Analytical Chemistry with Silica Sol-Gels: Traditional Routes to New Materials for Chemical Analysis

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Abstract

The versatility of sol-gel chemistry enables us to generate a wide range of silica and organosilica materials with controlled structure, composition, morphology and porosity. These materials' hosting and recognition properties, as well as their wide-open structures containing many easily accessible active sites, make them particularly attractive for analytical purposes. In this review, we summarize the importance of silica sol-gels in analytical chemistry by providing examples from the separation sciences, optical and electrochemical sensors, molecular imprinting, and biosensors. Recent work suggests that manipulating the structure and composition of these materials at different scales (from molecular to macromolecular states and/or from micro- to meso- and/or macroporous levels) promises to generate chemical and biochemical sensing devices with improved selectivity and sensitivity.

1. INTRODUCTION

The extremely rich chemistry of sol-gel-derived silica-based porous solids has propelled this family of materials to a prominent place in various areas of research. This increased prominence is due to the versatility of the (usually) low-temperature sol-gel processing, which combines the control of composition and microstructure at the molecular level with the ability to shape material in bulk, powder, fiber, monolith, and thin-film forms. The popularity of these materials can be attributed, in part, to three significant factors: (*a*) the ability to generate an almost infinite number of organic-inorganic hybrids that display both the mechanical stability of a rigid inorganic framework and the particular reactivity (e.g., selective recognition, optical properties, electrochemical activity) of the organic component; (*b*) the fact that sol-gel-derived materials can be used to encapsulate biomolecules (e.g., enzymes, antibodies, or other proteins) in a functional state; and (*c*) the discovery of the supramolecular template approach, which can generate ordered mesostructures over long length scales.

In this short review, we highlight the main uses of sol-gel-derived silica materials in traditional analytical chemistry. Rather than describing conventional analytical methods exploiting sol-gel technology, this paper distinguishes diverse families of silica sol-gel materials: sol-gel stationary phases, sol-gels doped with biomolecules, mesostructured materials and aerogels, molecularly imprinted sol-gels, and organofunctional sol-gels for pollutant uptake and detection. We devote special attention to the most recent exciting advances, whereas other key developments are summarized on the basis of related previously published overviews.

Monolith: a single, continuous piece of silica measuring ≥1 mm in length

Organic-inorganic hybrid: material made by linking (bio)organic groups (covalently or not) to an inorganic framework

Template: molecular, macromolecular, or supramolecular assembly used to generate porosity in a material during its preparation (i.e., by the sol-gel process)

Aerogel: a gel dried under supercritical conditions that is characterized by high surface area; low density; and a wide-open, interconnected, porous structure

TMOS: tetramethoxysilane

TEOS: tetraethoxysilane

Xerogel: a thoroughly dried gel that has undergone considerable shrinkage during drying and that is characterized by high surface area, porosity, and pore size

Mesoporous: refers to materials characterized by pore sizes ranging from 2 to 50 nm (microporous, <2 nm; macroporous, >50 nm)

2. SOL-GEL SYNTHESIS: AN OLD PROCESS FOR NOVEL MATERIALS

Sol-gel processing of silica is an intrinsically simple process. It usually involves hydrolysis of silicon alkoxide precursors [e.g., tetramethyoxysilane (TMOS) or tetraethoxysilane (TEOS)] and catalytic polycondensation to produce a macromolecular network of siloxane bonds (1). Less common aqueous silicates can also be used as precursors. Chemical reagents for the preparation of sol-gel materials normally include at least one precursor, a solvent to dissolve the precursor(s), a catalyst (acid, base, or ions as F^-), and water. Although gel formation from alkoxides has been performed for more than 150 years, with the first patent registered in the late 1930s (1), only in recent decades have we seen a revolution in the area of sol-gel-derived materials, with regard to both our fundamental understanding of their molecular-scale properties and their applications to analytical chemistry. Various aspects of sol-gel-derived materials are illustrated in **Figure 1** and are briefly discussed below.

The structure of evolving silicates is a consequence of the successive polymerization, gelation, aging, drying, and heating steps. Accurate tuning of the experimental parameters affecting these steps allows control over the microstructure of the final materials, from wide-open aerogels and highly porous monoliths or particles to less porous xerogels and fully dried silica thin films (2). A significant breakthrough in porosity control has been achieved with the emergence of ordered mesoporous silicates prepared by the surfactant template route (3), giving rise to novel materials that possess large uniform pore sizes (1.5–10 nm), highly ordered nanochannels, large surface areas (>1000 $m^2\ g^{-1}$), and tunable liquid crystal–like structures (4). Even larger pores (>10 nm) have been introduced into the silicate matrix via colloidal crystal templating, whereby the silica framework condenses around ordered arrangements of latex spheres ranging in diameter from 50 to 1000 nm (5). In both cases, the templates are removed via calcination or chemical treatments, leaving an array of ordered pores. More recent advances in this field rely on the creation of materials with hierarchical porosity, which are of special interest for chromatographic separations

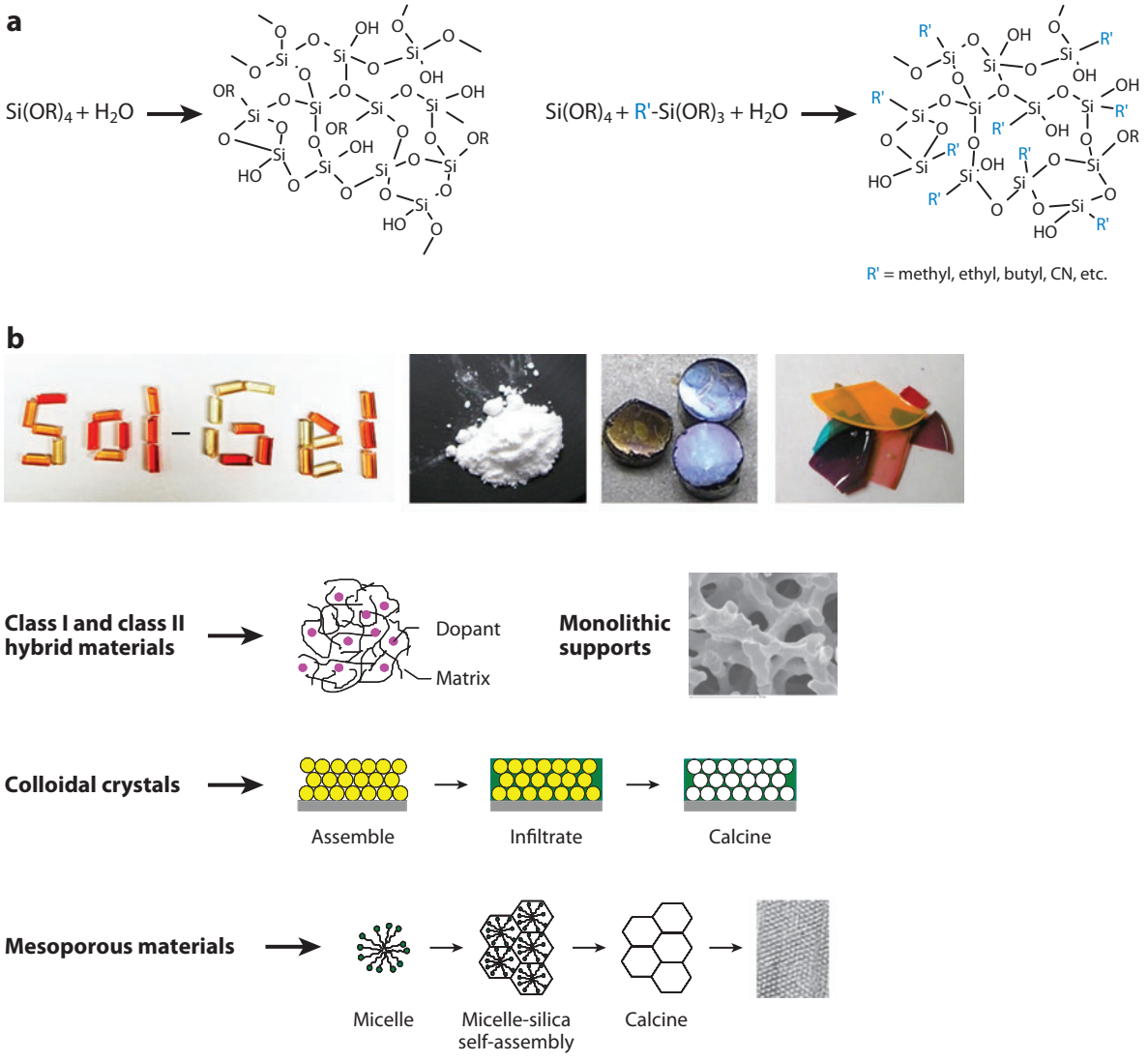

Figure 1

(*a*) A simplified view of sol-gel processing of silica and organosilica. (*b*) Photos and illustrations of some typical silica-based materials.

and chemical sensing (6). Another attractive feature of the sol-gel process is that the materials can be shaped at room temperature, for example by casting bulk gels in precision molds; spinning fibers; or dip-coating, spin-coating, or electrodepositing thin films, which may be useful in designing analytical sensing devices of various geometries and sizes.

Sol-gel chemistry is also a versatile tool for the synthesis of organic-inorganic hybrid materials with advanced properties that are often difficult to achieve either from totally inorganic or from totally organic materials. Hybrids of class I (weak interaction between organic and inorganic constituents) are obtained by impregnation, doping, or physical entrapment of organic, bioorganic, or organometallic species within sol-gel matrices. Hybrids of class II (organic component strongly attached to the siloxane network via covalent bonds) are typically prepared via

cocondensation of alkoxysilane and organosilane reagents (7). The latter approach benefits from a wide variety of commercially available organoalkoxysilanes, which enable the durable immobilization of the organofunctional groups; hybrids of class I, however, may suffer from leaching problems. An overlap between organic chemistry and the chemistry of ceramic materials has thus led to the development of numerous novel materials with controlled characteristics and tailor-made properties (8), including, for instance, polysiloxane-immobilized ligands (9), dye-containing sol-gels (10), mesoporous organic-inorganic hybrids (11), and silica gels encapsulating biomolecules (12). Among the most recent advances derived from the design flexibility of the sol-gel process in promoting host-guest interactions are molecularly imprinted xerogels (13), chiral sol-gel materials (14), and the successful immobilization of poorly stable membrane-bound proteins by sol-gel entrapment (15).

The past decade has seen intense activity in the development of sol-gel materials and in their applications [see, e.g., a special issue of Accounts of Chemical Research (16)]; however, it is beyond the scope of this review to describe all of these advances. Below, we specifically address their attractiveness to analytical chemistry.

3. INTERSECTION BETWEEN SILICA SOL-GELS AND ANALYTICAL CHEMISTRY

3.1. Advantages and Drawbacks

From an analytical standpoint, a solid-phase support for chemical applications ideally includes (*a*) a large surface area, (*b*) interconnected pores, (*c*) an open framework, (*d*) the ability to be doped with reagents, particularly biomolecules without loss of viability or reactivity, (*e*) the ability to be modified during synthesis or postsynthesis, (*f*) mechanical and chemical stability, and (*g*) feasibility (in terms of cost and time) of construction. Silica-based matrices thus offer several advantages over organic polymer–based materials, including physical robustness and resistance to abrasion; negligible swelling in organic solvents; chemical inertness; excellent optical transparency; and high photochemical, thermal, and biodegradational stability. The sol-gel process also provides flexibility in controlling the shape of materials with respect to the target application (e.g., thin film for sensors, fibers for online preconcentration, and monoliths for chromatographic or optical applications), the materials' porosity, their hydrophilic/hydrophobic balance, and most importantly, their chemical reactivity via a wide range of appropriate (bio)organofunctional entities. Depending on the application, drawbacks of the sol-gel process may include limited chemical stability in basic solutions, fragility, long-term changes in the materials' microscopic or macroscopic structure due to continued condensation between neighboring groups (or hydrolysis of existing groups), and shrinkage.

3.2. The Need for Porosity

High porosity is an important requirement for most analytical applications, particularly those that require analyte molecules to be separated and detected. An increase in the specific surface area of materials often enhances reactivity (as the materials have larger active surfaces) and improves recognition properties (meaning that more reactive groups are present, i.e., are attached to the silica walls), which helps to ensure high sensitivities. Furthermore, wide-open structures are likely to impart more rapid mass transport, which frequently constitutes the rate-determining step in chemical sensors. Silica and organically modified silica gel materials offer such advantages as high specific surface areas ($S > 200\ m^2\ g^{-1}$) and pore volumes ($Vp > 0.2\ cm^3\ g^{-1}$). In

recent years, significant efforts have been made to further increase the porosity of these materials ($S > 1000\ m^2\ g^{-1}$ and $Vp > 1\ cm^3\ g^{-1}$) via surfactant and/or colloidal crystal templating (1, 4–6, 16), as described above.

HPLC: high-performance liquid chromatography

3.3. Long-Term Usability Versus Response Time

Key parameters for successful applications in analytical chemistry are high sensitivity, good selectivity, long-term durability (which also implies good reproducibility and reversibility), ease of modification, and flexible processing. There are many attractive features of sol-gel-derived silica-based materials. First, organic-inorganic hybrids contain high local concentrations of reactive functional groups ($>1\ mol\ g^{-1}$), and their highly porous structures ensure easy and fast access for analytes, which contributes to high sensitivities in analytical devices. Selectivity is governed by the recognition properties of these active groups and can be easily tuned by introducing a wide range of reagents into the matrix (covalently and noncovalently). Long-term durability is best achieved with class II hybrids because of the nonhydrolyzable character of the Si–C bond. For class I hybrids, one must be able to achieve physical entrapment of doping reagents strong enough to avoid leaching when operating in solution (long-term usability) and to simultaneously keep the porosity of the material high enough to enable the fast diffusion of target analytes (short response time). This balance can be achieved by utilizing either thin films with short pathlengths for diffusion (e.g., optical or electrochemical sensors) or materials with multimodal porosity (e.g., both macropores, which ensure fast diffusion, and mesopores, which durably host the necessary reagents) in a single solid, as is done in separation sciences and in chemical sensor development.

4. SOL-GEL SUPPORTS FOR THE SEPARATION SCIENCES

4.1. Overview

Silane chemistry, particularly sol-gel chemistry, has played an important role in the development of supports for chromatography. Traditional supports for normal- or reverse-phase liquid chromatography, for example, were often made by derivatizing the inner surface of a glass or fused-silica column with functionalized chlorosilanes or alkoxysilanes (17, 18). In the mid-1990s, Guo & Colón (19) and Malik et al. (20) demonstrated the feasibility of using a traditional sol-gel-type approach to form high-surface-area, porous coatings on the inner walls of a capillary column for a wide variety of chromatographic separations (17, 18). These supports were relatively quick and easy to make, were more stable than the traditional direct-bonded supports, and achieved efficient separations of complex samples. Since these early days, the number of sol-gel-chemistry applications to separation science has escalated. Ordered mesoporous silica materials have been used as novel stationary phases and have improved performance in high-performance liquid chromatography (HPLC) based either on particles or on monoliths (21). The best results observed with packed columns were obtained with particles of spherical shape and large size ($>10\ \mu m$) that can be prepared via pseudomorphic transformation of spherical silica particles (22). Sol-gel chemistry has also been used to (*a*) create frits for electrochromatography and HPLC, (*b*) glue-pack materials together for liquid chromatography, (*c*) create microextraction columns, and (*d*) make monolithic columns, supports for microfluidics, and hierarchical supports (6, 23–28). Due to space constraints, the following sections focus upon sol-gel-derived monolithic supports and hierarchical supports, which are attracting considerable attention. We refer the reader to a number of excellent recent reviews for a more thorough account of the applicability of sol-gel chemistry to the broad field of separation science (6, 23–28).

4.2. Monolithic Supports

Monolithic columns can be considered as continuous-bed columns because they consist of one relatively large, continuous piece, namely a monolith. In contrast to the more traditional particle-based columns, monolithic columns do not need frits to hold the stationary phase in place, and they are more porous, have a higher surface area, and are more permeable than packed beds. Thus, they reduce pressures and allow for faster mobile-phase velocities (25–27). In addition, they can be directly prepared in the column and then chemically bound to it. There is no need to synthesize small, monodisperse particles and to pack long columns with such particles. The net results are often higher column efficiencies and better performance (25–27). The two approaches used to make monolithic columns involve (*a*) polymer and/or (*b*) sol-gel chemistry. The sol-gel approach has a number of distinct advantages that include good mechanical strength, negligible swelling in organic solvents, and ease of preparation and modification (25–27). However, due to shrinkage, inelastic deformation, stress-strain, and variations in local hydrolysis/condensation rates, the question of radial heterogeneity should be considered when making sol-gel-derived monolithic columns and evaluating their performance (29).

Various means of making these sol-gel-derived monolithic columns have been proposed (25–27). An early example described by Fields (30) used potassium silicate in formamide as the silica source. A capillary was filled with this solution and heated at 100° C, after which it was washed, dried, and modified with dimethyloctadecylchlorosilane. Tanaka and coworkers (31) hydrolyzed and condensed TEOS in the presence of a phase-separating agent/porogen, specifically polyethylene oxide (PEO). After gelation, the monolith was treated with ammonia, heat-treated at an elevated temperature (i.e., >300° C), and later derivatized with an octadecylchlorosilane. More details on these "hierarchical supports" are given below. Toyo'oka and coworkers (32) described a protein-encapsulation technique whereby proteins are encapsulated in a sol-gel-derived monolithic column for the separation of enantiomers via capillary electrochromatography. Zare and coworkers (33) created a monolithic column by doping a sol prepared from TEOS with octadecylsilica particles, then introduced this composite sol into a capillary. Upon gelation, the octyldecylsilica particles became trapped inside a porous silica monolith. A variant of this approach, used to make columns for ion chromatography, involves coating a silica monolith with appropriately functionalized latex nanoparticles (34).

Postderivatization protocols provide one way to attach particular functionalities to the silica framework. In situ methods, such as the use of organically modified silica sols to prepare hybrid monolithic columns, have also been described. For example, Hayes & Malik (35) prepared monolithic columns for capillary electrochromatography in a one-step method. In their report, a sol prepared from TMOS, *N*-octadecyldimethyl[3-(trimethoxysilyl) propyl]ammonium chloride, and phenyldimethylsilane was filled in a preconditioned capillary. After gelation, the column was heated under moderate temperatures and thoroughly washed. Because of the positive quaternary ammonium group, the electroosmotic flow was reversed. An inherent concern regarding the use of sols containing more than one alkoxysilane is that differences in their individual rates of hydrolysis/condensation can lead to phase separation and to column heterogeneity An alternative is to prepare supports from a single precursor. Recent work has shown promise in the use of methyltrimethoxysilane (MTMOS) as the sole precursor for the preparation of MSQ (methylsilsesquioxane) monolithic columns for liquid chromatography (36, 37).

4.3. Hierarchical Supports

An ideal support for separations has the correct balance of macro, meso-, and microporosity; surface area; and thickness (of the silica framework). Such a support also has an open structure

that enables high mobile-phase velocities and low pressure drop while enabling fast equilibration and optimal retention mechanisms (6, 25, 37). One way of achieving this ideal is to design and fabricate hierarchical supports, which are materials that exhibit multimodal porosity (6, 25, 38). Although many other approaches have been described, the most popular remains that in which polymerization-induced phase separation takes place in combination with gelation (6, 25). Water-soluble polymers and surfactants have been used as additives to induce phase separation (6, 25). For example, TMOS can be hydrolyzed in a limited amount of water with acid in the presence of polyethylene glycol (PEG) (31). After phase separation, the hydrophilic polymer resides in the fluid phase, which gives rise to the macropores after removal of the fluid phase. One can manipulate the size of the macropores by changing the concentration of the phase-separating agent/porogen (i.e., PEG) (6, 25). Many different surfactants and polymers used to prepare multimodal supports for separations have been reported in the literature. In one recent example, the triblock copolymer of P123 [poly(ethylene oxide)-block-poly(propylene oxide)-block-poly(ethylene oxide)] was used as the phase-separating agent/porogen to build supports for HPLC (39). Brennan and coworkers (40, 41) reported a protein-compatible variant of this approach, wherein the biocompatible silane (diglycerylsilane) was hydrolyzed/condensed in the presence of the phase-separating agent/porogen (PEG or PEO) in a two-step method.

Bioencapsulation: physical entrapment of a biomolecule or whole cell into a selected material

5. BIOMOLECULE ENCAPSULATION IN SOL-GELS: TOWARD BIOSENSORS

5.1. Sol-Gel Bioencapsulation

Immobilization of biomolecules (e.g., proteins, enzymes, antibodies, DNA, and whole cells) by entrapment in sol-gel materials has become a research area of intense interest (12, 15, 42, 43) since the discovery that a purified enzyme, alkaline phosphatase, can maintain some of its biological activity while entrapped in a TMOS-derived sol-gel matrix (44). Later, Ellerby et al. (45) modified this approach to improve the stability of biomolecules during encapsulation. Bioencapsulation in sol-gel matrices typically involves hydrolysis of tetraalkoxysilanes in an acidic medium followed by the addition of biomolecules in the presence of a buffer with a pH of $\approx$7, which initiates condensation of the hydrolyzed precursors around the biomolecules that become physically entrapped in an active form within the porous framework.

Since these pioneering studies, many enzymes and proteins have been immobilized in a functional state, and many have been protected against degradation by the sol-gel framework and have exhibited better activity and longer lifetimes than free enzymes [e.g., trapped alkaline phosphatase remains active at a pH as low as 0.9 (46)]. Recently, researchers have attempted to optimize this process by controlling the porosity of bioencapsulates and the chemical environment of trapped species to avoid the too-constrained motions of encapsulated proteins and to enable the necessary conformational changes for binding and release of substrates. Investigators have also proposed alternative synthetic routes to avoid enzyme denaturation due to alcohol release during the hydrolysis and condensation of the alkoxysilanes. Notably, avoiding denaturation requires the use of biocompatible silane precursors, aqueous silicate starting materials, protein-stabilizing additives, such as charged polymers, or sugars and amino acids (12, 15, 42, 43, 47, 48).

Bioencapsulation by sol-gel processing enables conversion of labile biological materials into reusable and physicochemically robust nanocomposites that can be interfaced with spectroscopic and electrochemical platforms to generate biosensing devices (49). The porous structure of the silica matrix ensures effective biomolecule entrapment while enabling small species (i.e., the analytes) to access the bioactive centers. To ensure that the biosensor can achieve the best possible

performance, one must provide suitable transduction (optical or electrochemical) of the biological recognition event into a measurable physical signal, and one must enhance both the accessibility of the analytes to entrapped proteins and the mass-transfer rates to improve the sensor sensitivity.

5.2. Optical Biosensors

The ability to produce transparent sol-gels with encapsulated biomolecules containing chromophoric or fluorescent groups, or alternatively, coimmobilized biomolecules along with a chromophore or fluorophore that responds to protein-mediated reactions, is at the forefront of optical biosensor development. Light absorption or reflection and fluorescence are the main detection techniques, although chemi- and bioluminescence have also been reported (49–51). Devices are based on monoliths (static or flow-through configurations) or on thin films deposited on flat surfaces (glass or quartz slides), optical fibers, or planar waveguides; the thin-film approaches give rise to faster response times. Array-based enzymatic optical biosensors have also been developed for multiple-analyte sensing (52). Detection limits obtained with optical biosensors are usually lower (down to single-molecule detection) than those of the corresponding electrochemical devices (49).

Several biomolecules have been used to build optical sol-gel biosensors, including (*a*) metalloproteins (e.g., hemoglobin, myoglobin, cytochrome *c*) to detect nitric oxide (NO) (51); (*b*) enzymes such as glucose oxidase (GOx) as well as cholinesterases, cholesterol oxidase, horseradish peroxidase (HRP), lactate dehydrogenase, nitrate reductase, urease, etc. (49, 50); (*c*) engineered fluorescence-signaling DNA enzymes for metal-ion sensing (53); and (*d*) bacteria to generate bioluminescent toxicity and fluorescent genotoxicity sensors (54). Performance improvement can be achieved via strategies to enhance the durability of chromophore or fluorophore immobilization via covalent binding to the inorganic framework or to silica nanoparticles (55) or via photochemical coenzyme regeneration (56). An example of the last approach is the photoinduced electron transfer between immobilized thionine and dinucleotide enzyme cofactors in sol-gels, in which the oxidized form of the coenzyme consumed by reaction with the substrate is photochemically regenerated by the photooxidizer thionine, enabling continuous detection of the reduced form of the coenzyme by fluorescence (56). Electrogenerated chemiluminescence biosensors constitute the remaining class of optical devices involving sol-gel materials (57), but their design requires effective charge transport (discussed in the context of electrochemical biosensors in the following section).

5.3. Electrochemical Biosensors

Sol-gel bioencapsulation has been widely used to immobilize enzymes (usually along with suitable charge-transfer cofactors) onto electrode surfaces to build electrochemical biosensors. In such devices, an electrode transducer converts the redox reaction that occurs at the active site of the enzyme into an electrical signal. Most achievements prior to 2000 have been described in previous reviews (58, 59). Those reviews described feasibility studies predominantly involving GOx and HRP enzymes and the use of mediators to facilitate communication between the biomolecules and the electrode materials (i.e., second-generation biosensors). Most common electrochemical devices were constituted of thin sol-gel films deposited onto the surface of a solid electrode in monolayer, bilayer, or sandwich configurations. Multilayers were especially exploited for optimal electrode/mediator/enzyme configurations and/or to add protective overlayers onto the devices. Obtaining crack-free films often required the addition of an organic polymer (or organoalkoxysilane) to the starting sol to avoid shrinkage. Bulk composite electrodes were also developed; these

include bio-sol-gel particles dispersed into carbon-paste matrices, ceramic-carbon composite electrodes made of interconnected dispersion of graphite powder and enzymes (+mediator) in a porous (organo)silica matrix (60), and thick-film carbon-ceramic devices prepared with screen-printing technology (58).

In addition to GOx and HRP, enzymes such as urease, acetylcholinesterase (for pesticide detection), cholesterol oxidase, lactate oxidase and lactate dehydrogenase, monoamine oxidase, tyrosinase, catalase, and other oxidoreductases have found use in sol-gel-derived biosensors. Bi-enzymatic immobilization has also been applied to improve the performance of such biosensors (61). The mediators employed included Prussian blue, ferrocene, and phenazine and phenothiazine derivatives, as well as electroactive polymers. Recent advances have been made in improving charge transport in bio-sol-gels, which has been achieved mainly through the addition of metal nanoparticles (especially gold) or carbon nanotubes (see, e.g., References 62 and 63). These systems are a promising means to develop third-generation biosensors, as they enable direct electron transfer between the electrode material and the active redox center in the biomolecule. Direct electrochemistry has also been claimed for metalloproteins encapsulated in sol-gel films, including those generated by a novel electroassisted sol-gel-deposition method (64). Another promising direction of research is the engineering of enzyme-linked silane precursors to improve the long-term operational stability of biosensors via covalent attachment of the biomolecule to the silica material (65).

5.4. Affinity Biosensors and Immunosensors

The specificity and sensitivity of antigen recognition by antibodies or enzyme-labeled antibodies immobilized in sol-gel materials have been exploited to design affinity biosensors and immunoassays. In addition to the obvious applications of these designs, namely determining biologically relevant species and detecting diseases, they have also been used for environmental monitoring (for instance, detecting contaminants that alter the biosensor response) (42). Although some optical detectors have been reported (e.g., on the basis of antifluorescein antibodies), transduction has mostly involved electrochemical methods, namely potentiometry, amperometry, and conductometry. Sol-gel-derived electrochemical immunosensors based on enzyme-labeled antibodies have experienced advances similar to those described above, including improvements in charge-transfer reactions, mass transport of analytes, and the durable immobilization of all (bio)components onto the electrode surface. Notably, these improvements have allowed us to take advantage of the chemistry of organosilane reagents to enhance the analytical performance and operational stability of the devices (66) and to use nanoparticles assembled in three-dimensional sol-gel networks to enhance the sensitivity of amperometric immunosensors (67).

5.5 Bacteria and Cells as Biosensors

Whole cells (e.g., *Escherichia coli*) have been encapsulated in sol-gel materials in a way that blocks their proliferation and prevents bacterial death upon entrapment (48), which are necessary prerequisites for sensor development. Most biosensors based on sol-gel entrapment of whole cells employ optical detection modes that exploit the transparency of the silica matrix. Recent examples include fluorescence detection of herbicides with immobilized *Chlorella vulgaris* (68) and naphthalene determination from the bioluminescence response of the bacterial bioreporter *Pseudomonas fluorescens HK44* (69). Other detection methods are based on piezoelectric or surface plasmon resonance measurements. In addition to bacteria, other microorganisms can be used for biosensing applications (70).

6. HIGH-SURFACE-AREA SILICA-BASED MATERIALS IN CHEMICAL ANALYSIS

6.1. Ordered Mesoporous Silica

Ordered mesoporous silica–based materials were first described in 1992, when researchers of the Mobil Oil Corporation used surfactant micelles instead of small cation-directing agents (which are usually used to prepare microporous zeolites) to build inorganic structures arising from silica polymerization around these larger templates (3). This gave rise to a novel class of solids composed of well-defined and uniform channels regularly arranged in various configurations (e.g., hexagonal, cubic, lamellar, wormlike) (4). These materials have sieving properties (with much larger pores than zeolites) and a surface chemistry very similar to that of nonordered silica gels that can be easily functionalized with organic groups (11).

6.1.1. Attractiveness of mesostructured materials. Mesoporous (organo)silicas offer all of the attractive features of sol-gel-derived materials along with additional properties that arise from the regular mesostructure generated by the template synthesis. These include (*a*) high specific surface areas and large pore volumes, which enable high functionalization levels and easy access to highly concentrated active sites that are likely to induce efficient analyte recognition and/or preconcentration prior to sensitive detection, and (*b*) faster mass transport (much faster than in nonordered silica gels) due to the regular spatial arrangement of mesopore channels of monodisperse size, which are expected to accelerate the rate of analyte recognition and/or preconcentration and thus improve the sensitivity of detection if mass transport is the rate-determining step (71). The vast number of organofunctional groups that can be introduced into mesoporous silica allows their reactivity to be tuned (11), which is promising for inducing selectivity to target analytes. Also, the molecular sieving properties of these materials and the ability to tune their hydrophobic/hydrophilic balance are attractive for rejection of interference. As with other sol-gels (namely particles, films, and monoliths), the morphology of mesostructured materials can be controlled and their porosity can be adjusted, typically over the 2-to-10-nm range and even more in so-called hierarchical pore structures. This phenomenon is known as multimodal porosity, where macropores facilitate diffusion-enhancing access to the mesopores (4).

6.1.2. Applications of powdered mesoporous silica. Mesoporous silica is usually prepared as powder. This morphology is not well suited to analytical devices because powders cannot be durably immobilized onto the surface of a sensing element unless they are embedded in coatings (72). However, there have been several examples of the use of mesoporous powders in chemical analysis.

Numerous mesoporous silica powders bearing various chromophores have been applied to the sensitive colorimetric analysis of metal ions. This method involves batch equilibration, in which metal ions are trapped by complexation to the immobilized chromophores, and the these colored complexes are subsequently optically detected after recovering solid particles by filtration (see Reference 73 for illustrative examples). Optical sensors based on mesoporous silica functionalized with fluorescent dyes have also been applied to multianalyte detection in water and to gas sensing (74). One can also prepare mesoporous materials functionalized with Co(III) corrole complexes that have almost infinite selectivity for CO and that have highly stable adsorption capacities, compared to less efficient silica gels (75).

Dispersion of mesoporous silica particles functionalized with N- and S-containing organic ligands into carbon-paste electrodes has been exploited to preconcentrate metal ions prior to their

detection by anodic stripping voltammetry (72, 76). Such electrodes have sensitivities higher by more than an order of magnitude than those of analogous devices based on silica-gel supports (71). Particle-based film electrodes, in which mesoporous silica powder is maintained on solid electrode surfaces by an organic polymer, have also been used, especially for electrocatalytic determinations (72). Such polymer binders are primarily exploited to strengthen the physical resistance of the film, but they can also act as antifouling barriers, which is especially useful in the analysis of non-pretreated natural samples [e.g., direct detection of heavy metal ions in natural waters and urine using composite electrodes based on thiol-functionalized mesoporous silica particles and Nafion® (77)]. Finally, the use of mesoporous silica as a host for enzymes (78) and other biomolecules allowed the development of biosensors that provide evidence of direct electron transfer to the immobilized biomaterials, but to date no significant advantage over the classical sol-gel bioencapsulation approach (see Section 5.3) has been demonstrated. However, one exception may be the bi-enzyme-channeling sensor recently constructed by entrapping GOx and HRP in the regular channels of mesoporous silica (79).

6.1.3. Analytical devices based on thin films. Thin films of nanostructured materials constitute the best configuration for sensing (80). Mesostructured silica films can be prepared on solid supports (including electrodes) via evaporation-induced self-assembly (EISA) with controlled thickness, porosity, and mesostructure type (81). The films' permeability to external reagents (i.e., from a solution, through the film, to the underlying substrate) has been found to be strongly dependent on these parameters (82). The presence of functional groups attached to the silica walls is also likely to induce permselective behaviors (83).

Mesostructured silica films have begun to be exploited in the field of electrochemical sensors (80). Examples of preconcentration electroanalysis, electrocatalytic devices, biosensors, and gas sensors include (*a*) Pb(II) determination with thiol-functionalized mesoporous silica film deposited on a gold-electrode array (84), (*b*) hydrogen peroxide sensing via concomitant use of an electrocatalyst (CdTe quantum dots) and a biomolecule (myoglobin) immobilized in amine-functionalized mesoporous silica (85), and (*c*) gas sensors based on resistive-type responses of mesoporous silica films to relative humidity changes or alcohol vapors (86). Note that sensitive gas sensing can also be performed using, for instance, cyclodextrin-functionalized, mesoporous silica films deposited on quartz resonators that measure the change in mass due to gas adsorption (87). The recently developed electroassisted self-assembly (EASA) method to generate mesoporous silica films on electrodes with well-ordered mesopore channels oriented normal to the underlying surface (**Figure 2*a***) is expected to further expand these films' applications (88). They offer an ideal configuration for mass transport and may be used as a hard template for electrogeneration of aligned nanowires. In addition, EASA can be applied to homogeneous film depositions on nonflat surfaces (**Figure 2*b***), unlike the conventional EISA process (88).

Thin film–based optical sensors may also incorporate dyes into the internal surfaces of mesoporous silica deposits. pH sensors with thin films were first developed on the basis of fluorescein covalently attached to the mesopore channels of the film, which gave rise to a very fast optical response to pH changes (89). A similar surface was covered with phospholipid bilayer and applied to the optical detection of ion-channel proton transport in a biological membrane (90). Also available are several optical sensors for heavy metal ions, which rely on dye incorporation into mesoporous silica films [for example, uranyl species detection via complexation to grafted β-diketone compounds (91)]. Optical sensing devices based on fluorescence have also been reported: coimmobilized coumarin and porphyrin derivatives on mesoporous silica films have been used to detect gaseous methanol (92).

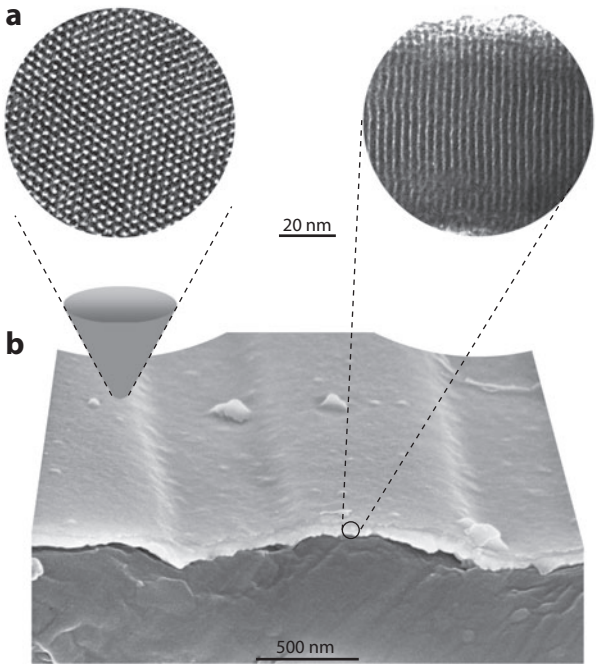

Figure 2

(*a*) Transmission electron micrographs of an electrodeposited surfactant-templated mesoporous silica thin film. Shown are the top view (*left*) and the cross-sectional view (*right*). (*b*) Scanning electron micrograph of the same film deposited on a gold compact disc (CD)-trode, which is a gold electrode made from a recordable CD that displays a regular streaked morphology at the micrometer level. Adapted from Reference 88.

6.2. Silica Aerogels in Chemical Analysis

Silica aerogels are high-surface-area mesoporous materials with open, interconnected pores of varying size (93, 94). These materials are typically made by supercritically drying a solvent-exchanged wet gel to avoid the capillary pressure that contributes to pore collapse. The porosity of an aerogel can be as high as 99%, which is close to twice the porosity of many xerogels (93, 94). Because of their open framework and high porosity, aerogels are ideal for applications that rely on fast and efficient mass transport, including sensing, catalysis, and energy storage (94). As platforms for chemical sensors or as supports for separations, however, silica aerogels have not received the attention they deserve. The problems originate from (*a*) the aerogels' lack of mechanical stability and (*b*) the leaching/chemical stability of the gel-encapsulated reagents during washings and supercritical drying. The use of reagents functionalized with alkoxysilane groups can help minimize or eliminate leaching. The preparation of mechanically strong, reinforced aerogels by chemically bonding a polymer to the silica surface may provide a solution to this problem (95). In a recent report, these mechanically strong, cross-linked aerogels were used to remove metal ions and were found to adsorb metal ions approximately eight times faster than did microporous gels (96).

The most promising applications of aerogels in chemical sensing involve gas-phase (particularly oxygen) sensing. Leventis et al. (97) incorporated a silylated fluorescent dye into an aerogel via bulk methods (doping in a silica sol before supercritical drying) and via postdoping (attachment of the dye to the outer surface of the wet gel). The dye-doped aerogels were highly fluorescent, and

the fluorescence was rapidly quenched with oxygen. The response times of the dye-doped aerogels to oxygen were significantly faster than those observed for comparable dye-doped xerogels (97). Further, Leventis et al. (98) synthesized ruthenium derivatives, postdoped them into an aerogel, and employed them as efficient, fast oxygen sensors. By using a rapid supercritical extraction method for aerogel preparation, Carroll et al. (99) showed that underivatized fluorescent dyes (i.e., ruthenium dyes) can be successfully entrapped in aerogels. These dye-doped aerogels also had a rapid response to oxygen; thus, they show considerable promise for the development of aerogel-based gas sensors.

Imprinting: process by which molecularly designed pores that show an affinity for the imprint are created in a polymer host structure

Another promising area of research is the use of aerogels in biosensing and biocatalysis. Rolison and coworkers (100) showed that a cytochrome *c*/colloidal gold complex can be encapsulated into a silica aerogel, wherein 80% of the protein remains viable after typical aerogel processing. The cytochrome *c*/gold colloid complex reversibly bound gas-phase NO (100). Also, Pierre's group (101, 102) has demonstrated that lipases can be encapsulated in aerogels and used as biocatalysts.

7. TOWARD THE NEXT GENERATION OF IMPRINTED SENSORS

Molecular imprinting is a powerful synthetic approach used to create artificial receptors for molecular recognition (13, 17, 103–107). In molecular imprinting, a polymeric framework is assembled and molded around a suitable imprint, which, upon removal, yields microcavities with a specific size, shape, and/or chemical functionality in a highly cross-linked matrix. Such molecularly designed cavities show an affinity for the imprinted molecule over other structurally and chemically related compounds. In contrast to biologically based receptors, artificial mimics are less costly, more stable, and better able to withstand harsh environments (13, 17, 103–107).

7.1. Attractiveness of Imprinting in Sol-Gel Processing

The polymeric framework that houses the imprinted sites must be porous to allow the imprint molecule to be efficiently removed and the internal imprinted sites to be easily accessed by analytes in solution. Mild polymerization conditions and processing flexibility also extend the range of molecules that can be imprinted and the types of applications in which the materials can be used. Powders are the most useful for chromatography, and thin films are important for chemical sensing. Compared to conventional organic polymerization methods, sol-gel processing has many important advantages, including needed flexibility in processing conditions, material preparation, and choice of monomers (e.g., organoalkoxysilanes) in addition to optical transparency, rigidity, stability in harsh environments, and tailorable porosity (13). As has been described in a comprehensive review (13), there has been incredible growth during the past decade in the use of sol-gel chemistry to design and construct imprinted materials. In the following sections, we highlight a few recent advances that pertain to the use of sol-gel processing in chiral and bioimprinting and to the construction of nanostructured mesoporous supports that improve site accessibility.

7.2. Small-Molecule Chiral Imprinting

The research groups of Avnir and Marx have been the strongest contributors to the development of small-molecule chiral imprinting in sol-gel materials via the use of chiral templates. Their work has recently been reviewed (14). In 2001, Marx and coworkers (108) briefly reported on the creation of a propranolol-imprinted sol-gel-derived silica thin film that could discriminate between

enantiomers. Later publications described in further detail this system and others, including those used to electrochemically detect electroactive enantiomers, D- and L-3,4-dihydroxyphenylalanine and (*R*)- and (*S*)-*N*,*N*′-dimethylferrocenylethylamine, in imprinted sol-gel-derived thin films (109).

Subsequently, an intriguing report described the ability of a templated cavity to selectively recognize the chirality of a molecule that is different from the template molecule (110). In this study, the researchers created the host by hydrolyzing and cocondensing phenyltrimethoxysilane (PTMOS) and TMOS in the presence of a surfactant containing two chiral centers: (1*R*,2*S*)-(–)-*N*-dodecyl-*N*-methylephedrinium bromide. The imprinted films showed a preferential readsorption for *R*-propranolol over *S*-propranolol and (*R*)-2,2,2-Trifluoro(anthryl)ethanol over the *S* enantiomer (110).

In more recent work, the authors (111) described a similar approach wherein the chiral surfactant induces chiral porosity in bulk silica materials upon surfactant removal. In addition, they described how the chiral surfactant doped into the silica material acts as a chiral center. The pairs of enantiomers included (*R*)- and (*S*)-propranolol, (*R*)- and (*S*)-binaphthyl-2,2-diyl hydrogen phosphate, and (*R*)- and (*S*)-naproxen. Enantioselective preference was reversed from the matrix that still contained the chiral surfactant to the material where the surfactant was removed.

7.3. Bioimprinting

Large-molecule imprinting has been less intensively studied than small-molecule imprinting for several reasons. Most importantly, imprinting proteins, enzymes, and viruses is more challenging because biomolecules are (*a*) large, which makes them harder to remove and rebind; (*b*) complex, in terms of both conformation and surface functionalities; and (*c*) often less stable, particularly in solvents commonly used in imprinting procedures then small molecules (112–115). Sol-gel processing, a milder and more aqueous process than conventional organic polymerization, provides a means to successfully imprint large biomolecules such as proteins, enzymes, bacteria, and viruses. However, this approach is not without challenges.

The approach that has been used nearly exclusively is surface imprinting (116). In surface imprinting, the binding sites are more accessible compared to bulk sol-gel processing, enabling easier removal of the biomolecule from the imprinted pocket and easier reinsertion. Considering the sheer sizes of biomolecules and their relatively slow diffusion, restricted access to and from imprinted pockets can be a significant limitation (113, 115). Surface-imprinting strategies involve the use of (*a*) thin films coated on porous particles, (*b*) thin films coated on planar substrates, and (*c*) stamping.

An example of the first approach was described by Sakaguchi and coworkers (117), who covalently attached hemoglobin to an aminopropyl silica particle and then polymerized organoalkoxysilanes on the surface of the hemoglobin-modified silica particle. An example of the thin-film method on a planar substrate was illustrated by Yao and coworkers (118). In this study, human serum albumin was added to a hybrid sol prepared by mixing TEOS with methyltrimethoxysilane (MTMOS) and PTMOS. A gold-coated quartz crystal self-assembled with thioglycolic acid was dipped into this composite sol several times to form a film (~150–500 nm thick). Piezoelectric quartz crystal impedance and electrochemical impedance were used to detect binding (118). An optical surface imprinting approach was demonstrated by Bright and coworkers (104, 119), which they termed PIXIES (Protein Imprinted Xerogels with Integrated Emission Sites). In the third strategy, described by Dickert and coworkers (120, 121), the imprint of a biomolecule (in this case, a microorganism) was formed on the surface of a suitable substrate (polymer- or sol-gel-derived coatings) using a stamp. Mass-sensitive techniques were used to detect binding.

7.4. Novel Sol-Gel Supports in Imprinting

For molecular imprints to be useful in most analytical applications, the imprinted cavities in the polymeric network must be accessible. To remove molecules residing deep within the center of the polymer, the template must be accessible, and the analyte in solution must be able to reach these same sites. The binding capacity and the binding kinetics are significantly influenced by accessibility. Traditional methods for dealing with accessibility include (*a*) grinding the polymeric matrix into small particles, thereby exposing more sites, (*b*) using a porogen, which is an inert solvent that is incorporated into the polymer during formation and later washed away, and (*c*) imprinting on the surface of a host structure. Modern approaches have utilized nanostructured materials as the support structure. Examples of these include ordered mesoporous materials (see Section 6.1), silica nanotubes and wires, and silica nanoparticles. The advantage of mesoporous supports is an open porous framework that facilitates removal and readsorption of the template. These materials demonstrate larger uptake capacities and significantly faster uptake rates (binding kinetics) than do traditional materials.

Dai and coworkers (122) were among the first researchers to describe how the inner surfaces of ordered mesoporous powders can be imprinted and used in metal-ion recognition. This group also described an approach, termed hierarchically double imprinting, that utilizes two templates: one that produces pores on the mesopore level (25 Å) and another that produces pores on the micropore level (1–2 Å). Yang et al. (123) used a surface-imprinting approach to prepare silica nanotube membranes, which were synthesized within the cylindrical pores of nanopore alumina membranes, that exhibit selectivity for the molecule estrone. Zhang and coworkers (124) recently showed that imprinted silica nanotubes can used for the detection of TNT (trinitrotoluene). These authors used silica nanoparticles, prepared by the Stöber method, as supports. They first derivatized the silica nanoparticles with 3-APS (3-aminopropyltriethoxysilane) and then with acryloyl chloride to form reactive vinyl groups (125). A polymer shell with sites imprinted with the template (TNT) was then formed around the silica nanoparticle using conventional acrylic organic polymerization procedures.

8. SOL-GELS BEARING COMPLEXING LIGANDS FOR ENVIRONMENTAL REMEDIATION AND SENSING

8.1. Pollutant Removal

Sol-gel-derived organic-inorganic hybrids incorporating complexing ligands have been widely used as selective adsorbents for metal ions (126–128). N- and S-bearing ligands are the most commonly used, but more sophisticated complexing agents are increasingly being exploited (9). Advantages of such adsorbents include their high levels of functionalization, which ensure great sorption capacities [e.g., 0.75 g Hg(II) per g of thiol-functionalized mesoporous silica (129)]; the great diversity of organofunctional groups that can be incorporated in the matrix [e.g., silica gels with engineered ligands for selective uranyl ion concentrations (130)]; and their ability to lower residual concentration of contaminants down to the established limits of toxicity. Again, mesoporous adsorbents prepared with the surfactant-template method (Section 6.1) are particularly attractive in terms of capacity enhancement and fast kinetics of metal uptake (128, 129, 131). Practical applications of sol-gel materials for environmental waste remediation are now in development (see, e.g., References 96 and 132 for discussion of toxic metals and fission by-products). Biofunctionalized adsorbents can also be engineered; for instance, thiol- and sulfonic acid–grafted silica can be applied to the reductive-sorptive uptake of chromium species (133). These approaches are not restricted to metal species: Hybrid sol-gel materials can be applied to the removal of

organic pollutants [e.g., pesticides on cyclodextrin-functionalized mesoporous silica (134)]. Catalytic biosorbents have also been developed from microbial consortia (nitrifying and denitrifying mud) immobilization on sol-gels applied to denitrification of natural waters (135).

8.2. Sensors for Environmental Monitoring

The above-described separation processes can also be applied as preconcentration steps prior to detection of target analytes in environmental samples. In addition to the various aforementioned materials and methods (Sections 4–7), hybrid materials functionalized with organic ligands have also been exploited in optical and electrochemical sensing devices directed to environmental monitoring. The most efficient analytical schemes require both the preconcentration and the detection steps to be performed in a single device. Examples in the literature include optical sensors (51, 136, 137) and bulk composite- and film-based silica-modified electrodes applied to potentiometric and amperometric sensing (59, 60, 138). Both the immobilized receptor properties of the hybrids and their permselective behavior have been exploited to improve selectivity of the detection (17). Numerous sol-gel-derived membranes have thus been developed, primarily on electrode surfaces and to distinguish analytes and interferences on the basis of their distinct size or shape (molecular sieving and imprinting effects), charge (electrostatic attraction/repulsion), or hydrophobic/hydrophilic balance (139, 140). Such permselectivity has further been exploited to build spectroelectrochemical sensors with three levels of selectivity: selective permeation of the film and both optical and electrochemical activities of the analyte (140). Bioaffinity materials prepared by entrapping highly selective bioligands in sol-gels offer advantages in the clean-up of complex sample matrixes and show great promise for environmental, food, and clinical analyses (141).

9. CONCLUSIONS AND OUTLOOK

The field of sol-gel chemistry has become an exciting area of research, with many opportunities in the fields of chemistry and material science. Today one can find numerous commercial products prepared using sol-gel processes including monolithic silica columns for chromatography (Merck(tm), Phenomenex(tm)), enzymes immobilized in sol-gels (Fluka(tm)), and mesoporous silica and organosilica nanoparticles (Claytec, Inc.(tm)). Sol-gel chemistry provides a relatively simple, flexible means to prepare a host for chemically reactive groups or species, chromatographic supports for efficient separations of complex mixtures on the traditional scale and on the microscale, and porous materials that can selectively complex an analyte in solution for removal and/or remediation.

This review has touched on only a subset of what those in the broad field of sol-gel chemistry have accomplished and will continue to accomplish over the coming decades. Due to the multidisciplinary nature of sol-gel chemistry, card-carrying analytical chemists may also perform the work of inorganic or physical chemists, material scientists, and/or nanotechnologists. They will not only continue to use the sol-gel approach to design and create new and better-performing materials for chemical analysis, but will also be involved in using these materials in the next generation of chemical sensors, supports for separation and filtration, and molecular recognition devices. The next decade is likely to see a push toward the continued development of the ideal support (i.e., one that has high surface area, interconnected pores, and open framework and that is mechanically and chemically stable), as well as its use in new and exciting areas that include chemical analysis as well as development of batteries, fuel cells, and renewable energy sources, the perfect superhydrophobic and self-cleaning surface, energy-efficient photonic devices, and biodegradable capsules for drug delivery.

SUMMARY POINTS

1. The application of sol-gel chemistry to separation science has escalated during the past decade. Sol-gel chemistry has been used to make micrometer-sized particles for packed columns; to create frits for electrochromatography and HPLC; to glue-pack materials together for liquid chromatography; and to create microextraction columns, monolithic columns, supports for microfluidics, and hierarchical supports with multimodal porosity for efficient and fast separations.
2. The low temperature processing of sol-gel chemistry can be advantageously applied to encapsulate biomolecules while maintaining their activity. Sol-gels can be used to design sensitive optical and electrochemical biosensors.
3. Highly porous sol-gel materials, especially those exhibiting a regular order on the mesoscale, are particularly attractive because they improve accessibility to active centers and mass transport of analytes, thereby increasing the sensitivity of analytical devices.
4. Due to its mild reaction conditions, its processing flexibility, the large selection of monomers and cross-linking agents, and its high surface areas, sol-gel chemistry has become a viable and popular means to prepare imprinted materials.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Errata

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