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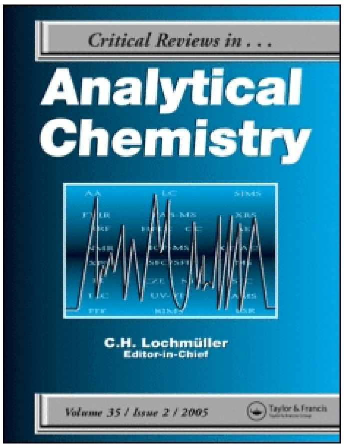

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Sol-Gel Strategies for the Preparation of Selective Materials for Chemical Analysis

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ABSTRACT: The sol-gel process provides a versatile method to prepare size, shape, and charge selective materials for chemical analysis. Ion-exchange sites or functionalities can be introduced into the inorganic framework as a means to preconcentrate an appropriately charged analyte into a film for detection. Template-based approaches can be utilized to design porous inorganic hosts with improved molecular recognition capabilities. Chromatographic stationary phases with excellent thermal and hydrolytic stability can be designed to separate complex mixtures. Through variations in the sol-gel processing conditions (silicon-to-water ratio, pH, type of silicon alkoxide), membranes with optimal porosity and/or hydrophobicity can be prepared for gas separation and facilitated transport applications. In this review some of the unique features and new applications of sol-gel technology are described as it pertains to the development of materials with improved molecular specificity for chemical analysis.

KEY WORDS: sol-gel, silica, silicate, ORMOSIL, ion-exchange, gas separation membranes, template, molecular imprinting, chromatography.

I. INTRODUCTION

The sol-gel route[1,2] provides a useful method to prepare inorganic and organic-inorganic hybrid materials for use in chemical analysis.[3–12] The inherent usefulness of this approach is largely due to the ease at which sol-gel-derived materials can be prepared, modified, and processed. The mild reaction conditions affords an opportunity to incorporate various molecules such a proteins, enzymes, dyes, organic, and organometallic reagents into a glass composite.[3–12] This can be readily achieved by simply doping the reagent into the sol prior to its gelation, as demonstrated by Avnir and co-workers[13] or alternatively via the use of organosilicon derivatives,[14–19] $R\text{-}Si(OR')_3$, where R is the desired reagent. The materials are optically transparent, chemically and mechanically stable, and can be prepared in a variety sizes and shapes, including thin films, monoliths, fibers, and powders.[3–11] Furthermore, the average pore size, pore size distribution, surface area, refractive index, and polarity of the resultant matrix can also be controlled and tailored via manipulations in the sol-gel processing conditions, including the type and concentration of the silane(s).[3–11, 1–19]

Among numerous applications, the sol-gel approach is being used extensively in the development of new materials for catalysis,[20,21] chemical sensors,[7,8] membranes,[22] optical gain media,[23] photochromic and nonlinear applications,[24–26] and solid-state electrochemical devices.[27,28] For example, sol-gel technology has been used to prepare both pure inorganic and organic-inorganic hybrid supports of catalytically active transition metal complexes, dispersed metal particles, and biocatalysts.[20,21] Silica gel-entrapped proteins and enzymes have been employed in numerous biological sensing applications,[3,12] whereas the organic and organometallic doped materials have been utilized as sensors for metals, ions, pH, and gasses.[4–11] The organically modified materials have been used recently to fabricate leak-free chemical sensors and materials for nonlinear optical applications.[10,17,19] A number of excellent well-documented review articles on sol-gel chemistry have appeared recently in the literature describing these and many other applications.[3–12,16–19]

A growing trend in analytical chemistry is the need to develop more selective materials. Materials that are able to differentiate among a diversity of different molecules based on size, charge, shape, and/or chemical affinity is needed to prepare more sensitive, selective, faster, and efficient devices. Sol-gel technology provides many advantages for the preparation of selective materials, and,as evidenced by the number of papers published in the last few years, has become of interest amongst researchers in the field. In this review, sol-gel approaches for the preparation of size, shape, and charge selective materials for chemical analysis are described. This review is not meant to be a comprehensive compilation of all papers in the field, but it is meant to give the interested reader a flavor of the chemistry involved and its applicability to the design and fabrication of selective materials for analytical applications. Following a brief introduction to sol-gel chemistry, various approaches to the development of ion exchange and permselective coatings, molecular sieving and controlled porosity materials, selective materials via molecular templating, and chromatographic stationary phases are described.

II. INTRODUCTION TO SOL-GEL CHEMISTRY

The sol-gel process provides a relatively straightforward means to prepare inorganic or organic-inorganic hybrid glasses through the hydrolysis and condensation of suitable metal alkoxides.[1–2, 29–33] The most widely used precursors to prepare materials for use in chemical analysis applications have been the silicon alkoxides, particularly tetramethoxysilane (TMOS) or tetraethoxysilane (TEOS).[1,2,29] These reagents can be readily hydrolyzed and condensed under relatively mild conditions as depicted in the simplified reaction sequence below.[1,2,29]

Hydrolysis:

$$\mathrm{Si(OR)_4} + n\mathrm{H_2O} \rightarrow \mathrm{Si(OR)}_{4\text{-}n}\mathrm{(OH)}_n + n\mathrm{ROH} \qquad (1)$$

Condensation:

$$\equiv\mathrm{Si\text{-}OH} + \mathrm{HO\text{-}Si}\equiv \rightarrow \equiv\mathrm{Si\text{-}O\text{-}Si}\equiv + \mathrm{H_2O} \quad \text{(water condensation)} \qquad (2)$$

and/or

$$\equiv\mathrm{Si\text{-}OR} + \mathrm{HO\text{-}Si}\equiv \rightarrow \equiv\mathrm{Si\text{-}O\text{-}Si}\equiv + \mathrm{ROH} \quad \text{(alcohol condensation)} \qquad (3)$$

In a typical procedure, TMOS is combined with water in a mutual solvent (i.e., methanol) and a suitable catalyst (acid, base, nucleophile) added. During the sol-gel transformation, the viscosity of the solution gradually increases as the sol (colloidal suspension of very small particles, 1 to 100 nm) becomes interconnected to form a rigid, porous network — the gel. Gelation can take place on the time scale of seconds to minutes to days to months (or longer) depending on the sol-gel processing conditions. After drying, a xerogel is formed. A large amount of shrinkage accompanies drying, often with cracking unless the monolithic materials are dried slowly or drying control additives added to the sol.[1,2]

The chemical reactions that occur during the formation of the sol, gel, and xerogel strongly influence the composition and properties of the final product. In brief, both reactions occur through a bimolecular nucleophilic substitution at the silicon center (S_N2-Si). The hydrolysis reaction under acidic conditions involves protonation of the alkoxide group followed by nucleophilic attack by water to form a pentacoordinate intermediate. The partial positive charge on the alkoxide group confers to it better leaving group character. Under basic conditions, the mechanism is believed to involve the nucleophilic attack on the silicon atom by the hydroxide anion to form a negatively charged penta-coordinated intermediate followed by displacement of an alkoxide anion.[1,2, 29a, 30,31]

The physical properties (i.e., average pore size, pore size distribution, pore shape, surface area) of the dried gel depend on the sol-gel process parameters and the method at which the material is prepared.[1,2,29–33] The water-to-silane ratio, the nature and concentration of the catalyst, and the alkoxide precursors strongly influence the relative rates of hydrolysis and condensation.[1,2,29–33] In general, low pH, low water preparations lead to denser materials with smaller average pore sizes, whereas high pH, high water preparations lead to more porous materials.[1,2,29,31] Under acid catalysis, condensation occurs preferentially between silanol groups located on monomers or the ends of polymers.[1,2,31] Under these conditions, the gels are composed of predominantly entangled linear chains that after drying forms a lower pore volume matrix.[1,2,29] Under basic conditions, condensation preferentially occurs between the more highly branched oligomers to form more particulate gels. After drying, materials with high interstitial porosity are produced.[1,2,29,31] The microstructural characteristics of thin films relative to bulk gels can be considerably different even when they are prepared with the same sol because in film formation gelation occurs simultaneously with evaporation.[1] In general, thin films are considerably less porous than bulk gels.[1] The formation of a wide range of chemically and physically distinct molecular scale environments within an individual sample is also likely due to microscopic variations in pore size, shape, surface composition, and local solvent composition produced during synthesis and drying. Recent work has shown that thin silicate films are more heterogeneous on the microscopic scale relative to polymer films prepared from poly(butyl)methacrylate.[34]

Organosilicon precursors of the general formula ($R_{4-x}Si(OR')_x$, where R represents the desired reagent or functional group and x = 1–3) can be hydrolyzed and condensed with the silicon alkoxides (i.e., TMOS or TEOS) to produce materials with properties superior to those prepared from either compound alone.[14–19] These materials have been coined ORMOSILs (Organically Modified Silicates) by Schmidt and co-workers in the early 1980s.[14] Specific organic modifiers that have been used include CH_3, C_2H_5, C_6H_5, $(CH_2)_nNH_2$, $(CH_2)_nSH$. A large diversity of organosilicon derivatives with various functional groups are commercially available. The most commonly used are the trialkoxide silanes (× = 3), where the functional group R is bound to the silicon via a nonhydrolyzable silicon carbon bond. These precursors are often preferentially crosslinked with tetraalkoxide (× = 4) components to impart suitable network connectivity and stability to the solid, although they can be also used alone.[15–19] One of the distinct advantages this approach provides is that the chemical properties (refractive index, polarity, surface functionality) of the silicate matrix can be readily tailored through the judicious choice of R. This enables composite materials with the desired hydrophobicity, porosity, flexibility, reactivity, and stability to be readily fabricated.[15–19]

The complexity associated with the polymerization process becomes even more apparent in the preparation of materials from organosilicon precursors. Here, the relative rates of hydrolysis and condensation strongly depend on steric and inductive factors.[1, 32,33]

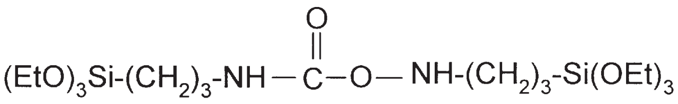
In many cases, acidic media are utilized due to the inherently slower reactivity of the organosilicon precursor in basic media.[32,33] If the organic functional group has acidic or basic properties (i.e., R = NH_2 or COO^-) and thus can influence the hydrolysis and condensation process, the polymerization processes can be even further complicated. Examples of this have been described in a previous review.[17] In the formation of mixed organic-inorganic hybrid materials, the chemical reactivity of the individual precursors becomes critically important. Careful control of hydrolysis and condensation is often necessary to prepare materials that incorporate the organic modifier homogeneously throughout the inorganic matrix.[17,19,30]

III. ION-EXCHANGE AND PERMSELECTIVE MATERIALS

Ion-exchange and permselective coatings are important in many applications, particularly those involved in chemical analysis. These materials can be used to selectively preconcentrate reagents at an electrode surface and/or at an optically transparent substrate for analysis or can be used as permselective coatings to essentially prevent interferents from being detected. The development of permselective and ion-exchange films becomes very important in many bioanalytical applications where it is necessary to exclude numerous interferents from the underlying surface or in analytical applications where detection limits can be extended via preconcentrating the analyte of interest in a thin film. One of the distinct advantages sol-gel-derived materials provide over other commonly used organic polymers is the inherent flexibility associated with material preparation and the processing. For example, the porosity, hydrophobicity, and network connectivity can be manipulated via changes in the sol-gel processing and drying conditions.[1–2, 29] This flexibility enables materials with ideal response time, permselectivity, and ion-exchange to be fabricated. In addition, sol-gel-derived materials can be made to have good optical transparency, chemical, photochemical, and electrochemical stability, and are less susceptible to solvent-induced swelling/shrinking that often plague polymer films.[3–6] To date, most work has focused on the incorporation of (1) quaternary ammonium salts, (2) polyelectrolytes, or (3) organosilicon reagents that contain acidic or basic functional groups into the sol as a means to introduce specific ion-exchange sites within the silica host structure.

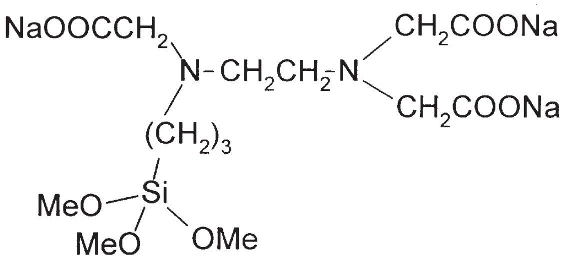
One of the first examples of the use of sol-gel materials in ion-exchange applications was reported by Lev and co-workers in 1992.[35] This study showed that it is possible to trap quaternary ammonium salts (e.g., cetyltrimethylammonium bromide (CTAB), cetylpyridinium bromide (CPB)) into a solid silica support by physically doping these compounds into a sol prepared from TEOS. The ion exchange properties of these immobilized quaternary ammonium exchangers toward chloride, bromide, sulfate, and nitrate were assessed with the ground glasses using ion chromatography. Dopant leaching was also evaluated using total organic carbon analyzer and ion chromatography. In terms of good ion exchange activity and good trapping, the quaternary amine ion-exchange compounds were found to be best.[35]

More recently, Park and co-workers have doped the quaternary ammonium salt tridodecylmethylammonium chloride (an ionophore for chloride) into a inorganic-organic composite prepared from the organosilicon precursor, **1a**.[36] This silane was chosen over the more commonly studied TEOS or TMOS because the materials thus produced are flexible enough to be cut into membranes and mounted in electrode bodies. The resultant membranes were selective for chloride over the concentration range of

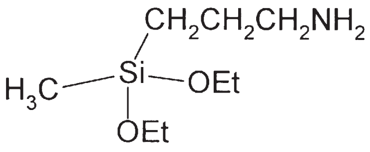


$(EtO)_3Si\text{-}(CH_2)_3\text{-}NH-\overset{O}{\overset{\|}{C}}-O-NH\text{-}(CH_2)_3\text{-}Si(OEt)_3$

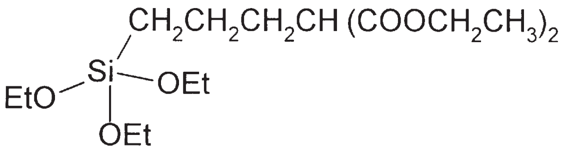
1a



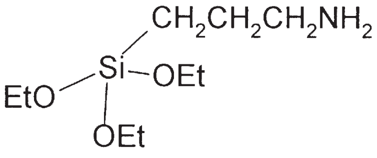
1b



1c



1d



1e

FIGURE 1. Examples of organosilicon derivatives used in the preparation of ion-exchange films.

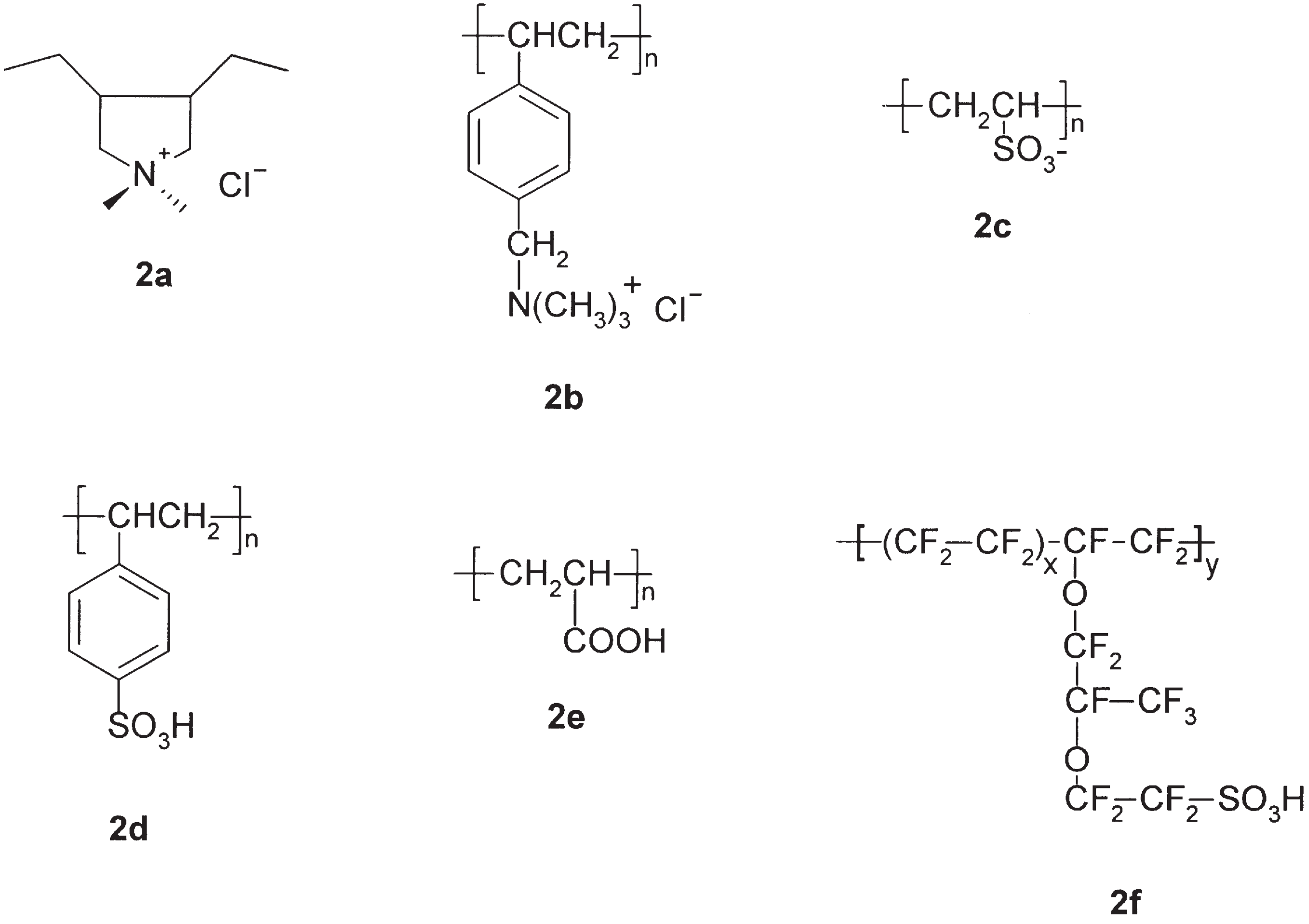
10^{-4} to 0.5 *M*. The potentiometric selectivity of these membranes toward bromide, iodide, salicylate, and other anions were also evaluated and satisfactory results obtained.[36]

Hsueh and Collinson have shown that organosilicon reagents that contain NH_3^+, COO^-, or COOEt functionalites can be hydrolyzed and co-condensed with methyltrimethoxysilane (MTMOS) to form materials that contain anion or cation exchange sites, respectively.[37] In this work, the sol was spin cast on the surface of a glassy carbon electrode and the ion-exchange and permselective properties of the resultant thin films evaluated using cyclic voltammetry. When placed in neutral pH buffer solutions, ORMOSIL films fabricated from **1b** (silane-$(COOH)_3$) ion-exchanged small cations such ruthenium hexaammine, dopamine, and methyl viologen and essentially excluded small anions such as potassium ferricyanide from reaching the underlying electrode surface. In contrast, ORMOSIL films prepared from **1c** (silane-NH_2) ion-exchanged small anions and essentially excluded small cations. Permselectivity against anions was also established using films prepared from **1d** (silane-$(COOEt)_2$).[37]

In more recent work, Wei and Collinson have shown that 3-aminopropyltriethoxysilane (**1e**, APTEOS) can be hydrolyzed and co-condensed in various ratios with different organosilicon reagents (R-Si$(OCH_3)_3$ where R = CH_3; $CH(CH_3)CH_3$, C_6H_5, or OCH_3) to form stable thin films.[38] The major objective of this study was to prepare materials with different amounts of ion-exchange sites, different hydrophobicity, and variable porosity to vary the selectivity and specificity of these composite materials.[38] These results showed that both the magnitude and the rate of ion-exchange of potassium ferricyanide can be controlled via the amount and type of organosilicon precursor introduced into the sol. For films prepared from isobutyltrimethoxysilane (BTMOS) or phenyltrimethoxysilane (BTMOS), the ion-exchange was at least 10-fold faster than that observed when either TMOS or MTMOS was used as the co-reactant. This is believed to be due in part to the reduction in network connectivity and/or the relatively greater porosity of these thin films. In terms of both permselectivity and ion-exchange, films prepared from a sol that contains a 1:1 mole ratio of functionalized silicon precursor to APTEOS were ideal.[38]

Heineman, Seliskar, and co-workers have taken a different approach to the incorporation of ion-exchange sites into a silicate matrix.[39–44] In their work, polyelectrolytes have been chemically doped into the hydrolyzed sol and the resultant composite spin cast on the surface of an electrode or an optically transparent substrate and used to preconcentrate analytes.[39–44] Specific examples of polycations that have been incorporated into a TEOS-based silica sol include poly(diallyldimethyl ammonium chloride) (**2a**,) and poly(vinylbenzyltrimethylammonium chloride) (**2b**, PVTAC). Specific examples of polyanions that have been used include poly(vinylsulfonic acid) (**2c**, PVSA), polystyrene sulfonic acid (**2d**, PSSA), poly(acrylic acid) (**2e**, PAA), and Nafion (**2f**).[39–44] Most of their work has focused on spin casting the ionomer-doped silica sol on the surface of a graphite electrode or on the surface of an ITO optically transparent electrode. Square wave voltammetry, cyclic voltammetry, UV-vis absorption and fluorescence spectroscopy, and most recently Attenuated Total Reflection (ATR) spectroelectrochemistry have been used to characterize the ion-exchange of analytes into these films.[41,42,44] ATR spectrometry is inherently useful because only those analytes that partition into the sol-gel-derived film will be interrogated optically providing the evanescent wave remains within the film.

The anion-exchange properties of films prepared from a PDMDAAC (**2a**) silica sol have been demonstrated using the redox probe, potassium ferricyanide, and a pH-



2a

2b

2c

2d

2e

2f

FIGURE 2. Examples of polyelectrolytes incorporated in sol-gel-derived films for ion-exchange applications.

sensitive dye 8-hydroxy-1,3,6-pyrenetrisulfonic acid trisodium salt (HTPS).[39–41] This anion exchange film has also been used in a "dual-analyte sensing" motif for the determination of two ions, Fe^{2+} and H^+, after first ion-exchanging the metal ion indicator ferrozine and the pH indicator HTPS into the film.[41] Similarly, the redox probes ruthenium (II) *tris*(bipyridine) and methyl viologen have been used to characterize the cation exchange properties of films prepared from a Nafion- and PVSA-doped sol. The Nafion-doped composites have been used in the spectroelectrochemical sensing of $Re(DMPE)_3^+$ where DMPE is 1,2-*bis*(dimethylphosphino)ethane.[44] In most cases, the gel-modified electrodes showed good stability (months) and reproducibility (ca. 10%) and reasonable limits of detection and calibration curve linearity. Preconcentration factors of approximately 10 to 50 were found for these materials via comparison of the response obtained at the ionomer-doped gel-modified electrode to that found at the bare electrode. For the Nafion-sol-gel composites, the accumulation rates were found to be significantly faster for both methyl viologen and $Re(DMPE)_3^+$ relative to those measured for a Nafion-modified electrode alone.[43,44]

IV. MOLECULAR SIEVING AND CONTROLLED POROSITY MEMBRANES

The ability to manipulate and/or control the porosity of organic, inorganic, and hybrid materials is important in many fields of analytical and material science. From an analytical perspective, the development of new materials with tailored made pore sizes and shapes lends itself to creation of chromatographic stationary phases (i.e., molecular exclusion, gas-solid partition chromatography), molecular selective chemical sensors, size- and shape-selective catalysts, and membranes for gas separation, gas recovery, and facilitated transport applications. In addition to molecular recognition-related applications, the ability to form voids of a prespecified size in a dense, inorganic host could be used to create nanosized reaction vessels for organic synthesis or to improve the response time of sol-gel-derived biosensors by creating pores in an otherwise dense matrix (i.e., film) as a means to facilitate diffusion of reagents to an entrapped biomolecule.

The sol-gel process provides a number of distinct advantages for the creation of materials with controlled porosity and morphology. These include good thermal, mechanical, and chemical stability, flexible solution chemistry, ease with which materials in various configurations (i.e., films, fibers, monoliths) can be processed, and the ability to control material porosity and structure through small changes in the sol-gel-processing variables (i.e., nature and concentration of the catalyst, ratio of water to silicon alkoxide).[3–8] To date, a number of different approaches have been utilized, including (1) carefully controlling the synthesis parameters, (2) creating molecular-sized voids in the silicate matrix via covalent and noncovalent templating, and (3) introducing "molecular sieving functions" or neutral carriers in the silicate framework.

The fabrication of thin silica microporous membranes via careful control over the sol-gel synthesis parameters has been studied for a number of years.[22,45–57] These membranes have been made by dip coating or spin casting a layer of a carefully prepared silica sol on commercial alumina supports, although unsupported membranes have also been reported. The thin top layer of microporous silica is responsible for gas permeation and separation, whereas the macroporous support provides strength.[22,45,46] The microstructural characteristics of sol-gel-derived membranes are largely determined by the sol-gel processing parameters, the support, and the drying conditions. The catalyst (i.e., acid) and water concentration in the sol can be readily tuned to synthesize microporous membranes with a wide range of porosities.[22] Membranes with pore sizes between 5 and 20Å have been commonly prepared,[221,45–47,53,57,58] as well as materials with small pore size (3Å) and molecular sieving capabilities.[49] Gas permeance studies on a number of gas molecules, including hydrogen, carbon dioxide, helium, nitrogen, oxygen, argon, methane, propane, and butane were conducted.[49,50,53,54,57] These materials have been shown to have a high activation energy for helium permeation and ideal CO_2/N_2 and He/N_2 selectivity, although nonselective diffusion through defects was also evident for larger molecules in some studies.[50]

Microporous materials that show chemical affinity in addition to high permeability have been prepared by incorporating organosilicon reagents into the inorganic-based sol.[58–65] Likewise, polymer-silica hybrid membranes have also been prepared.[66,67] Dire and co-workers, for example, have described the preparation and gas permeation properties of unsupported membranes prepared from hybrid sols of TEOS and methyltriethoxysilane (MTEOS).[59,60] Recently, de Vos and co-workers have described the preparation of hydrophobic silica membranes for gas separation by co-hydrolyzing TEOS with MTEOS.[61] Guizard and Lacan fabricated composite membranes on a porous alumina support using a sol prepared from organosilicon precursors containing two trialkoxysilyl groups that were synthesized by coupling terepthaloyl chloride with either 3-aminopropylmethyl**di**ethoxysilane or 3-aminopropyl**tri**ethoxysilane.[62,63] The research groups of Okui and Smaihi have focused on composite membranes prepared by combining TMOS with either diphenyldimethoxysilane or PTMOS in various ratios and coating the resultant hybrid sol on a porous support.[64,65] Gas permeance studies showed that these materials had a greater affinity for CO_2 than the other gases studied. Okui and co-workers have also examined other organic functional groups, including methyl, propyl, 3-chloropropyl, 3,3,3-trifluoropropyl.[65] The permeation and/or the selectivity of the membranes toward different gases (i.e., CO_2; He; N_2) were examined and shown to be a complex function of the structure and chemical functionality in the membranes.[65]

Template-based strategies have also been used as an effective means to increase and control the porosity and morphology of sol-gel-derived materials. As described in a recent review,[68] the templating of silica can be achieved via two general procedures: (1) noncovalent or (2) covalent. In the noncovalent approach, the silicate framework is formed around a suitable molecule or assembly that later is extracted from the matrix through washing or thermal treatment to yield cavities in the host. In the covalent approach, the template is covalently bound to the framework through the formation of a hybrid organic-inorganic nanocomposite and then removed via thermal or chemical treatments.[68] Both strategies have been used to design porous silica for gas separation and chemical sensing-related applications.

Lev and co-workers have described the preparation of macroporous silicate films for planar chromatography using a silica sol prepared from MTMOS using bromocresol purple as the catalyst/pore-forming dopant.[69] When the dopant was rinsed out of the matrix with ethanol, appropriate-sized voids remained in the film. This particular work focused on the optimization of the sol-gel process parameters to prepare thick films (10 to 60 μm) of the appropriate film thickness, porosity and connectivity, and uniformity.[69] Porous silicas have also been obtained using macromolecules such as dendrimers,[70,71] polymers,[72] or glucose[73] as the template. Chujo et al., for example, have incorporated various starburst dendrimers into a silica sol prepared from the acid-catalyzed reaction of TMOS.[71] After pyrolysis at

600°C for 24 h, the starburst dendrimers were completely eliminated from the hybrid material leaving molecular size voids in the host.[71] Recently, Hedrick and co-workers have also showed that hyperbranched aliphatic polyesters can be used as the template to prepare a porous inorganic structure with a film morphology that appears to mimic that of the template after thermal treatment.[70]

Perhaps one of the more thoroughly studied examples of noncovalent templating involves the preparation of mesoporous silica hosts with uniform channels and long-range crystallographic order by combining a suitable silica source (i.e., TEOS) with water, surfactant, and catalyst.[68,74–81] The surfactant/surfactant assemblies act as templates (or pore directing agents) and serve to direct the polymerization of the silicate precursors into a three-dimensional network of uniform channels/arrays.[74] After formation, the template can be removed from the silica framework by calcination or soxhlet extraction.[74–78] Through variations in the size of the surfactant/surfactant assemblies, the channel diameter can be controlled from ca. 15 to 100Å.[68,74–78] The interior surface of these channels can also be readily modified with specific organic groups (i.e., $–NH_2$, $–SO_3$, $-C_6H_6$, $-CHCH_2$, etc.) via direct or "post" synthesis procedures to form a wide range of functionalized hybrid materials with uniform channels.[79–81] The large nanometer-sized channels of this crystalline host matrix have served as hosts for the inclusion of transition metal complexes, polymers, photoactive molecules, and metal particles for catalyst, photonic, and electronic applications.[75–78]

Covalent approaches to molecular templating have also be used to create materials with controlled porosity and morphology.[68,82–88] As mentioned above, this approach involves the fabrication of an organic-inorganic hybrid material followed by removal of the organic functionality (i.e., the template) via pyrolysis or chemical treatment.[68,82–88] In the ideal case, the size and shape of the pores will be determined by the size and shape of the template, whereas the pore volume will be dictated by the amount of template introduced into the sol.[68,82,88] This is not easily achieved; however, as a number of parameters, including the volume fraction of the organic group, the extent of cross-linking in the support, and the extent of microstructural induced changes after template removal strongly influence the microstructural characteristics of the resultant glasses (i.e., pore volume, pore size, pore size distribution, pore connectivity).[82–88]

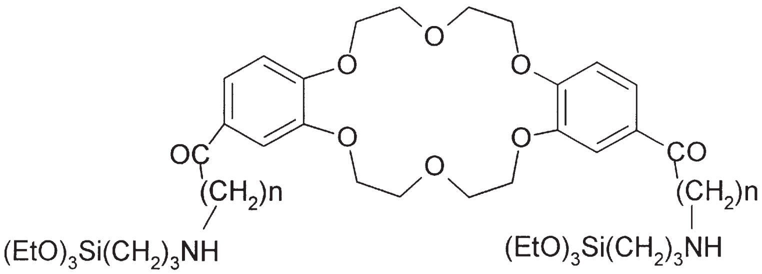
Brinker and co-workers have shown that molecular-sized voids can be created in a silica framework via the thermal removal of the organic "template" in hybrid materials prepared from organosilicon derivatives of the general formula, $R\text{-}Si(OR')_3$ where R = CH_3 or $H_2C{=}C(CH_3)CO_2(CH_2)_3$.[86–88] The hybrid sols were prepared by mixing TEOS with the organosilicon derivative in various mole ratios. The materials were studied as xerogel powders or as "molecular sieving" membranes prepared by casting the sol on a mesoporous alumina support. Prior to calcination, the methacryloxypropyl templated materials were dense with no porosity accessible to N_2 and limited porosity accessible to CO_2.[87,88] Likewise, membranes were dense and nearly gas tight.[87,88] After calcination at 350°C for 3 h to remove the template, a microporous network with a narrow pore size distribution was obtained. Gas permeation measurements showed the flux of SF_6 to be 1000 times less than that of propene, N_2, and He indicative of a pore diameter between 4.5 and 5.5Å, which is consistent with the estimated size of the template.[87,88]

Corriu and co-workers likewise have described the formation of both mesoporous and microporous silica via covalent templating of hybrid xerogels prepared from precursors of the general formula, $(RO)_3Si\text{-}C{\equiv}C\text{-}(CH_2)_n\text{-}C{\equiv}C\text{-}Si(OR)_3$ (where n = 2–8) or $(RO)_3Si\text{-}C{\equiv}C\text{-}C_6H_4\text{-}C{\equiv}C\text{-}Si(OR)_3$.[82–85] Removal of the organic fragment from the hybrid materials was achieved either by (1) thermal treatment or (2) chemically via cleavage of the Si-C bond using fluoride as the catalyst.[82–84] The silica prepared after chemical treatment yielded high surface areas with a narrow pore size distribution of mesopores (30 to 50Å). For the small-chain-length derivatives, elimination of the organic spacer was quantitatively achieved. The average pore diameter was shown to decrease with decreasing size of the organic fragment in the network and with decreasing the amount of fragment incorporated into the hybrid gel. This pore diameter, however, was considerably larger than the organic spacer eliminated from the gel and is believed to be due to an association type mechanism and/or to rearrangement of the silica network, which was evidenced by NMR data.[82–84] In direct contrast to these results, porous silica obtained after direct thermal treatment is completely different — microporous with a broad-size distribution.[82–84]

In related work, Shea and co-workers have reported on the preparation of micro- and mesoporous materials that also involves the use of bis(triethoxysilyl) alkane, alkylene, and aryl derivatives.[89–93] These precursors can be hydrolyzed and condensed either alone or with TEOS to yield polysilsesquioxane xerogels after drying. It was envisioned that the pore sizes of these xerogels could be controlled by the size of the organic spacer introduced into the network. While no simple correlation was observed between the type and size of the spacer and the resultant pore size, rather distinct differences between materials prepared with "rigid" spacers and "flexible" spacers were observed.[89–93] Materials prepared with arylene bridged monomers were porous and had extremely high surface areas, whereas xerogels prepared from the alkylene bridged precursors were significantly less porous with nonporous gels obtained from the long-chain derivatives.[89–93]

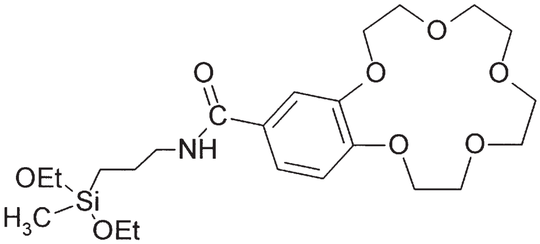
Another approach for the preparation of size-selective materials for sensor or gas phase separations has involved the incorporation of molecular specific functionalities such as zeolites[45,94–96] or crown ethers[97–101] into the silicate framework. For example, Bien, Brinker, and co-workers have shown that zeolite crystals (faujasite and ZSM-5) can be incorporated into a dense silicate matrix via doping the zeolite into the silica sol.[45,94–96] After sintering, gas permeability occurred through the zeolite channels exclusively. Both FTIR and a surface acoustic wave (SAW) device were used to evaluate the selective adsorption of gas vapors. Depending on the specific zeolite incorporated into the nonporous framework, different size-based molecular selectivity was observed.[45,94–96]

Ion-selective materials for sensor and transport applications have also been prepared by incorporating crown ethers of differing cavity size (i.e., 12-crown-4, 15-crown-5, 18-crown-6, 16-crown-5) into the silicate network.[97–101] This can be achieved by simply physically doping the complexing agent into the sol or via the use of specific trialkoxysilyl crown ether derivatives. Guizard and co-workers have described the preparation of fixed-site carrier membranes that contain covalently immobilized crown ether derivatives (**3a** or **3b)** for facilitated ion transport of either K^+ ions vs. Li^+ ions or Ag^+/Cu^{2+} ions.[98–99] Kimura and co-workers have reported on the physical entrapment of the neutral carriers, valinomycin or a *bis*(12-crown-4) derivative into a hybrid matrix prepared from TEOS and diethoxydimethylsilane as a means to prepare an ion sensor. The organosilicon derivative was used to impart flexibility into the matrix as materials prepared from TEOS alone were brittle.[100] The valinomycin and *bis*(12-crown-4) doped materials showed Nernstian response to Na^+ and K^+, respectively, and relatively fast response times (ca. 3 sec), and good selectivity and long-term stability.[100] In more recent work, results from the chemical immobilization of alkoxysilyl *bis*(crown

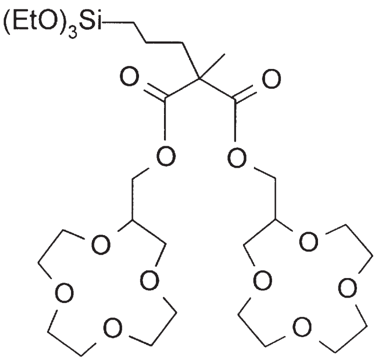


n = 2, 10

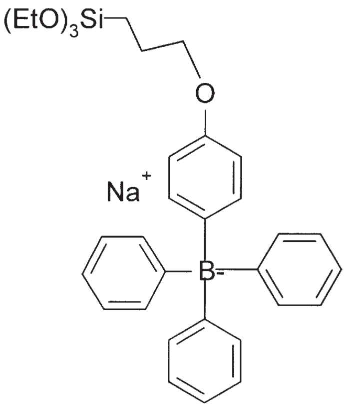
3a



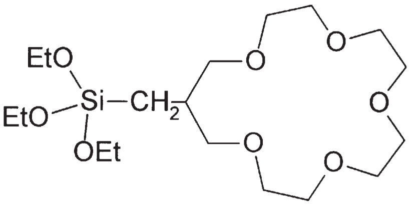
3b



3c



3d



3e

FIGURE 3. Examples of trialkoxysilyl crown ethers derivatives used to prepare membranes for sensor and transport applications.

ether) derivatives, **3c/3d or 3e**, within the hybrid membrane was reported.[101] In general, the selectivity coefficients of the chemically bound derivatives were not as good as that reported for the unbound derivatives,[100] but the membrane response was stable for considerably longer periods of time (>100 days).[101]

V. MOLECULAR TEMPLATING OF SILICA

During the last decade, considerable interest has been given to the design and development of new materials with improved molecular recognition properties. Materials with tailormade porosity, morphology, and chemical functionality are vitally important in the development of highly selective chemical sensors, efficient stationary phases for liquid chromatography, improved transport membranes, and catalytic supports. One promising method to fabricate materials with improved molecular specificity involves molecular imprinting or templating.[68,102–105] In this approach, a polymeric network is assembled around a suitable template molecule. After removal of the template, molecular cavities with a distinct pore size, shape, and/or chemical functionality remain in the crosslinked host. These “molecularly designed cavities” show an affinity for the template molecule over other structurally related compounds.[68,102–105]

Most of the current studies have utilized organic polymerization chemistry as a means to introduce molecular imprints in an organic polymer.[102–105] For example, Mosbach and others have shown that polymerizable functional organic monomers (i.e., methacrylic acid, vinylpyridine), chosen for their affinity for the template molecule, can be combined with a large excess of the crosslinking agent (i.e., ethylene glycol dimethacrylate) and a free radical initiator to form a rigid polymer that shows an affinity for the template molecule once it has been extracted from the host.[102–105] The molecular recognition properties of these synthetically designed binding sites are attractive, and thus these polymeric materials have been applied routinely to the development of the chromatographic stationary phases.[102–105] Inorganic materials have also been used in templating schemes, albeit to a lesser extent. It is likely too soon to tell how effectively silica imprinted procedures and materials will compare with those prepared using organic polymerization routes.

Relative to organic-based polymerization schemes, sol-gel processing affords a number of viable advantages for the preparation of templated materials. The mild reaction conditions enables specific molecules, particularly those that are water soluble, to be readily introduced within a highly crosslinked porous host without problems associated with thermal or chemical decomposition.[3–7] Materials in various configurations (e.g., films, fibers, monoliths, powders) can be prepared easily. The ability to form thin films is important in chemical sensor applications due to the inherent reduction in the path length for reagent diffusion and hence improvement in the response time of the device. Specific organic functional groups can be combined with the inorganic precursor (i.e., TEOS) to introduce specific chemical functionalities into the framework and improve molecular selectivity and specificity.[19] Furthermore, the materials are stable and the sol-gel processing conditions can be varied to control the porosity and surface area of the resultant material.[1]

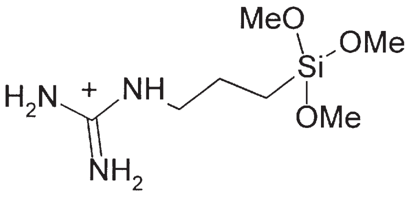
One of the first examples of molecular templating was that of Dickey’s work that showed that silica gel synthesized from a sodium silicate solution in the presence of a specific dye molecule had an increased adsorption capacity for that particular dye once it had been removed from the gel.[106,107] Specific dyes utilized in this study were methyl orange, ethyl orange, propyl orange, and butyl orange. Methanol extraction was used to remove most of the dye from the gel after drying.[106,107] The mechanism for selectivity may involve a "footprint" mechanism as originally proposed by Dickey or it may involve an association (or recrystallization) type mechanism argued by Hodgson and co-workers.[108] Since that time a few other studies have utilized related procedures and shown enhancements in template readsorption relative to control samples for silica-based materials.

Dai and co-workers showed that sol-gel glasses prepared with the template $UO_2(NO_3)_2.6H_2O$ show an enhanced capacity for the Uranyl (UO_2^{2+}) ion relative to that observed for a similarly prepared blank control gel.[109] The templated silica was prepared by the acid-catalyzed hydrolysis of TEOS, and the template removed from the dried gel via overnight soaking in nitric acid.[109] Pinel and co-workers also prepared silica gel solids from the acid, base, or F-catalyzed hydrolysis and condensation of TEOS that showed a greater adsorption of the template, menthol, relative to blank samples.[110] Similar results were also observed for *o*-cresol and *p*-cresol when *o*-cresol was used as a template.[110]

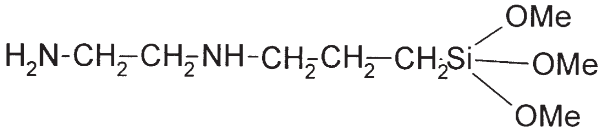
Recently, Brinker, Shea, and co-workers have described a surface imprinting procedure for the creation of "synthetic receptors" for phosphates and phosphonates in a xerogel host.[111] In this work, the organosilicon reagent 3-trimethoxysilylpropyl-1-guanidinium chloride (**4a**) was condensed onto the surface of a xerogel host prepared from TEOS in the presence of the template molecule phenylphosphonic acid. The materials were ground, sieved, and packed into a HPLC column and the relative affinities of the templated materials to acetone, diisopropylphenylphosphonate, and phenylphosphonic acid evaluated as a function of pH and ionic strength. The phenylphosphonic acid-templated materials "show an enhancement greater than 2 in the binding constants for phosphate and phenylphosphonic acid relative to a randomly functionalized polmer."[111] Hydrogen bonding and electrostatics are believed to be important in this work.[111]

Recently, Collinson and Makote have described a template-based approach for the preparation of thin films that exhibited selectivity toward the neurotransmitter dopamine.[112] In this work, a composite sol was prepared via the hydrolysis and condensation of TMOS, MTMOS, and PTMOS. Dopamine was added to the hydrolyzed sol and the resultant mixture cast as a thin film on the surface of a glassy carbon electrode. Dopamine was extracted from the dried film by soaking in phosphate buffer, and the affinity and selectivity of the dopamine-templated films characterized with cyclic voltammetry.[112] The dopamine templated films had a relatively fast response time and showed an increased affinity for dopamine over related molecules, including serotonin, ascorbic acid, and DOPAC. Film porosity, electrostatics, and hydrophobicity are believed to play a role in governing diffusion and permeation into the film.[112]

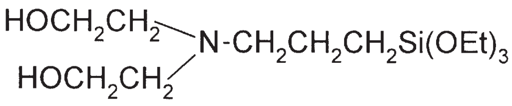
In addition to these applications, surface imprinting of silica has also been accomplished by combining silica particles with suitable organosilicon reagents.[113–116] For example, Mosbach and co-workers have described approaches for molecular imprinting and enzyme entrapment based on the condensation of organosilanes on the surface of porous silica particles.[113] In one approach phenyltriethoxysilane, *N*-2-aminoethyl-3-aminopropyltrimethoxysilane (**4b**), and *bis*(2-hydroxyethyl)aminopropyltriethoxysilane (**4c**) were combined with a dye template (either rhodanile blue or safranine O) and porous silica. In another approach, these three organosilanes were combined with a boronate silane (**4d**, synthesized in-house) and a protein substrate (i.e., transferrin) and the porous silica particles. In both cases, the substrate was removed by washing and HPLC was used to characterize the affinity of the imprinted porous silica. Both the Rhodanile Blue- and



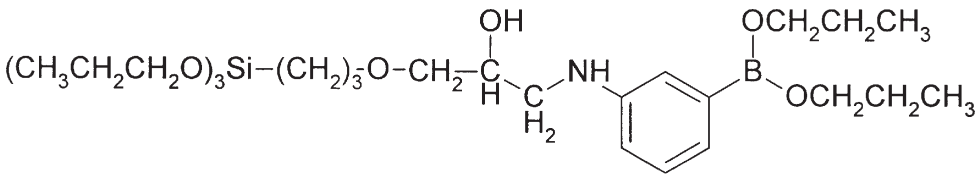
4a



4b



4c



4d

FIGURE 4. Selected examples of organosilicon precursors used in the preparation of templated materials.

Safranine O-imprinted polymers showed an affinity for their respective dye substrate. The transferrin imprinted polymer also showed some affinity for the substrate transferrin relative to bovine serum albumin.[113]

In more recent examples, a silica surface was "imprinted" with a tridentate metal complex, Ru[bpy-$CH=NCH_2CH_2CH_2Si(OC_2H_5)_3]_3$. to yield reactive functionalites (amino groups) with a defined geometry on the surface after removal of Ru(bpy-$CHO)_3$ via hydrolysis of the Shiff base.[114] Morihara also showed the feasibility of creating cavities on a silica gel surface that are complementary to a template molecule via formation of a Lewis acid-base coordination complex.[115] Lulka and co-workers described the feasibility of fluorescence detection in molecular imprinting-based approaches using surface imprinting. In this work, silica particles were combined with two organosilanes, *bis*(2-hydroxyethyl)-aminopropyltriethoxysilane (**4c**) and TEOS followed by addition of the fluorescent substrate, fluorescein or *N*-acetyltryptophanamide.[116]

VI. STATIONARY PHASES FOR CHROMATOGRAPHY

One promising application of sol-gel technology has been the development of stable stationary phases for liquid chromatography.[117–129] Sol-gel-derived stationary phases can be used to separate complex mixtures based on selective interactions between an analyte and the support. Silicon chemistry has been used for quite some time to prepare direct bonded stationary phases for reverse or normal phase chromatography via covalent attachment of a suitable organosilicon precursor as a monolayer(s) on a silica support.[130] The sol-gel approach to column preparation is relatively new and different than the conventional methodologies in the sense that it is a "bulk" rather than a strictly "surface" modification method. In the sol-gel approach, a fused silica capillary column is exposed to a silica sol for a specified period of time, which after removal and thermal treatment yields a high surface area porous coating on the inner walls of the support.[117–121,123–125] Specific polar and/or non-polar organic functional groups (i.e., NH_2, $-(CH_2)_7CH_3$) can be incorporated into the sol via the use of organosilicon reagents (R_{4-x}-$Si(OR')_{x,}$, x = 1–3). These functionalites become an integral part of the silicate network after film formation and are accessible to specific chromatographic interactions with analytes in the mobile phase.[117–121] The resultant columns are relatively quick and easy to prepare, have efficient separations, high mass loadability, enhanced thermal stability, and excellent hydrolytic stability at low and high pH.[117–124,124–125] Relative to conventional technology, the sol-gel approach is incredibly flexible in that it can be used to prepare a variety of columns for a number of different chromatographic techniques, including gas chromatography, high-performance liquid chromatography, capillary electrochromatography, immunoaffinity chromatography, and capillary electrophoresis.[117–121,124,125] Perhaps one of the most promising features of this method is the ease with which the selectivity and the performance of the column can be tailored via changes in the ratio of the organosilicon to TEOS precursor and the choice of the organic functional group.

One of the first groups to apply sol-gel technology to the preparation of thin film chromatographic stationary phases for liquid chromatography was that of Colón and workers.[117–121] Stable stationary supports for open-tubular chromatography, capillary electrophoresis, and electrochromatography have been fabricated using sol-gel methods. Preparation of the columns involved (1) pretreatment of the fused silica capillary with strong base to expose the maximum number of silanol functionalities on the support, (2) preparation and aging of the silica-based sol, (3) and coating of the capillary by filling the column with sol followed by removal with pressurized gas.[117–121]

One of their first applications was the preparation of an organically modified silica glass coating for reverse phase open tubular liquid chromatography and electrochromatography.[117,118] The silica sol was prepared with the silicon alkoxide precursors, n-octyltriethoxysilane (C_8-TEOS) and TEOS. Plate numbers for the separation of a mixture of polyaromatic hydrocarbons varied between 200,000 to 500,000/m for the open tubular columns. Retention of the solutes as well as the electroosmotic mobility in the silica gel-coated capillaries could be changed by alterating the ratio of TEOS to C_8-TEOS in the sol.[117,118] The hydrolytic stability of these columns was evaluated by exposing the supports to acid (1% trifluoroacetic acid) or base (sodium phosphate) for 32 to 48 h.[117] The capacity factors for a sample mixture containing naphthalene and phenanthrene did not change after acid/base treatment indicative of the good stability of silica glass stationary phases. The enhanced stability of the sol-gel-derived columns relative to conventionally prepared supports can be attributed to the improved hydrolytic stability of the Si-C bonds and formation of a highly crosslinked network.

In more recent work, the reaction kinetics of the individual precursors (TEOS, C_n-TEOS, where n = 1, 2, or 8) as well as the composition of the sol used to coat the chromatographic columns were studied with^{29}Si and ^{1}H NMR.[121] The primary goal of this work was to identify the precursors present in sol at the time the column is coated in order to design better coatings with improved chromatographic characteristics. The authors found that for the conditions utilized in their work, the rate of hydrolysis for the C_8TEOS was slower than that observed for TEOS alone. However, in a mixture of 1:1 TEOS:C_8-TEOS, the rates appear to be similar. The maximum degree of condensation, which occurred after a reaction time of 7 h, correlated with maximum chromatographic retention for the text compounds: toluene, naphthalene, and biphenyl.[121] Albert and co-workers have also reported on the use of solid-state NMR spectroscopy to characterize reversed phase materials for HPLC.[122]

In another report, Colon and co-workers showed the ease at which sol-gel-derived stationary phases can be used to prepare suitable columns for capillary electrophoresis.[119] In this work, 3-aminopropyltriethoxysilane was use to fabricate ORMOSIL sols that were used to coat the inner walls of fused silica capillaries. Relative to a chemically bonded capillary, the gel-modified capillary showed exception stability after exposure to acidic and basic conditions. The net charge on this column can be changed readily via alterations in the pH of the electrolyte buffer, thus allowing both the magnitude and direction of the electro-osmotic flow to be changed and difficult separations to be performed. These columns had high separation efficiencies in the separation of basic proteins and peptides.[119]

Sol-gel technology was also used to prepare columns for open-tubular capillary electrochromatography with an on-line ion trap storage/reflection time of flight mass detector for peptide analysis.[123] The columns were prepared using a two-step procedure: (1) introduction of the sol prepared from TEOS and *n*-cotyltriethoxysilane into the column as described by Colón et al.[117–121] followed by (2) modification of the resulting silanol functionalities with 3-aminopropyltrimethoxysilane.[123] The amine-coated column enhanced the electroosmotic flow and also reduced nonspecific adsorption of the peptides on the column wall.

Malik and co-workers have utilized sol-gel methods to prepare high-resolution capillary columns for gas chromatography.[124] The capillary columns were prepared in a manner similar to that reported by Colón and co-workers,[117–121] whereby the capillary column was filled with the sol and allowed to set for a prespecified period of time before removal with inert gas. The sol in this work was a composite that consisted of a silicon alkoxide precursor (i.e., TMOS or MTMOS), a hydroxy terminated stationary phase (i.e., poly (dimethylsiloxane) or Ucon 75-H-90000), and a surface-derivatizing agent (poly(methylhydrosiloxane). The hybrid coatings in this work were distinguishably rough as evidenced from SEM images. Rough, high-surface-area coatings are important in that they increase the amount of sample that can be loaded on a column and should also help provide "an enhanced surface area for solute-stationary phase interactions".[117,124] In this work, the columns were able to separate a range of analytes with good resolution and little tailing even for amine or hydroxyl-containing compounds.[124] This composite sol (i.e., MTMOS-PDMS) has also been used to coat the distal end of a fused silica fiber for solid-phase microextraction gas chromatography (SPME-GC).[125] The sol-gel derived SPME fibers had high thermal stability (320°C) and were able to extract both polar and nonpolar analytes with equilibration times that ranged from 10 min (for naphthalene) to 60 min (*N*-methylaniline).[12]

Alternative methods for the fabrication of stationary phases for chromatographic applications have utilized either a continuous xerogel phase or powdered xerogel networks.[126] Silica xerogel columns have been prepared for HPLC. In this work, the capillary column was filled with a potassium silicate solution, heated, and then filled with a dimethyloctadecylchlorosilane solution in toluene. A continuous network chemically bound to the inner wall of the fused silica was formed. This column provided reasonable efficiencies, ca. 5000 for ethyl benozate and 13,000 for naphthalene at a flow rate of 0.5 μl/min.[126]

Similarly, immunoaffinity columns have been prepared for the enrichment and determination of 1-nitropyrene, pyrene, and related polycyclic aromatic hydrocarbons by encapsulating antibodies (IgG) within the porous silicate network.[127–129] In this study, the sol was prepared with TEOS using "standard" protocol for the immobilization of bioactive molecules.[3,4,12] After gelation and drying, the glass was ground and packed into a column. Relative to other methods for the formation of immunoaffinity columns, this method is relatively simple, inexpensive, and rapid. However, cross-reactivity and nonspecific adsorption are critical issues, although several methods have been described recently minimize nonspecific adsorption on the silicate support.[129]

VII. CONCLUSIONS

Sol gel technology can be utilized effectively to prepare molecular selective coatings, membranes, and bulk gels for use in chemical analysis. Ionic and molecular recognition in these materials can be achieved by controlling the pore size and morphology of the silicate host structure, by introducing specific functionalities such as zeolites, crown ethers, or ion-exchange sites into the dense framework, or by utilizing molecular imprinting or templating strategies. Sol-gel-derived inorganic and organic-inorganic hybrid materials can be cast on a porous alumina support or an electrode surface, for example, and utilized in gas separation applications or electroanalytical applications, respectively. Chromatographic stationary phases can be prepared via sol-gel technology and employed to separate complex mixtures based on the selective interactions between an analyte and the high surface area support. Alternatively silica gel monoliths or high surface area powders can be prepared and utilized.

While the sol-gel process is incredibly flexible, it is also inherently complex. The preparation of these materials, particularly the hybrid composites, is often empirical and seems to invoke a lot of trial and error combined with some chemical intuition. Considerable efforts are being undertaken to unravel some of the complexities associated with the nature of entrapment, degree of leaching of gel-encapsulated reagents, the preparation of hybrid composites, and the formation of homogeneous (or controlled heterogeneous) materials. A detailed examination of these materials at the molecular level via the development and application of surface analytical measurements, molecular modeling, and imaging techniques will help provide researchers with the fundamental knowledge on how to better design and fabricate new materials. Although still in its infancy, the sol-gel approach holds considerable promise for the development of materials for a diversity of different analytical applications.

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