation of the nanoparticles in biological media still remains a challenge. Resolving them could create new applications of mesoporous solids in nanomedicine.

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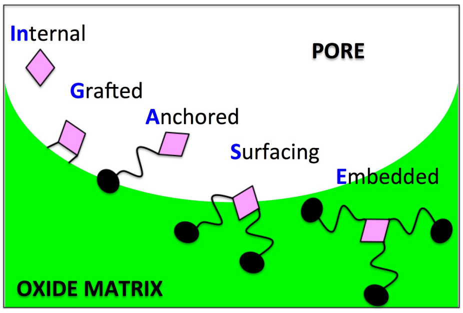

Late development of molecular surface engineering inside the confined space of porous materials is surveyed including a new nomenclature proposal.

20 words-127 characters (without space), 146 characters with spaces.