

FEATURE ARTICLE

Better Chemistry through Ceramics: The Physical Bases of the Outstanding Chemistry of ORMOSIL

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Twenty years after their invention, sol–gel organically modified silicates (ORMOSIL) are finding a number of impressive applications that range from efficient deliver of genes into mouse brains to self-ordered helices of interest to fields as diverse as optics, catalysis, molecular recognition, and chromatography. The physical bases of this multifaceted chemistry, therefore, are of immense importance to scientists working toward new applications such as photovoltaics and catalysis that are crucially important in making sustainable global development. The purpose of this article is to provide a general picture of ORMOSIL's physical chemistry that will be useful in the creative development of new materials capable to solve a number of relevant open problems.

1. Motivation and Background

Exactly 10 years ago, commenting on the physical nature of the sol–gel entrapment of molecules in porous oxides, the inventor of sol–gel doped materials (first reported in this journal¹ 10 years earlier) was emphasising how it was “really remarkable to see how many applications of the entrapment have been reported, without fully understanding the picture at molecular level”.²

In year 2005, this understanding has naturally evolved and we owe a broader picture of the factors governing the chemical behavior of these materials, whose mild preparation conditions were soon proven to be compatible with the effective entrapment of biomolecules in silica-based materials (with minor or no loss of biological activity), opening the route to the merger of chemistry, biology, and materials science.³

Yet, these factors are subtle and are often overlooked in a field that literally exploded with some 8000 research papers published in ISI-indexed journals between 1990 and 2005.⁴ Doped sol–gel silica oxides, and organically modified silicates (ORMOSIL)⁵ in particular, are finding a number of impressive applications that range from efficient delivery of genes into mouse brains,⁶ to fast drug assessment for toxicity;⁷ from self-ordered silica helices⁸ to highly sensitive photochemical oxygen sensors⁹ and to “biochemical reactors” made up of entrapped enzymes,¹⁰ whole cells,¹¹ and even bacteria.¹² Moreover, ORMOSIL present a number of optical applications due to the excellent optical quality of transparent silicate-based material along with easy shaping and good mechanical integrity.¹³

The purpose of this paper is to elucidate the physicochemical bases of ORMOSIL's superior performance in so many applications¹⁴ which, in its historic development, is a clear example of

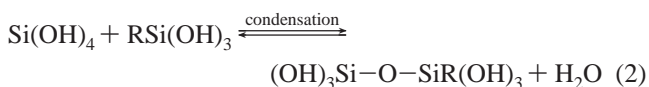
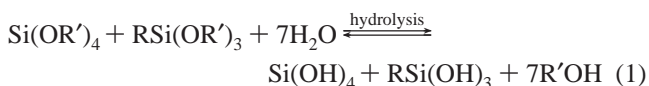
the interdisciplinary nature of modern chemical research¹⁵ in which biology, physics, materials, and computational science are all used together to afford a variety of chemical devices with enormous applicative potential.

Referring to a selection of recent achievements, we show how these concepts were actually translated into practice. The resulting general picture will hopefully be used as reference in the development of novel functional materials for advanced applications, in fields as diverse and crucially important as photovoltaics, medicine and catalysis.

2. Tailored Structures through Control of the Sol–Gel Process

Governing the sol–gel process at the molecular level implies the ability to control the monomer → oligomer → sol → gel → xerogel transition that affords the resulting porous oxide. Being soluble in common organic solvents, undergoing rapid hydrolysis, and being easily functionalized with organic groups, silicon alkoxides such as $\text{Si}(\text{OR}')_4$ and $\text{R}_n\text{Si}(\text{OR}')_{4-n}$ are conveniently used as source of the monomers undergoing the sol–gel hydrolytic polycondensation. The large availability of organosilanes with phenyl, amino, carboxyl, etc. functionalities affords a potentially enormous class of ORMOSIL materials.

Taking a trialkoxysilane as co-precursor for an initial 1:1 mixture of alkoxysilane and organoalkoxysilane, and recalling that in the case of ORMOSIL condensation takes place *only* through elimination of water¹⁶ and not by alcohol formation, the mechanism involves hydrolysis and condensation reactions (eqs 1–2):



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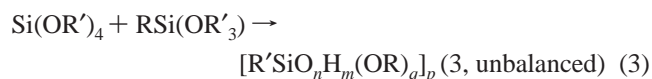


Mario Pagliaro obtained his Ph.D. in chemistry in 1998 upon working at the Hebrew University of Jerusalem under the guidance of Professor David Avnir and at Zeist's TNO with Arjan de Nooy. In 1999 he joined the CNR's chemistry Institute based in Palermo where until 2003 he also led the activities of the management school "Quality College del CNR", using its revenues to finance research. His research interests focus on the overlap of biology, materials science, and photochemistry. In 2005 he was "Maître de conférences associé" at the Ecole Nationale Supérieure de Chimie de Montpellier.



Rosaria Ciriminna obtained her graduate degree in chemistry at the University of Palermo in 1995. Following research on natural products as a CNR fellow at the same University, she joined the CNR's Institute of Natural Products based in Palermo (today Institute of Nanostructured Materials), where she has worked as a full-time research chemist since the year 2000. She has worked at the Universities of Reading (UK) and Padova and at Montpellier's Ecole Nationale Supérieure de Chimie. Her work led to the development of one of the most active Ru-based heterogeneous oxidation catalysts. Her current research interests include sol-gel materials, enantioselective conversions, and photochemistry.

The overall hydrolytic polycondensation reaction can be written as eq 3:



The hydrolysis rate of organosilanes is a strong function of the size of the alkyl group and steric hindrance. Actually, however, these reactions never result in the formation of pure silica oxides, and it is precisely the fact that $m \neq 0$ and that a large number of unreacted silanol groups exist at the material's surface that gives rise to the impressive variety of chemical applications of doped silica xerogels.²

The resulting gel is chemically unstable, since its alkoxy (OR) groups are subject to further hydrolysis by the presence of unreacted water. Consequently, the dry gel (xerogel) obtained by removal of the residual solvent is also unstable, since the remaining hydroxyl (OH) groups can further condense. The net result



Michel Wong Chi Man obtained his Ph.D. in chemistry from Montpellier's University under the supervision of Professor Robert Corriu. Following postdoctoral work in Germany in the early 1990s he joined the CNRS unit of research led by Professor Joël Moreau at the Ecole Nationale Supérieure de Chimie de Montpellier, where he is now a director of research. His work has resulted in the joint development of the first inorganic chiral silica helices. His current research interests include functional sol-gel materials, chirality, ionic liquids, nanotubes, and catalysis. He is involved in the EU-funded FAME (Functionalized Advanced Materials Engineering of Hybrids and Ceramics) research network and recently coordinated successful efforts for the selection of Montpellier as host of the 14th International Workshop of Sol-Gel Science and Technology.



Sandro Campestrini received his Ph.D. from the University of Padova under the supervision of Professor Fulvio Di Furia working on peroxo complexes of Mo(VI). After postdoctoral work with Professor Bernard Meunier at Toulouse's CNRS and with Professor Cynthia J. Burrows at New York University at Stony Brook, he joined the University of Padova where he is currently associate chemistry professor. His current interests focus on the development of catalytic oxidation systems using "green" primary oxidants as well on reactions in nonconventional solvents.

is a "living" material that undergoes structural modifications, even months after preparation so that, for instance, an entrapped transition metal catalyst migrates to the surface of newly formed porosity, affording a solid catalyst several times more active compared to the freshly prepared material (Figure 1).¹⁷

In general, the structure of sol-gel material evolves sequentially as the product of successive and/or simultaneous hydrolysis, condensation, and their reverse reactions (esterification and depolymerization). Thus, in principle, by chemical control of the mechanisms and kinetics of these reactions, namely the catalytic conditions, it is possible to tailor the structure (and properties) of the gels over a wide range.

For example, stable silica xerogels of tailored particle dimensions, pore morphology, density and porosity, from relatively dense to highly porous ones, are easily obtained carrying out the two-step sol-gel process (hydrolysis under acidic conditions followed by base-catalyzed condensation) by tuning the acid and base contents in each step.¹⁸

The silicon alkoxide is first hydrolyzed in a strong acidic medium (in which the consumption of water due to silane

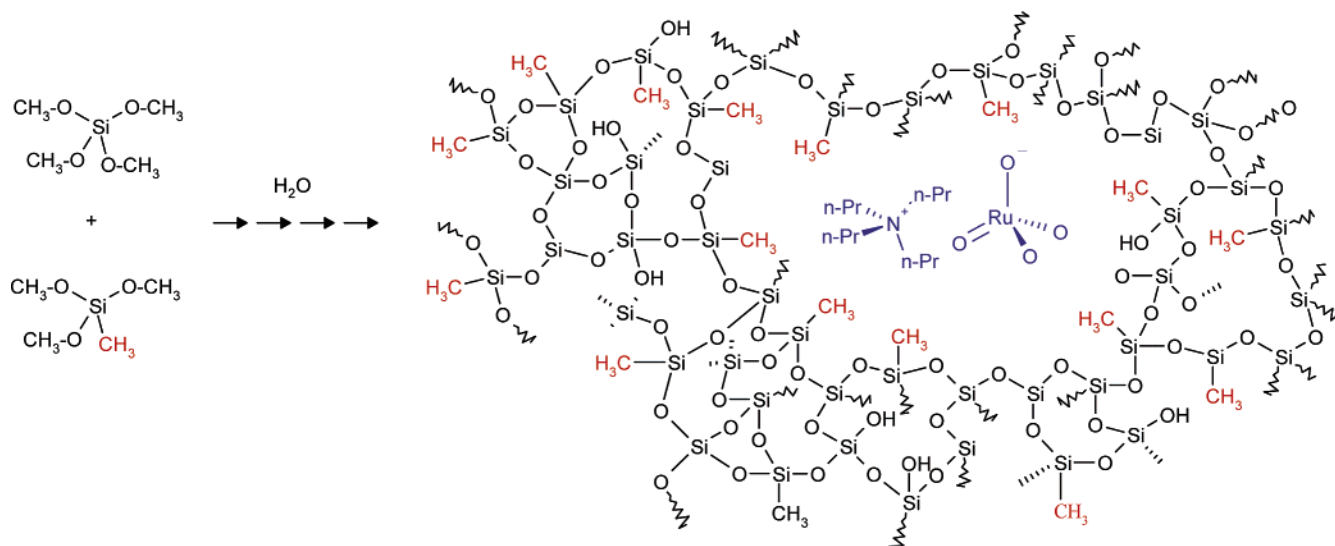


Figure 1. Pseudomicellar aggregates form in the early stage of the polycondensation of TMOS/MTMS catalytic mixed gels in which lipophilic TPAP (in red) tends to concentrate in the core of inaccessible cages. With time, the material continues to evolve, these segregated TPAP molecules migrate and disperse in newly formed inner microporosity resulting in 10-fold improvement in catalytic activity. (Image courtesy of Massimo Carraro, ref 17.)

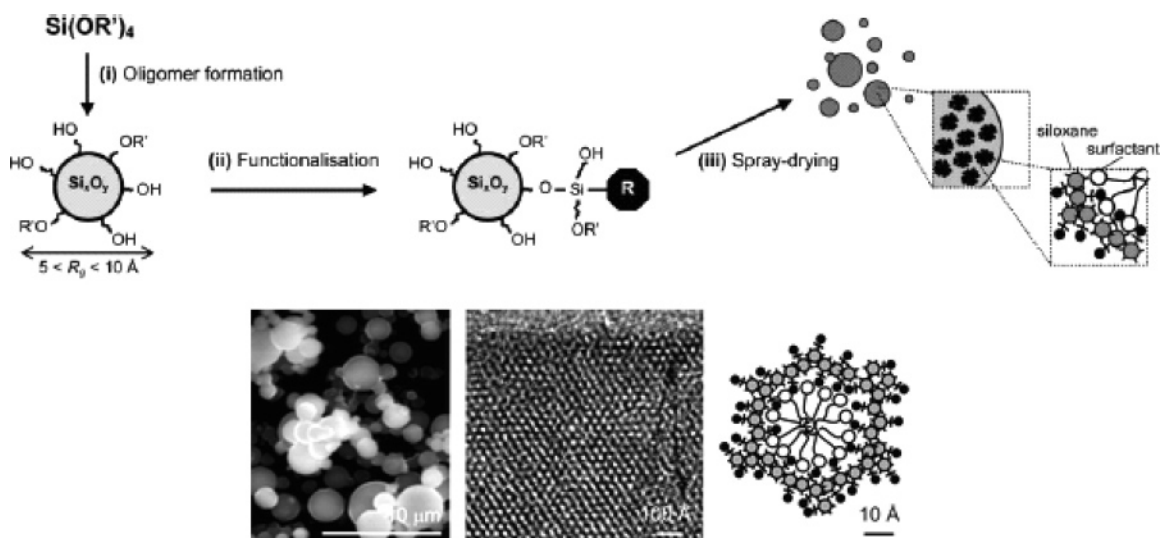


Figure 2. In a novel synthetic route made possible by the sol–gel process versatility, using spray-drying of the precursor sol affords spheres of mesoporous ORMOSIL whose surface is made of highly ordered hexagonal domains. (Reproduced from ref 20, with permission.)

hydrolysis is *very* fast, complete within minutes); the sol is then neutralized to promote condensation under a base-catalyzed mechanism. In this two-step process, at the onset of condensation there are mostly hydroxyl groups bonded to silicon, favoring cross-linking. Furthermore, the base-catalyzed polymerization mechanism also favors cross-linking, since the extension of the condensation reaction increases with the Si–OH acidity, which is stronger for the already more cross-linked clusters. The net result is that the *larger* polymers grow at the expense of the smaller ones, originating a highly cross-linked gel, which is essentially pure silica.¹⁸

2.1. From Disordered to Ordered Structures. In the absence of a templating agent, ORMOSIL are obtained in glassy, amorphous structures. Yet, highly ordered, organic–inorganic silica gels can be easily obtained in one-pot in the presence of a surfactant acting as a templating agent in which a micelle directs self-assembly of the polymeric siloxane precursors affording, to cite a leading practitioner in the field, “new materials whose *hierarchical* structure determines material properties and function”.¹⁹ Such highly porous ordered silicas are made of amorphous silica walls spatially arranged into periodic arrays:

the regular mesopores of monodisperse size (typically in the range from 20 to 100 Å in diameter) mimic the liquid crystalline phases exhibited by templates. The mesopore volume is usually greater than 0.7 mL g^{−1} with narrow pore size distribution and extremely high surface area (up to 1400 m² g^{−1}).

As usual, these solids can be derivatized with a variety of organic groups to give mesoporous ORMOSIL either by post-synthesis grafting (reaction of organosilanes on mesoporous silica) or directly by sol–gel co-polycondensation of a tetraalkoxysilane and organoalkoxysilane in the presence of a surfactant.

Using a spray-drying process to disperse the precursor sol, for example, affords spheres of mesoporous ORMOSIL with functionalized surfaces made of highly ordered hexagonal domains (Figure 2).²⁰ However, co-polycondensation of organosilane with terminal groups such as RSi(OEt)₃ with TEOS is limited in scope since it tends to reduce the degree of long-range order and the mechanical stability for organic content >20% (in molar terms).²¹ It is enough to use as precursor of the silica gel bridge-bonded silsesquioxanes of the form (EtO)₃Si–R–Si(OEt)₃ to afford a whole set of periodic meso-

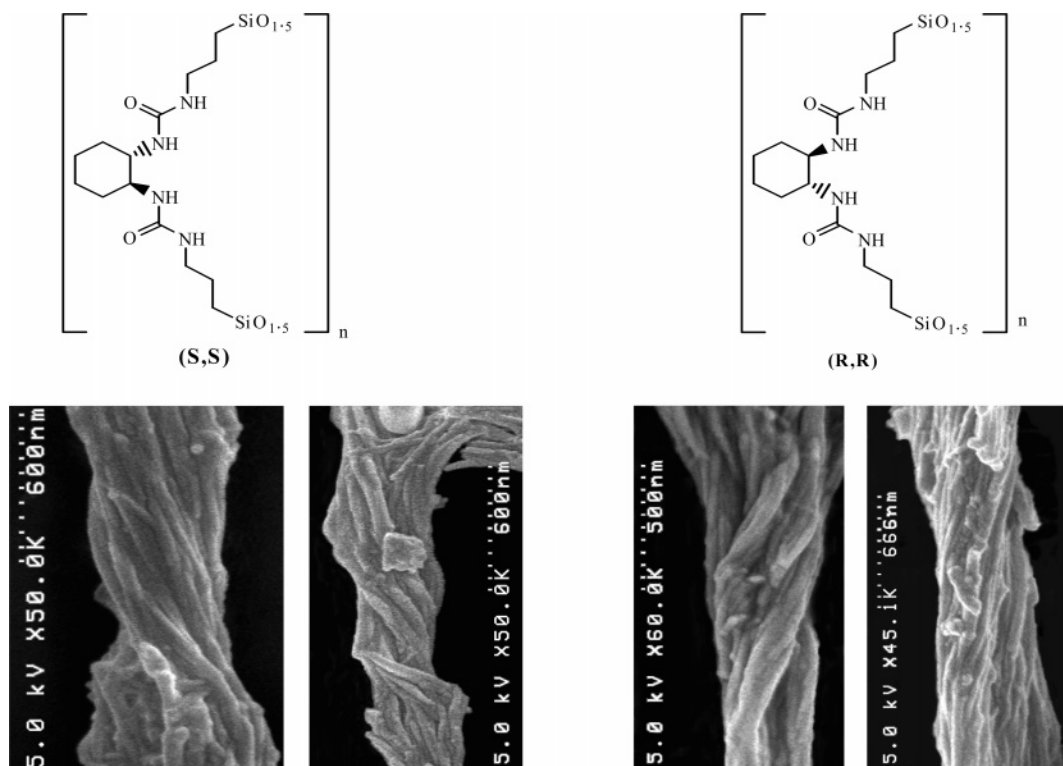


Figure 3. Helical hybrid silicas: chirality transcription from the precursor molecule to the hybrid solid. (Reproduced from ref 8, with permission.)

porous organosilicas: ORMOSIL with an high organic content (of $\text{SiO}_{1.5}\text{R}_{0.5}$ approximate stoichiometry) that are emerging as promising materials for applications such as nanocomposite hosts, sensors, catalyst support, and dielectric layers. For instance, low- k thin films are easily made from a mixture of a silsesquioxane of the type $(\text{C}_2\text{H}_5\text{O})_3\text{Si}-\text{R}-\text{Si}(\text{OC}_2\text{H}_5)_3$, with R = methene ($-\text{CH}_2-$) and tetramethyl orthosilicate (TMOS) precursors.²²

The dielectric constant (k) of the resulting ORMOSIL decreases with organic content with values as low as 1.9 for films entirely made of organosilica (i.e., using no TMOS). Also, the films show good thermal stability and, thanks to their hydrophobicity (further enhanced upon calcination at 500 °C to cause a “self-hydrophobizing” bridging-to-terminal transformation of the methene to methyl groups with concomitant loss of silanols), excellent resistance to moisture.²¹

The merger of materials science and organic chemistry here is actually realized in its full potential, and the number and type of materials obtainable is only limited by chemists’ ingenuity. In the past few years a plethora of hybrid organic–inorganic materials of controlled molecular organization, nanoscale periodicity, and macroscopic morphology were thus introduced, recreating the hierarchical organizations of many natural materials and thereby obtaining functional materials for new, advanced applications.²³

Structuring of bridged silsesquioxanes via cooperative weak interactions, for instance, leads either to impressive organosilica helices⁸ (Figure 3) or to lamellar structures. In the former case, chirality is simply transcribed from the precursor molecule to the hybrid solid as the chiral molecules undergo self-assembly prior to the sol–gel polycondensation.⁸

On choosing between ordered mesoporous organosilicas and related amorphous organosilica gels, a delicate *balance* between enhanced accessibility and restricted diffusion must be found. In heterogeneous catalysis applications, for example, confinement of the catalyst in the regular mesostructure generates a

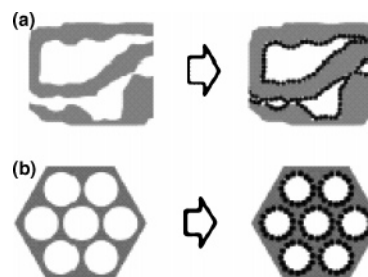


Figure 4. Schematic and comparative illustration of grafting (a) an amorphous silica gel and (b) an ordered MCM-41 silica material. (Reproduced from ref 51, with permission.)

shape-selective catalyst with a large concentration of well-defined active sites.²⁴ Yet, this excludes from conversion molecules whose size does not fit that of the pore, whereas amorphous glassy materials show a *distribution* of porosity that makes them versatile; i.e., they can be employed in the conversion of structurally different substrates. For example, whereas the solid oxidation catalyst MCM-41-entrapped perruthenate can be used for the conversion of benzyl alcohols only,²⁵ a similarly perruthenated-doped amorphous ORMOSIL is equally well suited for a variety of largely different alcohol substrates.²⁶

On the other hand, the *uniform* pore structure ensures access to the active centers while in an amorphous material made of non regular porosity hindered or even blocked sites can well exist (Figure 4), rendering the choice of the polycondensation conditions of paramount importance.²⁴

This is well demonstrated for mercury(II) binding to thiol-functionalized mesoporous silica for which effective access to all the binding sites (100% of SH groups complexed with $\text{Hg}(\text{II})$) was achieved in micelle-templated mesostructures with pore diameters larger than 2.0 nm, whereas incomplete filling was always observed with corresponding amorphous silica-based adsorbents.²⁷

The study of similar ORMOSIL prepared by self-assembly and co-condensation of (3-mercaptopropyl)trimethoxysilane

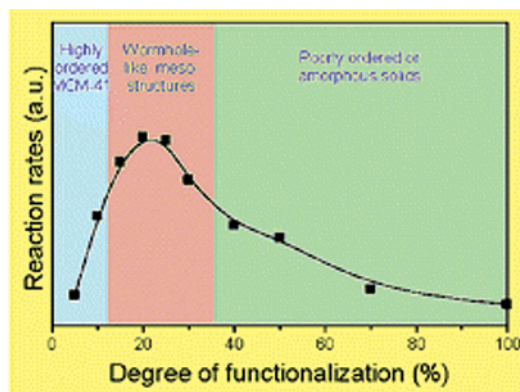


Figure 5. The sorption rates of mercaptopropyl-functionalized ORMOSIL depend on their relative long-range versus short-range structural order/disorder and their intrinsic hydrophobicity: Ordered materials with 20–30% alkylation perform best. (Reproduced from ref 28, with permission.)

(MPTMS) and TEOS in the presence of a cationic surfactant by varying the MPTMS content from 5 to 100%, shows that the resulting porous solids exhibit clearly distinct structural order/disorder over different length scales (Figure 5).²⁸

Total accessibility (expressed on the basis of a 1:1 S/Hg stoichiometry) was demonstrated for well-ordered materials containing up to 30% MPTMS. Less open structures characterized by a high degree of functionalization were subject to less-than-complete sorption capacities, while, however, reaching maximum loading values as high as 750 mg g⁻¹. The diffusion coefficients is strongly affected by both the structure and density of functional groups in the MPS sorbents.

Whereas the long hexagonally packed one-dimensional channels of MPS-5% and MPS-10% may induce some diffusional restrictions for Hg^{II} to reach the binding sites located deep in the mesopores, transport issues within MPS-15% to MPS-30% sorbents is facilitated by a shorter range structural order in the form of three-dimensional wormhole framework structures.

Increasing further the content of organic groups in the materials led to poorly ordered (MPS-40% and MPS-50%) and even amorphous (MPS-70% and MPS-100%) solids, resulting in considerable lowering of mass transfer rates, to which the concomitant increase of hydrophobicity may also contribute to a significant extent. The differences in sorption rates exhibited by MPS materials appear therefore to result from differences in their relative long-range versus short-range structural order/disorder and their intrinsic hydrophobicity, which are induced by their functionalization levels.

Another application due to the unique adsorptive properties of ORMOSIL, potentially of enormous value in medicine, is demonstrated by controlled drug release of *cis*-platin (*cis*-[Pt-(NH₃)₂Cl₂]), a potent, and yet toxic, anticancer drug. Here fast removal of excess drug shortly after administration and site-specific drug release is a potential partial solution of this problem. By simply comparing the properties of a silica gel silylated with MPTS and of this silica (SiSH) with an organically modified silica sol–gel material (ORMOSIL) using MPTS as modifier and with nonderivatized silica (SiOH), the adsorption isotherm of both the CP/SiSH and the CP/ORMOSIL system revealed a *cooperative* mechanism of adsorption, namely, an increase in adsorption affinity with coverage, as clearly indicated by the S-type adsorption isotherm (Figure 6).²⁹

3. The Nature of the Sol–Gel Entrapment

3.1. Consequences of Entrapment. Encapsulation of molecules into the inner porosity of a sol–gel matrix affords

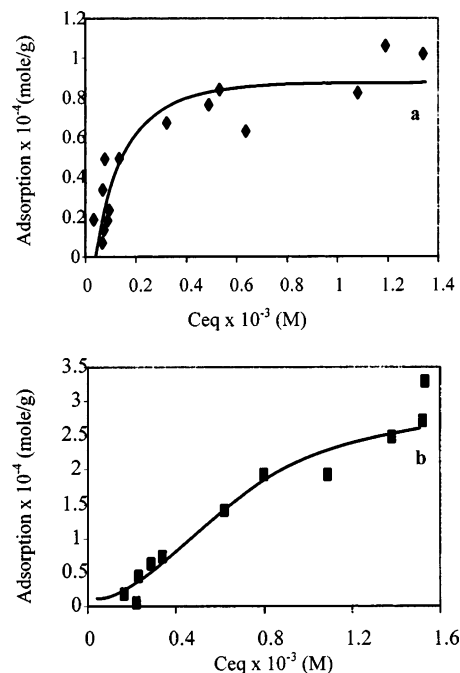


Figure 6. Adsorption isotherms of *cis*-platin on (a) nonderivatized silica (SiOH) and on (b) mercapto-ORMOSIL (OrSH). (Reproduced from ref 29, with permission.) The differences in adsorption affinities between SiSH and SiOH allow the ability to achieve interparticle migration of an adsorbate (CP) from one matrix to another.

unprecedented molecular dispersion in a solid phase. The question of dopant aggregation in the sol cages emerged in the early studies of sol–gel doped materials: whereas, studying the entrapment of Ru(bpy)₃²⁺ in a SiO₂ matrix, it was originally assumed that single molecule caging was taking place,¹ it was later established that at the high concentrations (in the order of several mmol/g) typical of doped sol–gel applications some dopant aggregation was actually occurring.³⁰

The physical and chemical properties of the entrapped dopants are generally retained. Yet, the efficient isolation of one molecule from the other and the active role played by the sol–gel cage, for instance in dictating accessibility, gives place to a vast *new* chemistry and physics of sol–gel entrapped molecules which encompasses and largely goes beyond traditional solution chemistry.

Thus, for example, new optical applications become possible since entrapped excited molecules cannot diffuse (giving place to the thermal energy dissipation typical of molecules in liquid phase), such as in the case of photoinduced electron transfer in SiO₂-co-entrapped pyrene and methyl viologen.³¹ Or, in catalysis, much higher selectivities are achieved in delicate organic syntheses as the reactants approaching the entrapped catalyst are forced to assume preferred configuration.³²

In general, confinement of a molecule in solid microporous cages of a solid modifies the electron energy of the molecule, altering in particular the frontier molecular orbital energy. For instance, *ab initio* calculations of a guest molecule (toluene) located inside a microporous zeolitic cavity show that the highest occupied molecular orbital (HOMO) energy of the dopant increases when going from the gas phase state to restricted microporous environments and that the smaller the cavity the higher is the rise in HOMO energy.³³

This effect has subtle consequences, as toluene reactivity in zeolite catalyzed reactions is expected to change toward a more covalent behavior in which electronic transference from the toluene molecule to an electronic acceptor will be more favored

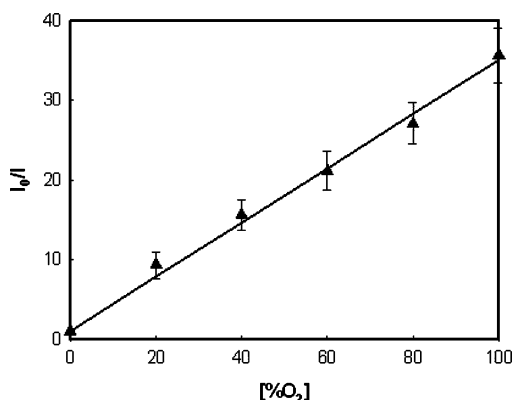


Figure 7. Stern-Volmer plot for a $[\text{Ru}(\text{dpp})_3]^{2+}$ -doped TFP-TriMOS: *n*-propyl triMOS-based sensor film. (Reproduced from ref 9, with permission.)

than in gas-phase reactions. Clearly, entrapped molecules interact with the ORMOSIL cage with noncovalent interactions that include van der Waals interactions, π -stacking, electrostatic attractions, and hydrogen bonding, depending on the specific structure of the organosilica and the dopant molecule. Yet, surprisingly, there seem to be a lack of theoretical studies devoted to understanding more profoundly the electronic properties of sol-gel entrapped molecules.

Homogeneity of the entrapment, a property that has profound consequences on the ability of doped sol-gel materials to work as photochemical sensors or efficient catalysts, was immediately revealed by the first-order decay profiles of entrapped dyes¹, as nonlinear kinetic plots arise when the dopant catalysts report simultaneously from more than one microenvironment that exhibits different chemical properties (Figure 7).³⁴ Furthermore, silica-entrapped molecules are physically and chemically protected. For example, organic fluorophores sol-gel encapsulated in ORMOSIL nanoparticles (20 to 30 nm in diameter) become 20 times brighter and more photostable than their constituent fluorophore due to the cage protecting the fluorophore from bleaching due to oxygen dissolved in the solvent.³⁵ Similarly, a radical species such as TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) heterogenized at the external surface of commercial silica rapidly degrades due to mutual quenching of the radical species,³⁶ once entrapped in an ORMOSIL matrix, becomes largely stabilized and can be reused several times with no reduction in activity (Figure 8d).³⁷

Returning to fluorescent silica-entrapped dyes, Figure 8c shows evidence that the silica nanoparticles are largely impermeable to solvent as the spectra show little spectral red shift in the excitation and emission spectrum upon solvent exchange from ethanol to water.

3.2. The Nature of the Sol-Gel Cage. Normally, ORMOSIL's organic groups are located at the cage's interface.³⁸ The hydrolysis of organosilanes is slower compared to fully hydrolyzable silicon alkoxides, and the slowly generated $\text{R-Si}(\text{OH})_3$ monomers rapidly condense in micellar-like structures typical of the very early stages of the sol-gel process, in which these hydrolyzed monomers tend to arrange themselves with the polar heads made of $-\text{Si}(\text{OH})_3$ groups at the forefront of the growing sol-gel material, and the hydrophobic nonpolymerizable residue *R* orientated away from the interfacial solvent water/alcohol (strongly hydrogen bonding).³⁹

As a result, the pore boundary (interface) of the resulting ORMOSIL has a "fuzzy" nature; i.e., the density varies continuously at the pore boundary instead of changing discontinuously from a value of zero in the empty pore to the

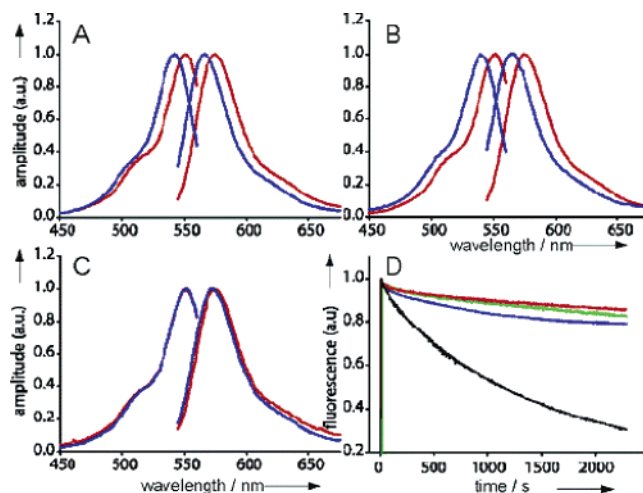


Figure 8. Solvent accessibility and photobleaching behavior of nanoparticle synthesis intermediates. Panels A–C: Excitation and emission spectra of nanoparticle intermediates ((A) TRITC; (B) core; (C) core/shell) in ethanol (blue) and water (red). (D) Photobleaching behavior of nanoparticle intermediates (blue, TRITC; green, core; red, core/shell) and fluorescein (black). (Reproduced from ref 35, with permission.)

essentially constant density characteristic of the bulk SiO_2 . Small-angle X-ray scattering from fully and partially derivatized porous ORMOSIL, indeed, gives place to power-law-scattering exponents of magnitude greater than 4, with the magnitudes of the exponents increasing with the alkyl chain length and with the degree of surface derivatization.⁴⁰

3.2.1. Tuning the HLB. Early analysis of absorption and emission spectra of a laser dye (R&G) in sol-gel SiO_2 indicated that the polarity of the microenvironment of the dopant is high and, due to hydroxyls, less polar than water.¹ On the other hand, the possibility to freely tailor the HLB (hydrophilicity–lipophilicity balance) by varying the amount and the nature of the organosilane employed as precursor is one of the most important features of sol-gel entrapped ORMOSIL. For example, by modifying the polarities of a series of organically modified sol-gel silicas doped with the solvatochromic dye ET-(30) (2,6-diphenyl-4-(2,4,6-triphenyl-N-pyridino)phenolate) by copolymerizing, in various proportions, methyltrimethoxy-, vinyltrimethoxy-, propyltrimethoxy-, isobutyltrimethoxy-, and phenyltrimethoxysilanes with TMOS, the various doped ORMOSIL exhibit a clearly distinct solvatochromic effect when in contact with organic solvents that make these materials suitable as solvent sensors.⁴¹

On the other hand, increasing organic content for ORMOSIL-entrapped lipase¹⁰ and perruthenate²⁵ has a tremendous effect on the reactivity of the resulting catalytic material. A recent structural study⁴² based on DRIFT spectroscopy aimed to investigate the origin of such large variations, has shown that, in the absence of MTMS (methyltrimethoxysilane), the silica structure obtained by TMOS only is dominated by four member rings (the percentage of six-member units in **SiOMe** is only ~15%), but a spectacular increase in the fraction of six member rings (Figure 9) to 20, 56, 84, and 97% is observed as the MTMS content increases to 25, 50, 75, and 100%.

Conversely, the structure obtained when the precursor is only MTMS is almost entirely formed by the larger, less tensioned, six-member rings, more able to accommodate the unreactive methyl groups. Quantification of the hydrophilicity of the ORMOSIL may be given by the contribution of dangling oxygen atoms relative to the silica structure ($\%\text{Si-O}_\text{d}$).

The relative area of the $\nu\text{Si-O}_\text{d}$ band varies abruptly from

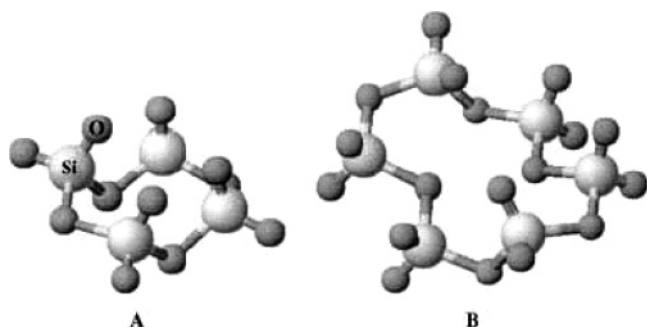


Figure 9. Schematic diagram of the more common types of primary cyclic arrangements of the structural units, SiO_4 , in xerogels: (A) four-member siloxane ring (SiO_4) and (B) six-member siloxane ring (SiO_6). (Reproduced from ref 42, with permission.)

$\sim 13\%$ to $\sim 5\%$ when MTMS content is changed from 0 to 25%, but it is not much affected from that content on. Within this slight variation, a minimum may be observed for 75% MTMS. Obviously, the hydrophobicity increases significantly for the organically modified silica gels, and, although it is not very sensitive to the modifier content, it reaches a maximum for 75% MTMS.

The deconvolution of the $850\text{--}700\text{ cm}^{-1}$ region allows inferring on the main origin of the lipophilic methyl groups in each hybrid material. The relative contribution from the $\rho(\text{O})\text{--CH}_3$ component, at $\sim 840\text{ cm}^{-1}$, varies from 1 to 4%, while that of $\rho(\text{Si})\text{CH}_3$, at $\sim 770\text{ cm}^{-1}$, varies from 0.5 to $\sim 17\%$ with increasing MTMS content. These values substantiate the evolution suggested by observation of the methyl stretching region of the spectra. The hydrolysis extent of the --OCH_3 groups depends on the MTMS content, and therefore on whether they belong to TMOS or MTMS, but the lipophilicity of the modified ORMOSIL is essentially due to the stable, unreactive Si--CH_3 groups.

The DRIFT spectral analysis allows concluding that the presence of the co-precursor MTMS affects the structure and the HLB of the sol–gel catalysts. A rough estimate of the HLB trend was obtained by the ratio of the absorption peak areas:

$$\text{HLB} \approx [\text{A}(\text{Si--O}^-) + \text{A}(\text{Si--OH})] / [\text{A}(\text{O})\text{C--H}_3 + \text{A}(\text{Si})\text{C--H}_3] \quad (4)$$

Again, this shows that although a modification with 25% of MTMS imparts a significant decrease in the catalyst's hydrophilicity without major structural changes, an increase in the MTMS content does not affect appreciably the catalyst hydrophilicity, but is responsible for a gradual lipophilicity increase, and therefore for a decrease in the HLB, and for striking structural changes in the silica network.

Interestingly, similar findings obtained for isobutyltrimethoxysilane (BTMOS) derived thin films that exhibit a “discrete” change in polarity for films of greater than approximately 50% organic content are attributed to phase separation and/or the formation of micelle-like domains in BTMOS-derived films.⁴³ These findings provided a long-awaited explanation to the “alkyl effect” observed in catalysis⁴⁴ where a catalytically optimal 75% alkylation degree is required for optimal catalysis: along with enhanced hydrophobicity (promoting diffusion of the hydrophobic reactant molecules within the porous network), enhanced cage flexibility is needed to substantially enhance the reactivity of ORMOSIL-entrapped catalysts in liquid phase.

The modified sol cage dictates accessibility to the external reactants and reduces the constraints imposed to the dopant molecules by strongly hydrogen bonding silanols, ensuring

transition to 6-fold siloxane units. Furthermore, by hydrophobic interaction with the organic moiety of the entrapped dopant, it ensures optimal encapsulation which, to cite only one case, makes possible the conversion of readily available olefins into precious alpha-hydroxyacids (Scheme 1).³²

This trend is general and was verified for a number of catalysts.⁴⁵ It is enough to use a different organic-precursor to target specific conversions. Hence, fluorine-modified ORMOSIL are among the most active Ru-based aerobic catalysts for highly selective oxidative dehydrogenations in scCO_2 ,⁴⁶ whereas fluorinated, sulfonic acid-modified ORMOSIL obtained by co-condensation of the suitable precursor and TEOS are excellent catalysts for Brønsted acid catalyzed transformations due to enhanced adsorption/desorption kinetics.⁴⁷ As mentioned above, ORMOSIL's organic groups are normally located at the cage's surface. However, if they are forced to migrate to the bulk of the material, even organically modified silicates suddenly become superhydrophilic.⁴⁸

This is what happens on heating a methyl-modified ORMOSIL foam beyond such transition temperature (typically $400\text{ }^\circ\text{C}$) to thermally induce contact angle change.

$$\cos \theta_r = f \cos \theta_s \pm (1 - f) \quad (5)$$

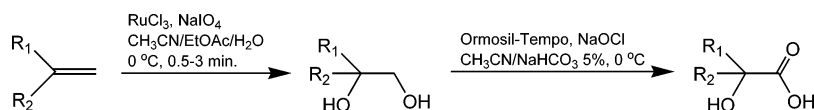
Equation 5 (θ_r is the contact angle of the liquid on the rough surface, θ_s the contact angle of the liquid on a smooth surface having the same chemistry as the rough surface, f is the fraction of the base of the drop in contact with the solid and $(1 - f)$ is the remaining fraction of the drop base) governs the behavior of a drop sitting on a heterogeneous surface. If the material has a high volume fraction of pores (such as in the case of mesoporous sol–gel organosilica foams), f will be small so the second component of the equation will dominate and one would expect liquid to switch from very high (nearly 180°) to very low (nearly 0°) contact angles when the contact angle on a flat surface is varied by a small amount around the value of 90° ; at this point sudden intrusion into the pores will occur (Figure 10).

Another major example of the active role played by the sol–gel cage HLB in dictating reactivity and accessibility of the entrapped dopant concerns the first case of gene delivery into (mouse) brain.⁶ Here, in place of dangerous viruses traditionally used as the gene delivery vehicle, ORMOSIL amino-functionalized nanoparticles obtained by adding 3-aminopropyl triethoxysilane to the polymeric precursor made of triethoxyvinyl silica chains self-assembled from $(\text{H}_2\text{C}=\text{CH})\text{Si}(\text{OEt})_3$ in the core of an oil-in-water microemulsion (surfactant aerosol-OT)/DMSO/water). These particles can efficiently introduce a healthy version of the gene into the patient, thus opening path to gene therapy which involves treating diseases caused by missing or defective genes, and even to repair neurological damage caused by disease, trauma, or stroke (Figure 11).

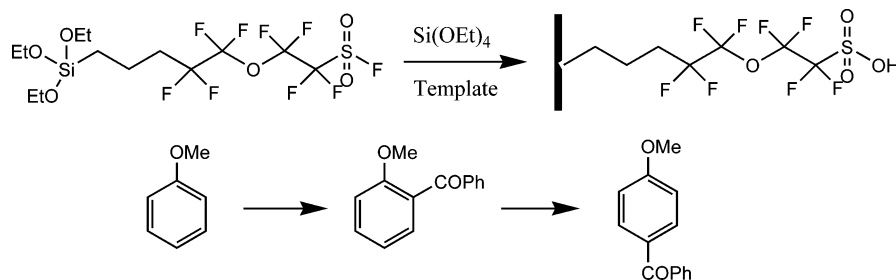
The cationic amino groups at the ORMOSIL's cage surface readily bind with negatively charged DNA plasmids, and the resulting doped material, using plasmids that contained a gene coding for enhanced green fluorescent protein (EGFP), injected into various regions of the mouse brain (Figure 11a) was even more effective than some viral vectors at delivering the EGFP gene to nerve cells without any damage to the mice nerve cells.

Release of DNA *in vivo* takes place due to the increased acidic conditions inside living cells that result in the destabilization of the ORMOSIL–DNA complex. SiO_2 -based nanoparticles, in fact, do *not* release encapsulated biomolecules because of the strong hydrogen bonding between the biomolecule's polar centers and the silanols at the cage surface (as ORMOSIL-

SCHEME 1: Using ORMOSIL-entrapped TEMPO, Readily Available Olefins Are Converted to Precious Alpha-hydroxyacids in Two Steps Only. (Reproduced from ref 32, with permission.)



SCHEME 2: Sulfonic Acid-modified ORMOSIL Are Excellent Catalysts for Brønsted Acid Catalyzed Transformations. (Reproduced from ref 47, with permission.)



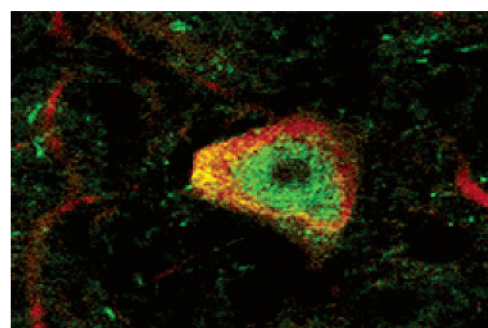
entrapped hydrophobic molecules are not leached in aqueous systems due to strong hydrophobic interactions, Figure 11b). Hence, by using an amino-functionalized ORMOSIL of intermediate HLB to entrap amphiphilic molecules such as DNA, the plasmids bound to the amino-functionalized nanoparticles are completely protected against enzymatic activity due to hindered access of the enzymes to the DNA that is immobilized at the cage's surface, while a controlled release behavior, with an initial burst ($\approx 10\%$ release in the first 3 h), followed by a slow release ($\approx 30\%$ release in 48 h) is observed.

Similarly, thiol-functionalized organosilica microspheres synthesized via a novel surfactant-free emulsion-based method show large potential for optical encoding and in biomolecular screening applications.⁴⁹ The microspheres—synthesized via a two-step process (acid-catalyzed hydrolysis and condensation of MPTS in aqueous solution, followed by condensation catalyzed by triethanolamine)—have a narrow size distribution (Figure 12) and are considerably more stable than polystyrene-divinylbenzene microspheres. This is shown in phosphoramidite oligonucleotide synthesis by excellent retention of fluorescence intensity in each of the reagent steps involved in phosphoramidite DNA synthesis (Figure 13, in which the organosilica-microsphere-free thiol groups are derivatized with ATTO 550 maleimide coupled to the entrapped dye).

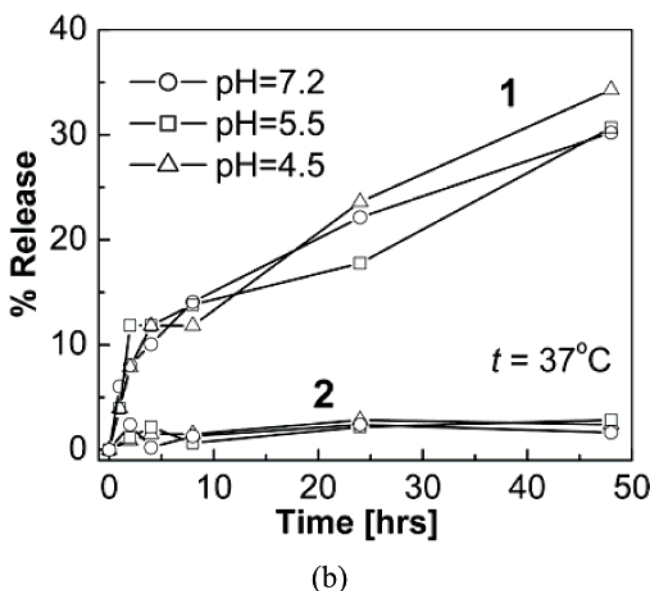
A similar major advancement that in this case will largely speed up the drug discovery process, is due to efficient biocatalysis of ORMOSIL-entrapped cytochrome enzyme P450.⁷ By simply spotting a precursor solution of P450 in MTMS and aqueous HCl over a MTMS-coated glass slide, a device is obtained (MetaChip, Figure 14) that combines high-throughput P450 catalysis with cell-based screening on a microscale platform.

This technology, demonstrated by using sol-gel encapsulated P450 to activate the prodrug cyclophosphamide (a major constituent of the anticancer drug Cytoxan), allows rapid and

inexpensive toxicity assessment at early phases of drug development, providing a high-throughput microscale alternative to currently used *in vitro* methods for human metabolism and toxicology screening based on liver slices, cultured human hepatocytes, or isolated P450 itself.



(a)



(b)

Figure 11. Nanoparticle-delivered EGFP (green, Figure 11a) expressed in a nerve cell (red). The release kinetics of an amphiphilic dye (Rh6G; curves 1, Figure 11b) and hydrophobic dye (HPPH; curves 2) from ORMN20 nanoparticles shows that encapsulation of hydrophobic dyes in ORMOSIL nanoparticles can be used for optical tracking of nanoparticle delivery, whereas that of amphiphilic drugs/dyes can be exploited for controlled release. (Reproduced from ref 6a and 6b, respectively, with permission.)



Figure 10. Phenolphthalein in water on methyl-modified silica foams heated to 390 °C (left) and 400 °C (right). (Reproduced from ref 48, with permission.)

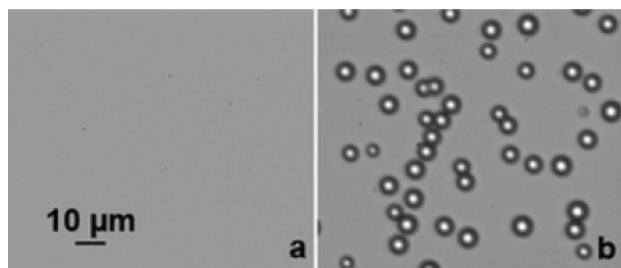


Figure 12. 12. Formation of emulsion droplets. (a) Aqueous MPS solution after acid-catalyzed hydrolysis and condensation. (b) Micron-sized emulsion droplets are rapidly formed upon addition of a base catalyst, TEA. (Reproduced from ref 49, with permission.)

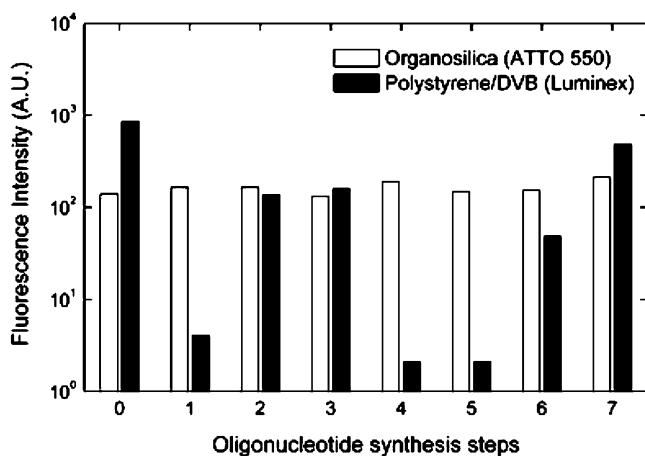


Figure 13. 13. Stability of optical encoding toward oligonucleotide reagents. Organosilica microspheres covalently labeled with ATTO 550 dye are stable toward each of the reagents used in phosphoramidite oligonucleotide synthesis. In contrast, optically encoded polystyrene-divinylbenzene (DVB) beads are unstable in most steps, in particular those involving dichloromethane and tetrahydrofuran. (Reproduced from ref 6b, with permission.)

Here, again, the fully alkylated silica matrix provides the cage's flexibility necessary to the enzyme to change conformation and react with the incoming reactants, that in this case are the cell metabolites; 45% of the enzyme activity in solution is retained upon encapsulation in the sol-gel ORMOSIL film, regardless of the fact that the enzyme was entrapped starting from an acidic solution and that toxic methanol is released in the sol-gel polycondensation of the monomers.

Another advanced application was recently demonstrated with the encapsulation of vesicles (membrane-bound proteins) in a silica matrix resulting in usual sol-gel stabilization of liposomal solution into a robust material along with high activity of the incorporated proteins as shown by photoinduced proton gradients and ATP biosynthesis thus opening the route to a variety of applications from power generation and energy storage.⁵⁰

Counter to intuition (that would exclude nonconductive glassy materials from electrochemistry), organically modified silica-based materials have a rich and varied electrochemistry⁵¹ made possible by the large accessible inner porosity that allows the oxidant and reducing reactant molecules to diffuse through the material and eventually to the surface either of a conducting electrode or of a conductive material (such as carbon) (Figure 15).

Once again, the possibility to fine-tune the ORMOSIL HLB provides the unique advantage of controlling diffusion in the material. Indeed, changing the HLB of the interfacial region of the host (the walls of the silica sol-gel cage) significantly alters the diffusional rate of dopant molecules through the inner porosity of the matrix.

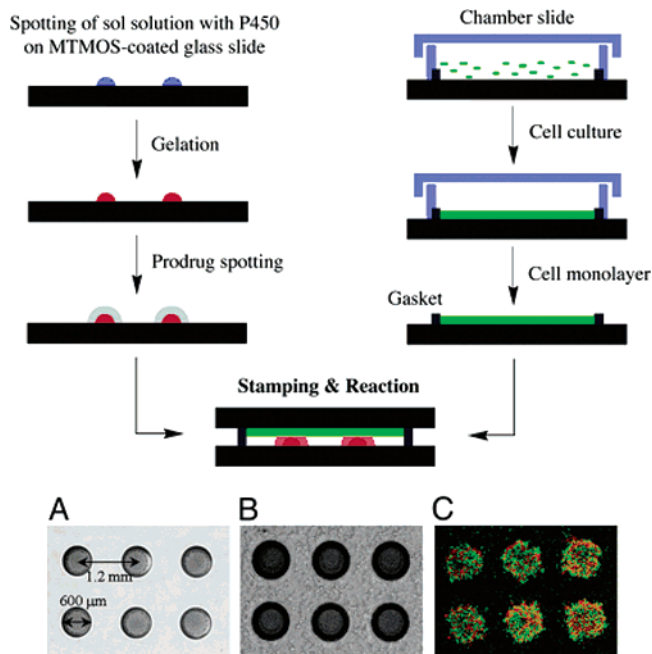


Figure 14. Schematic of MetaChip platform and microscopic photographs of sol-gel spots. Shown are (A) 30-nl P450 sol-gel spots, (B) 30-nl sol-gel spots with 60 nl of prodrug solution after being stamped by a cell monolayer, and (C) cell monolayer after removal from sol-gel array and staining. (Reproduced from ref 7, with permission.)

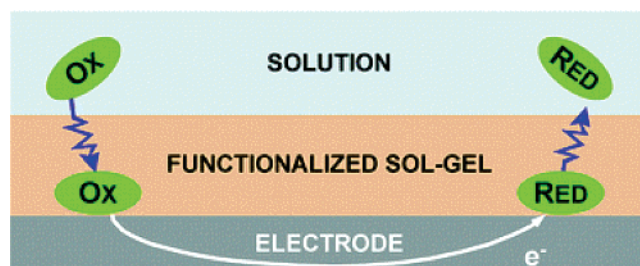


Figure 15. Electrochemical applications of ORMOSIL are due to the accessible porosity and to the possibility to coat electrodes with sol-gel thin films. (Reproduced from ref 51, with permission.)

For example, the addition of a small amount of $-\text{CH}_3$ groups to an electrode coated with doped sol-gel silica enhances the diffusion coefficient of entrapped $\text{Co}(\text{bpy})_3^{2+}$ by a factor >3.3 ;⁵² whereas addition of a quaternary ammonium (using organoalkoxysilane containing such functional group) enhances the diffusion coefficient of the same cobalt species by 1 order of magnitude, and causes that of $\text{Fe}(\text{CN})_6^{3-}$ to decrease by 1 order of magnitude relative to those measured in SiO_2 (Figure 16).⁵³

Analogously, for ORMOSIL-encapsulated $\text{Ru}(\text{bpy})_3^{2+}$ -tripropylamine in an ultramicroelectrode, comparison of the results to those obtained with the gels prepared solely from TMOS revealed enhanced diffusivity and reactivity of the reagents encapsulated in the ORMOSIL matrix. Invariably, in fact, the magnitude of electrochemiluminescence (light emission upon application of an electric potential) by ORMOSIL hosts shows a significant increase in the amount of light production due to a decrease in the extent of intramolecular interactions between the co-reactant and the silica walls.

Remarkably (see below the case of fluorinated ORMOSIL photosensor), the very first study of the electrochemistry of encapsulated reagents showed that the current decreased with age of the solid due to pore shrinkage.⁵⁴ Indeed, by monitoring the voltammetry of ferrocene during the gelation of a sol, the point at which diffusion becomes restricted is manifested by a

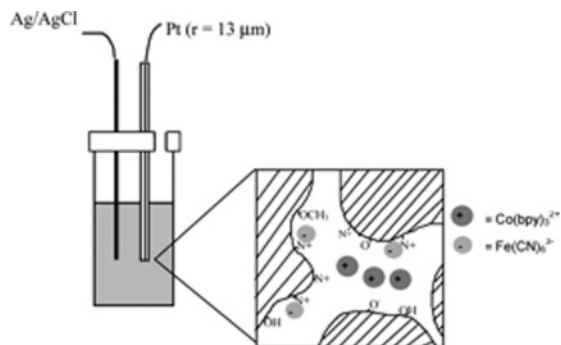


Figure 16. Diffusion in hydrated ORMOSIL gels coated over electrode can be controlled by simply changing the charge on the walls of the silica host. (Reproduced from ref 53, with permission.)

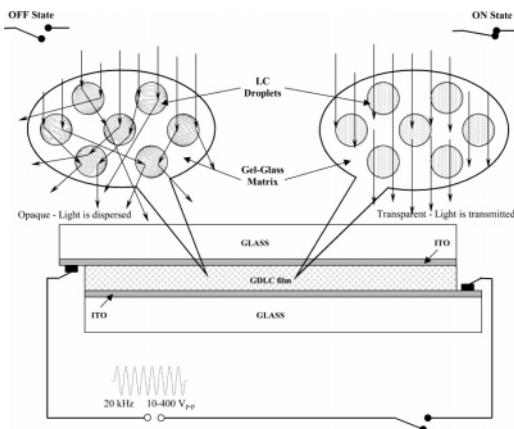


Figure 17. Encapsulation of microdroplets of the liquid crystal 4'-pentyl-4-biphenylcarbonitrile in ORMOSIL matrices results in materials with better transparency and thermal stability than polymer-dispersed liquid crystals. (Reproduced from ref 56, with permission.)

change in current, which signals the gelation point. The resulting voltammetry was similar to that in the analogous bulk liquid phase, which supported the model of facile diffusion in these sol–gels.

For freshly prepared sol–gels or with those processed with templating agents to have a mesoporous structure, the apparent diffusion coefficients of dopants can approach the values observed in liquids (e.g., $10^{-6} \text{ cm}^2 \text{ s}^{-1}$). Reduction of activity with time is again due to the shrinkage of the xerogel porosity, a common problem with SiO_2 -based gels that requires organic modification of the matrix⁵⁵ and, in particular, the optimal use of fluorinated organosilane as co-precursor of the ORMOSIL matrix.

Encapsulation of microdroplets of the liquid crystal 4'-pentyl-4-biphenylcarbonitrile in ORMOSIL matrices prepared from TEOS and triethoxy derivatives results in materials with better transparency and thermal stability than polymer-dispersed liquid crystals PDLCs and with a larger refractive index differential between matrix and liquid crystal, leading to higher light scattering (opacity) in the OFF state.⁵⁶ Remarkably, samples prepared from TEOS or mixed TEOS/MTES precursors showed switching times between ON and OFF states of 10 and 300 ms, respectively and required peak-to-peak voltages (the driving voltage for operation) of 200–300 V (Figure 17).

On the other hand, samples using TEOS/Et-TES and TEOS/Pr-TES precursor mixtures required much lower activation voltages of 100 and 40 V, respectively, and exhibited a very slow electrooptical response ranging between 1 and 3 s. The developed procedure forms 2 mm thin gel-glass dispersed liquid crystals (GDCL) layers, a 10-to-25-fold decrease compared to

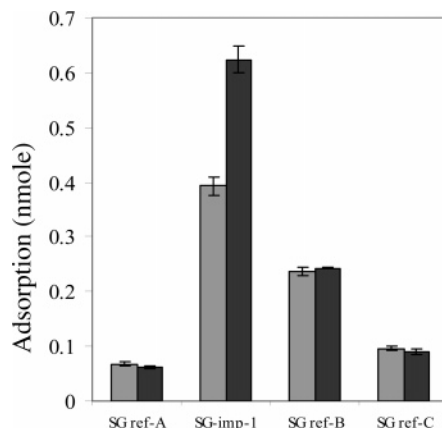


Figure 18. Fluorescent assay for (S)-propranolol (gray bars) and (R)-propranolol (black bars) adsorption to unextracted ORMOSIL-entrapped DMB and to the references thin films. (Reproduced from ref 57, with permission.)

previous state-of-the-art 20–50 mm sustaining similar electrooptical responses.

3.2.2. Imprinting the Sol–Gel Cage. Sol–gel ORMOSILs are, literally, chemical sponges: they adsorb and concentrate reactants at their surface, thereby enhancing reaction rates (for instance, in catalysis) or sensitivity (in sensing applications). The possibility to tune the material's HLB, therefore, allows an enormous potential to selectively adsorb (and detect) external reactants, such as in the case of imprinted materials, i.e., ORMOSIL in which the polymeric structure is assembled around a suitable “template” such as a surfactant micelle or a protein.

The versatility of sol–gel processing, and the enormous flexibility associated with material fabrication, is well suited in particular for the preparation of thin films because of the short path length for reagent diffusion into the matrix. A recent, impressive example is provided by thin films which are generally enantioselective, namely, where the chirally imprinted cavities can discriminate between enantiomers of molecules not used in the imprinting process and that are completely different from the imprinting one (Figures 18 and 19).⁵⁷ Using the *chiral* cationic surfactant (–)-*N*-dodecyl-*N*-methylephedrinium bromide (DMB) as the surfactant template, and after its extraction, chiral domains were created. The ORMOSIL thin films were prepared by spin-coating an aqueous sol of TMOS and phenyl trimethoxysilane (PTMOS) (under acidic conditions) and the resulting material, characterized by TEM, diffraction, and surface area measurements, was found to be semicrystalline with short-range ordered domains (50 Å) of hexagonal symmetry. Enantioselective adsorption was demonstrated using (R)- and (S)-propranolol, and (R)- and (S)-2,2,2-trifluoro-1-(9-anthryl)ethanol as chiral probes examining the sol–gel ORMOSIL thin films with pure enantiomer solutions for rebinding. The chiral selectivity factors were found to be between 1.6 and 2.25, and in both cases, (R)-enantiomer was adsorbed preferably.

4. Concluding Remarks

Doped ORMOSIL are functional materials with a multifaceted and exceptional chemistry that are literally “repeating the revolution that plastics did in the 1940s”⁵⁸ and are eventually finding a number of commercial, practical applications.⁵⁹ Among other advantages, these materials offer the opportunity to utilize in a positive way geometric imperfection. In other words, similarly to what happens in Nature, complicated structures can be constructed with the sol–gel process allowing “correlations and disorder to compete and to come to terms with each other

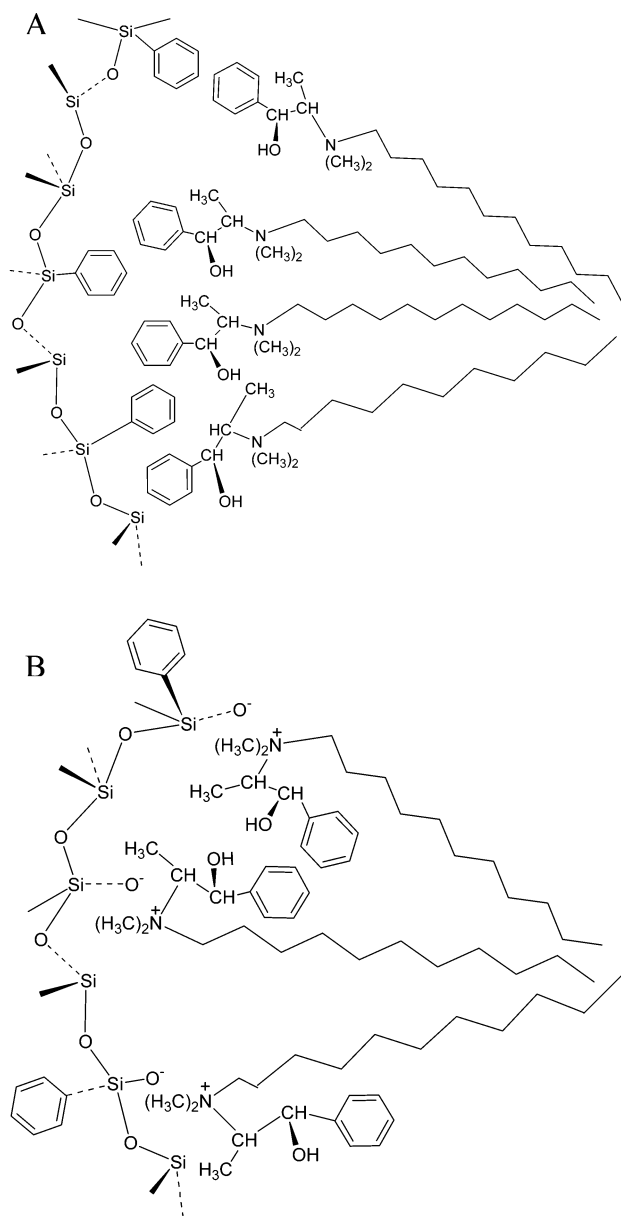


Figure 19. The enantioselective discrimination takes place either through π - π interactions (Figure 19a) between the long hydrophobic chains pointing away from the silica backbone and the formed matrix or (Figure 17b) through electrostatic attraction in a folded manner. This surfactant orientation is supported by the d spacing values that were obtained from the TEM measurements. In the first suggested orientation (Figure 19a) the surfactant length is 2.4 nm, and in the latter orientation (Figure 19b) 1.85 nm. (Reproduced from ref 57, with permission.)

through an optimal solution".⁶⁰ This was shown above for heterogeneous catalysts, sensors, and adsorbent surfaces. And yet, despite tens of practical applications,⁵⁹ the full applicative potential of these materials remains far from being realized.

We argue that a number of urgent practical problems in chemistry may well have a solution, through the employment of these functional materials. One of such problems, for instance, certainly resides in the use of enormous amounts of toxic (and carcinogenic) chlorinated and aromatic organic solvents to carry out chemical conversions that need urgent replacement with alternative, non toxic solvents.⁶¹ Intense current studies point to ionic liquids and carbon dioxide in supercritical state, but certainly no solvent is more environmental friendly and readily available than water.

Doped ORMOSIL, in this case, recently opened the way to the use of water as reaction medium for (catalytic) organic

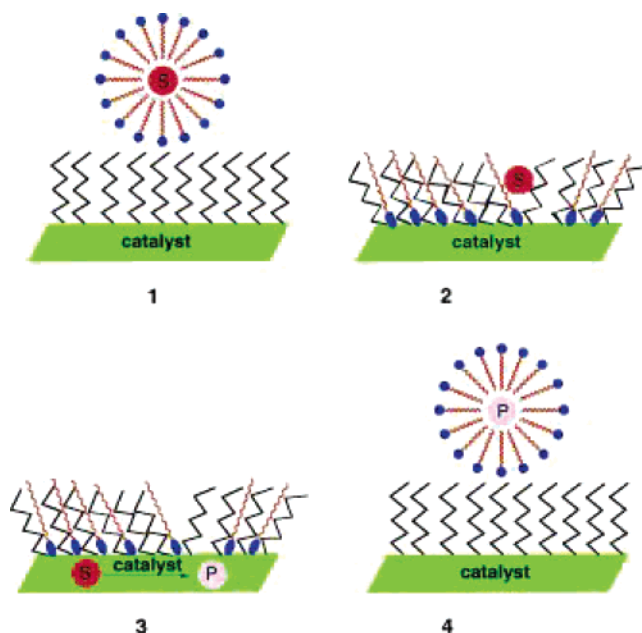


Figure 20. Illustration of the transport, reaction, and adsorption/desorption steps of the EST process. The emulsion that contains the substrate (1) spills its content into the catalytic material (2), the catalytic process takes place (3), and then the adsorbed surfactant carries the product back into solution (4). (Reproduced from ref 62b, with permission.)

reactions by simply emulsifying the organic reactants. In this manner, a general reaction procedure using a rhodium-doped 10–20% alkylated silica matrix in an elegant three-phase emulsion-solution-transfer process (EST) (Figure 20) was demonstrated for hydrogenations converting alkenes, alkynes, C=C aromatic bonds, cyano, and nitro groups.⁶²

Clearly, the method needs urgent extension to other catalytic reactions under different conditions with the development of robust sol-gel catalysts for the majority of the conversions employed in fine chemicals production, where an astonishing 30 kg of waste are generated along with 1 kg of useful product. By the same token, in a visionary 1912 paper entitled "The Photochemistry of the Future"⁶³ Ciamician predicted that in the future man would have made "batteries based on photochemical processes" as well as "catalysts to effect solar energy conversion". Almost one century later, even one of the leading scientist in the field admits that "we have only begun to inch toward the future that Ciamician foresaw".⁶⁴ The reasons of such low achievement mostly resides in our inability to master the destiny of excited molecules: Whereas in Nature, efficient light use affords of 90%, in man-made processes rapid thermal dissipation of energy occurs.

For instance, the most efficient and stable dye-sensitized solar cell uses an amphiphilic ruthenium complex in conjunction with a quasi-solid-state polymer gel electrolyte to reach an efficiency of ca. 6% in full sunlight;⁶⁵ with widespread use further limited by poor thermostability. Yet the enormous rise in oil prices makes clear the urgency of readily available cells of higher efficiency, at least comparable to that (20%) of the expensive silicon-based solar panels. Well architected doped organically modified silicates might largely contribute to such an advancement, as their enormous photochemical potential remains largely unexploited, similarly to what is happening with the new tailored organic light-emitting diodes (OLEDs) of enhanced durability and efficiency promising revolutionizing display technologies formed via sol-gel self-assembling or spin-coating of organosilane-functionalized molecular precursors.⁶⁶

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