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Thermolytic Synthesis of Imprinted Amines in Bulk Silica

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The synthesis of bulk, hydrophilic imprinted silica is reported via a novel method relying on the thermolysis of carbamates. This method is used to synthesize single-site materials consisting of either isolated primary amines or multiple organized primary amines within an imprinted site. Materials are characterized by multinuclear solid-state NMR spectroscopy, high-resolution thermogravimetric analysis, and potentiometric titration. Diffuse-reflectance UV/Vis and solid-state fluorescence spectroscopies of probe molecule-bound materials are used to demonstrate the site-isolated and polar nature of the imprinted sites resulting from this process. The polar nature is due to hydrophilic silanol groups ingenerate to the framework of the material. These permit the partitioning of polar reagents, such as 1,3,5-trinitrobenzenesulfonic acid (TNBS), which are unable to access the imprinted sites when framework silanols are end-capped with hydrophobic trimethylsilyl functionality. The latter observation provides a mechanism to elucidate diminished reactivity of TNBS with lysine residues that are buried within the hydrophobic pocket of a protein.

Introduction

There has been much interest in using imprinting to synthesize selective single-site molecular receptors for specific adsorption and catalysis.[1,2] Recent advances in the imprinting of bulk silica have successfully synthesized microporosity and chemical functional group organization at the imprinted site.[2,3] However, progress has been constrained to date by both the limits of wet chemical modification as well as the framework hydrophobicity required for processing bulk imprinted silica with trimethylsilyliodide (TMSI). We report the synthesis of bulk imprinted silica with a hydrophilic material framework via the use of mild heat at temperatures below 240 °C to achieve thermolytic imprint deprotection. Our approach involves using imprints such as **1**, **2**, and **3** consisting of primary amines that are protected as thermally labile carbamates derived from tertiary alcohols and an isocyanate. Thermolysis of carbamates has been used routinely for synthesizing amines in high yield and under relatively mild conditions.[4] The technique has also seen application in the design of reactive polymers for lithography[5−8] and the synthesis of inorganic-oxide materials,[9,10] but it has not been used previously for the synthesis of imprinted materials. Other approaches to imprinting silica have used combustion of immobilized imprint to generate porosity, but this negates the possibility of organizing organic functionality.[11−13] Hydrolysis of isocyanates resulting from thermally reversible bonds has recently been reported for the synthesis of primary amines on silica particles.[14] Our approach is advantageous because the imprinted amine is synthesized within bulk silica in a single step, does not require treatment with wet-chemical reagents, and does not require high temperatures that can compromise the integrity of organic tethers.

Materials are synthesized via sol−gel copolymerization of the imprint organosilane with a silica source such as tetraethyl orthosilicate (TEOS). The resulting optically transparent glass is ground and then heated, releasing carbon dioxide and an olefin to yield imprinted amines. The imprinting process is schematically illustrated in Figure 1. The carbamate protecting group provides both a nascent primary amine and spatial organization constraints for the ensuing binding site. Imprint **1** demonstrates the feasibility of this approach with a *tert*-butyl carbamate (*t*-BOC) protecting group, which is a commonly used protecting group in synthetic chemistry. Imprint **2** provides more steric bulk than that afforded by a *t*-BOC group, and imprint **3** demonstrates the first organization of multiple chemical functional-

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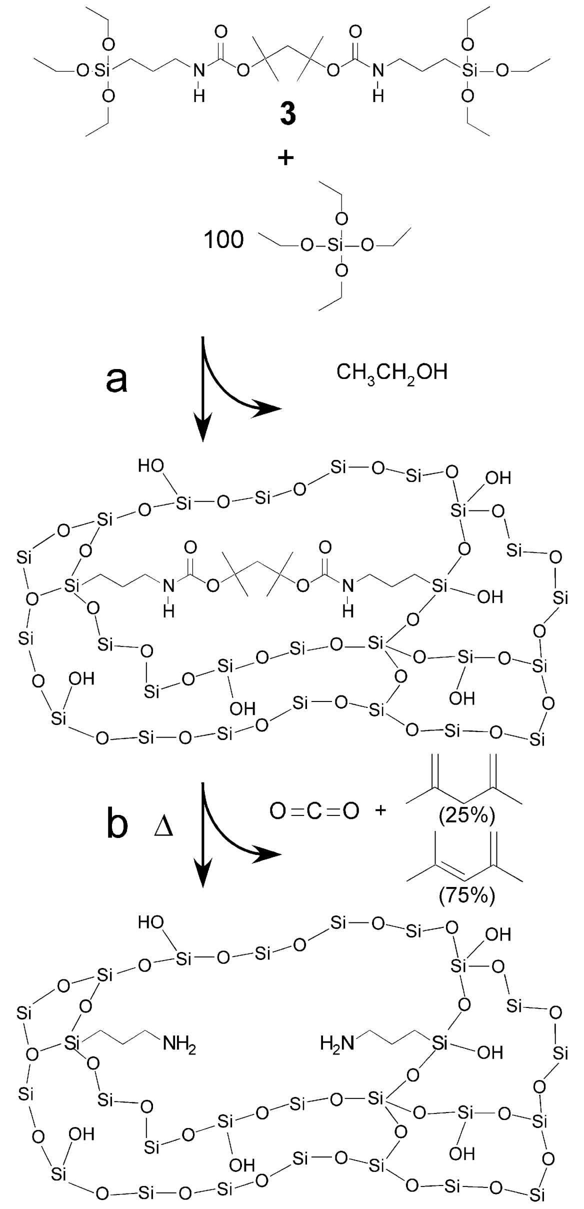
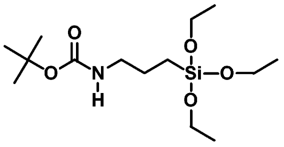


Figure 1. Synthesis of imprinted silica with a hydrophilic framework involves (a) sol−gel hydrolysis and condensation of imprint and TEOS, which forms an optically clear glass and releases ethanol; and (b) thermal treatment under an inert atmosphere at 240 °C, which generates the primary amine-containing imprinted site and liberates carbon dioxide and olefin.

ities via thermolysis, resulting in two primary amines per imprinted site.



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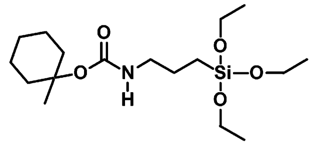

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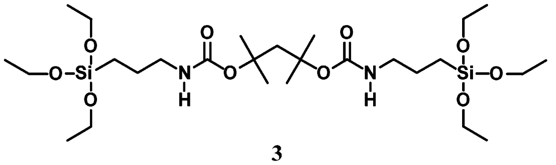

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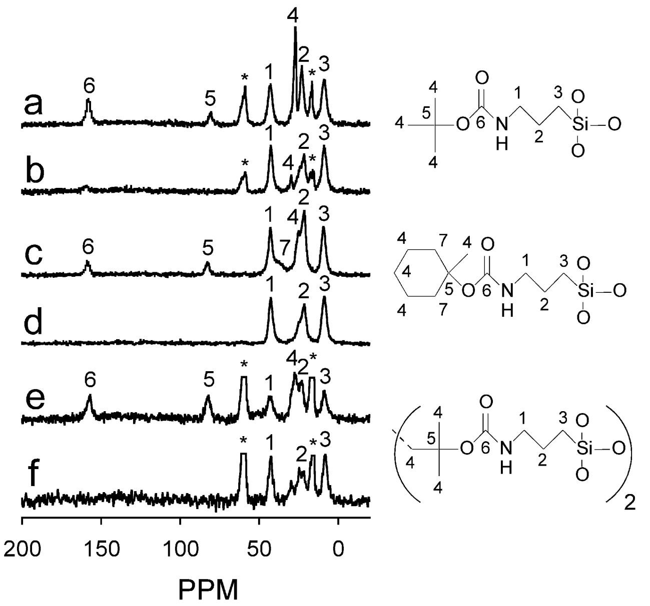

Figure 2. Typical solid-state ^{13}C CP/MAS NMR spectra of imprinted materials. Asterisks denote resonances corresponding to a small amount of ethoxy functionality. A mesoporous material synthesized with imprint **1** (a) before and (b) after thermolysis, a microporous material synthesized with imprint **2** (c) before and (d) after thermolysis, and a mesoporous material synthesized with imprint **3** (e) before and (f) after thermolysis. A 7-mm probe was used with a cross polarization contact time of 1 ms.

Results and Discussion

The material synthesis conditions are chosen to control the framework porosity of the silica, whereas active site characteristics are controlled independently through the selection of the imprint. Site isolation of the imprinted sites is achieved by combining a large excess of TEOS with the imprint so as to minimize the condensation of multiple imprint species to each other. After a brief acid-catalyzed sol−gel hydrolysis in ethanol−water mixture, condensation and gelation can be conducted under basic conditions to produce mesoporosity for facile mass transport.[15−17] These conditions are chosen on the basis of our previously reported two-step acid−base sol−gel hydrolysis and condensation procedure for synthesizing bulk imprinted silica.[3] Alternatively, hydrolysis and condensation can be conducted solely under acid-catalyzed conditions to yield a microporous material with immobilized imprint, as reported previously for the synthesis of bulk imprinted silica.[2] The ability to control the size of the framework porosity independently from the imprinted site characteristics affords greater flexibility in tailoring the final material.

Typical ^{13}C CP/MAS NMR spectra of imprinted materials are shown in Figure 2 for imprints **1**−**3**. These spectra demonstrate that the carbamate remains intact immediately following materials synthesis, as shown by the tertiary carbon resonances at 82 ppm (labeled 5 in Figure 2), carbonyl resonances at 158 ppm (labeled 6

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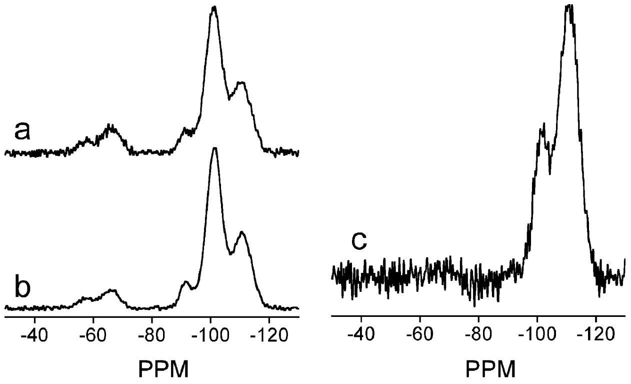


Figure 3. Solid-state ^{29}Si NMR spectra of a mesoporous material imprinted with **1**. A comparison of CP/MAS spectra of the material (a) after and (b) prior to deprotection showing that the T^3 region of the spectrum centered at −66 ppm remains unchanged under the mild heating required for thermolysis. (c) Bloch decay spectrum shows a Q^4/Q^3 ratio of 2.5:1 indicating that 72% of the silica is fully condensed. CP/MAS NMR spectra were collected using a cross polarization contact time of 2 ms. The Bloch decay spectrum was collected with a repetition delay of 300 s.

in Figure 2), and propyl tether resonances at 43, 22, and 9 ppm (labeled 1, 2, and 3 in Figure 2). The latter two groups of resonances are consistent with assignments reported previously for bulk imprinted silica relying on benzyl carbamates.[2]

The rigidity of imprinted materials is determined in large part by the degree of condensation and is important in the retention of imprinted information. Illustrative ^{29}Si CP/MAS and ^{29}Si MAS NMR spectra of bulk imprinted silicas are shown in Figure 3 for a mesoporous material imprinted with **1**. The strong T^3 resonance at approximately −66 ppm in the cross polarization experiment shows that the imprint is highly condensed in the framework of the material as observed previously in the imprinting of bulk silica.[2] The ^{29}Si MAS NMR Bloch decay spectrum allows for quantitative determination of the degree of condensation within the bulk of the imprinted materials. A Q^4:Q^3 ratio of 2.5 for this material indicates that 72% of the silica is fully condensed. There are very few observable Q^2 species, indicating a framework polymer network that is almost completely cross-linked. Similar silicon solid-state NMR spectra are obtained using imprints **2** and **3**, as well as imprinted materials with microporous frameworks.

Thermolysis under inert atmosphere produces primary amines directly from the immobilized imprint via carbamate deprotection while preserving the covalently bound propyl tether. This is reflected in the ^{13}C CP/MAS NMR spectra, Figure 2, by a disappearance of resonances associated with the carbamate protecting group while the resonances of the propyl tether are retained. The ^{29}Si CP/MAS NMR spectra in Figure 3 show qualitatively that the relatively mild conditions required for carbamate deprotection do not change the connectivity of the silica during thermolysis.

Thermolysis can be followed by high-resolution thermogravimetric analysis and mass spectrometry as shown in Figure 4, in which a material imprinted with **1** is heated at a programmed ramp rate of 1 °C/min. The rate of thermolysis is seen, via mass spectroscopy, in a mass loss accompanied by the appearance of the allyl fragment of isobutene. Thermolysis at this heating rate becomes significant at approximately 100 °C, reaches a maximum at 185 °C, and subsides sharply above 240 °C. This temperature range is consistent with that employed in homogeneous thermolysis of the *t*-BOC protecting group.[4] The olefin thermolysis products for imprints **2** and **3** can be isolated using a liquid nitrogen trap and detected via ^1H NMR spectroscopy. This experiment shows that 1-methylcyclohexene is released upon thermolysis of the carbamate in immobilized imprint **2**, whereas thermolysis of immobilized imprint **3** yields a mixture of the preferred olefin product 2,4-dimethyl-1,3-pentadiene, and a secondary product. 2,4-dimethyl-1,4-pentadiene, in a molar ratio of 3:1, respectively. Weight loss from thermogravimetry provides only an upper-bound on the amount of thermolyzed imprint, due to competing weight loss from dehydration of the silica surface.

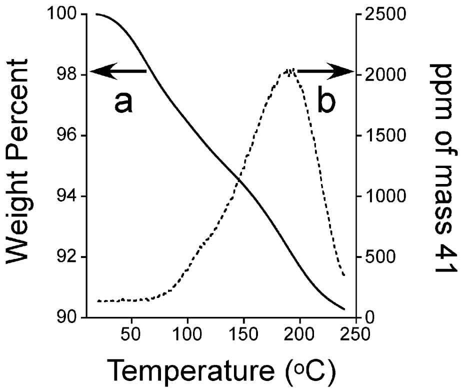


Figure 4. (a) High-resolution thermogravametric analysis of the thermolysis of a mesoporous material imprinted with **1**, and (b) the corresponding mass spectrum showing the evolution of the 41 amu allyl fragment corresponding to isobutene.

Quantification of the number of primary amines synthesized via thermolysis was achieved using nonaqueous potentiometric titration with perchloric acid in acetic acid solvent. A typical titration curve for a material prepared with **3** is shown in Figure 5 and corresponds to a number density of 0.25 mmol amines per gram, or 87% of the total possible number of amines based on the amount of imprint used. Similar amine site densities can be achieved upon thermal deprotection of imprints **1** and **2**. Importantly, titrations of mesoporous materials before thermolysis show no detectable amines present. Materials prepared with a microporous material framework, however, show a certain amount of adventitious primary amines prior to thermolysis, typically corresponding to between 25 and 50% of the total number of imprinted amines present for imprints **1**−**3**. These primary amines are created after gelatin while drying the microporous materials. Thus, materials prepared with a mesoporous framework appear to show preference for exhibiting no imprint carbamate deprotection prior to thermolysis.

An important advantage of using thermolysis over chemical methods of deprotection is the ease of deprotecting multiple functional groups within an imprinted site, as in the case of imprint **3**. When using nonthermolytic methods of deprotection (i.e., TMSI), it becomes significantly more difficult to deprotect imprints with multiple points of attachment to the silica framework. For instance, immobilized imprints consisting of dicarbamates can undergo almost no deprotection using the

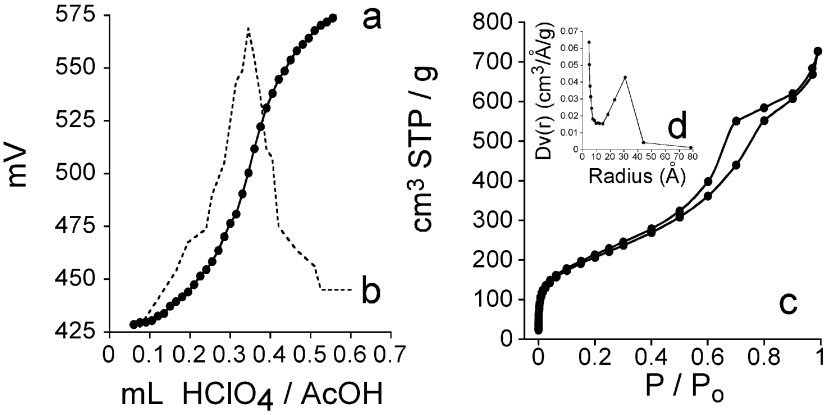


Figure 5. (a) Nonaqueous potentiometric titration of a mesoporous material imprinted with **3**. (b) Derivative of the potential with respect to acid volume added demonstrates the location of the equivalence point. (c) Physical adsorption/desorption isotherms of nitrogen at 77 K using a mesoporous material imprinted with **3**. (d) The corresponding BJH pore-size distribution based on the desorption branch of the isotherm in (c).

same reaction conditions that are used to successfully deprotect immobilized monocarbamates.[18] Using thermolysis, however, there is no increased difficulty in creating multiple functional groups from one imprint. Data in Figure 2 and titration experiments show almost complete thermolysis for both monocarbamate, **1**, and the dicarbamate, **3**. Thermolytic deprotection is a unimolecular reaction event that does not require the entropically unfavorable simultaneous collision of several chemical reagents within the time scale of a deprotection event.

Nitrogen porosimetry can be used to measure the pore structure of the imprinted solids. The adsorption/desorption isotherm and corresponding Barrett–Joyner–Halenda (BJH) pore size distribution are shown in Figure 5 for a mesoporous material imprinted with **3**. This material possesses a bimodal pore-size distribution typical of imprinted mesoporous materials[3], consisting of micropores with a radius less than 10 Å and mesopores with a mean radius of 32 Å. This material has a Brunauer–Emmett–Teller (BET) surface area of 740 m^2/g.

Nonaqueous potentiometric titration of imprinted amines can be corroborated with covalent binding of the probe molecule salicylaldehyde, which reacts with imprinted primary amines to form imines in quantitative yield with no measurable background binding to the silica framework. The resulting hydrogen bond stabilized imine is a strong chromophore and can be used as a sensitive probe for characterization of the environment in the immediate vicinity surrounding the imprinted amines. The diffuse-reflectance UV/Vis spectra in Figure 6 corroborate the titration data discussed above by showing that few primary amine sites exist in a mesoporous material prior to thermolysis. The spectrum of the thermolyzed material in Figure 6a shows a strong band at 392 nm similar to other reported products resulting from the condensation of salicylaldehyde with a primary amine in polar protic solvents such as ethanol (392 nm band reported).[19] Previous investigations of imines in silicates have suggested that this band is due to a zwitterionic species, **4**, in which the imine is protonated.[20] This is consistent with assignments made in homogeneous solution using polar solvents,[21] and assignments made in the microporous pockets of zeolites X, Y, and ZSM-5.[21–23] The relatively large wavelength of this band compared to those reported for the phenol tautomer (typically around 314 nm) suggests that the imprinted amines resulting from thermolysis are located within a hydrophilic, polar local environment.

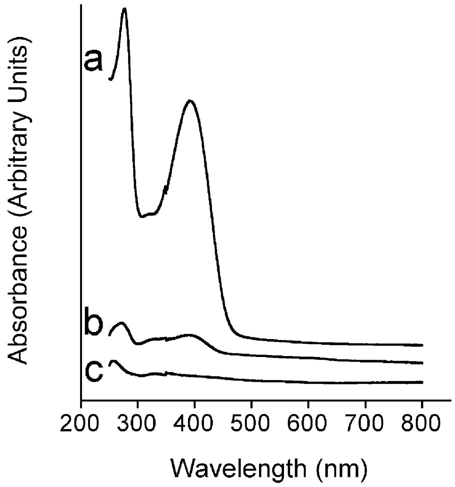
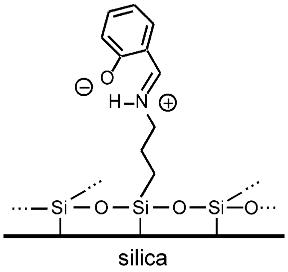


Figure 6. Diffuse-reflectance UV/Vis spectra of mesoporous materials imprinted with **2** after treatment with salicylaldehyde. These spectra demonstrate (a) presence of a band at 392 nm in a thermolyzed material; and absence of this band (b) in a material prior to carbamate deprotection, and (c) in a material prior to carbamate deprotection that was not treated with salicylaldehyde.



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To investigate the degree of site isolation in the imprinted materials, we relied on the fluorescence

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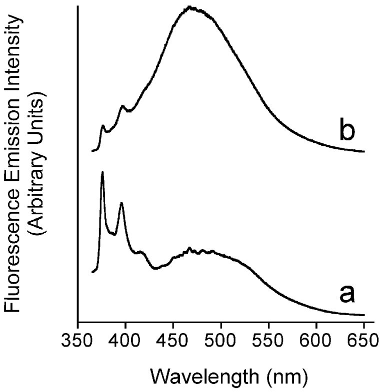
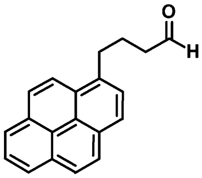


Figure 7. Fluorescence emission spectra of a mesoporous material synthesized with two mol % of imprint **2** relative to TEOS (−) and surface-functionalized silica consisting of a monolayer of aminopropyl functional groups on the interior surface of mesoporous silica (-----) upon covalent binding of 4-pyrenebutyraldehyde at the same loading of 0.15 mmol/g.

emission characteristics of the probe molecule, **5**, which can covalently bind to the imprinted primary amines via imine linkage and is expected to be sensitive to the local density of immobilized amines.



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Fluorophore **5** was synthesized via a Swern oxidation of 1-pyrenebutanol with oxalyl chloride and dimethyl sulfoxide.[24,25] It was contacted with a hydrophilic mesoporous silica imprinted with **2** and a surface-functionalized control silica comprising a monolayer of amines on the interior surface of mesoporous silica. The amount of covalently attached **5** in both materials was determined (via UV/Vis spectrophotometry) to be 0.15 mmol/g, which corresponds to loadings of 68% and 12% of the sites for the imprinted and surface-functionalized materials, respectively. The fluorescence emission spectra of these pyrene-bound materials are shown in Figure 7. The imprinted material reveals mainly emission from monomer, whereas the surface-functionalized material shows primarily excimer emission under the same loading of **5** per gram of material. These data indicate a high degree of site isolation in imprinted silicates that cannot be achieved by silica surface modification with aminosilanes. The difference between surface-functionalized and imprinted material in Figure 7 is all the more significant considering the higher fractional loading of sites with **5** in the imprinted material. The pyrene emission characteristics shown in Figure 7 are performed at much higher surface coverages as compared with previous studies in imprinted materials.[2] Although they indicate that some imprinted sites in the mesoporous materials may be paired on the length scale of the pyrene probe, this length scale appoaches the linear distance for the separation of amines based on the bulk site density of the solid (ca 19 Å). Therefore, it is not clear whether the small amount of excimer formation observed for the imprinted material in Figure 7 is due to excimer formation between closely adjacent sites (intersite excimer) or to the presence of a small amount of imprint molecules condensed to one another (intrasite excimer). However, considering the conditions employed in material syntheses, the latter scenario is unlikely.

To demonstrate the hydrophilic environment of the silica framework surrounding the imprinted amines, a study of the binding of 1,3,5-trinitrobenzenesulfonic acid (TNBS) was conducted. This polar compound is commonly used as a probe molecule for assaying primary amine (lysine) residues in proteins. A hydrophobic control imprinted material was synthesized using **1** for comparison. This was accomplished using TMSI to deprotect the carbamate, as described previously,[2,3] instead of thermolysis. The two procedures are illustrated in Figure 8. Because they are derived from the same starting material, the resulting two imprinted materials have similar imprinted sites and framework porosities, as well as site densities, but they do vary in their degree of framework hydrophobicity. The arylation of imprinted amines with TNBS can be characterized qualitatively with diffuse reflectance UV/Vis spectroscopy, and these results are shown in Figure 9. The spectrum for the thermolyzed material shows pronounced bands between 340 and 410 nm, indicative of TNBS binding, whereas the equivalent hydrophobic material shows virtually no binding of TNBS. These results demonstrate that reagents previously inaccessible to imprinted amines in bulk silica are able to partition into the hydrophilic framework of the new imprinted silicates synthesized via thermolysis. This observation may also have interesting repercussions on quantitative assays of lysine residues in proteins, as TNBS has been used routinely for this purpose.[26−29] Studies of the binding of TNBS to proteins indicate that the binding of hydrophobic small molecules in the vicinity of lysines can protect them from reaction with TNBS.[30−32] In our silica materials we observe protection afforded by the hydrophobic silica framework consisting of trimethylsilyl groups. The results above demonstrate that a primary amine-containing residue can be inaccessible to TNBS if it is buried in a hydrophobic pocket.

We have begun to investigate the catalytic applications of this new class of bulk imprinted silicas. The hydrophilic framework in these materials offers interesting potential to offer stabilization of polar reactive intermediates and transition states at the active site. These results will be reported in due course.

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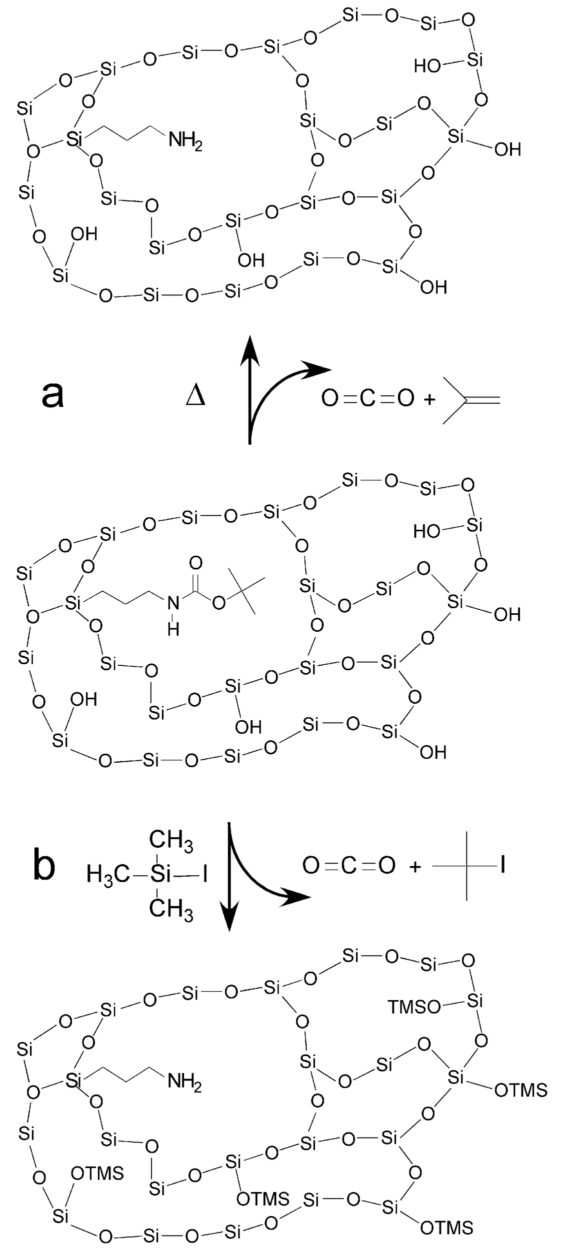

Figure 8. Two independent routes for carbamate deprotection comprising: (a) thermal treatment resulting in a material that retains bulk silanol groups and (b) deprotection using TMSI resulting in a material where the silanol groups are replaced with trimethylsilyl functionality. The two materials differ only in their degree of framework hydrophobicity.

Experimental Section

General. ^{1}H and ^{13}C NMR spectroscopy were performed on Bruker AMX 300 and 400 MHz machines at the University of California at Berkeley (UCB). FAB mass spectra were recorded at the UCB Mass Spectrometry Facility. Solid-state NMR spectroscopy was peformed at the Caltech Solid-State NMR Facility using a Bruker DSX 200 operating at 200 MHz and a spin rate of 4.0 kHz. UV/Vis spectroscopy was performed on a Varian Cary 400 Bio UV/Vis spectrophotometer equipped with a Harric Praying Mantis accessory for diffuse reflectance measurements on solids at room temperature. Nonaqueous potentiometric titrations were performed using a Brinkmann/Metrohm 765 Dosimat with an Accumet AR15 pH meter and a Corning High Performance glass combination electrode with a Silver Scavenger reference. Gas chromatography was performed on an Agilent 6890 GC system equipped with an FID detector. High-resolution thermogravimetric analysis was performed on a TA Instruments TGA 2950 system connected to an Inficon 074 Transpector with a quadrupole mass filter. Nitrogen physisorption was performed on a Quantachrome Autosorb-1 using samples that had been degassed for at least 20 h at room temperature. Fluorescence measurements were performed on a Hitachi F-4500 spectrophotometer equipped with a solids accessory.

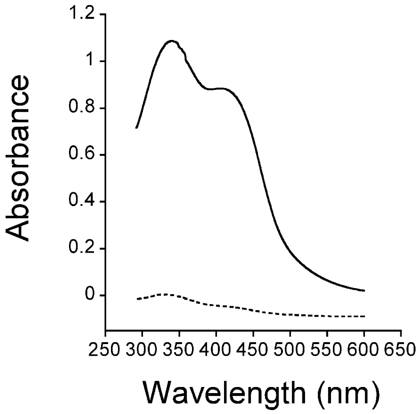

Figure 9. Arylation of imprinted amines with the probe molecule TNBS as followed by solid-state UV/Vis spectrophotometry. The material deprotected via thermolysis (—) shows bands at 340 and 410 nm resulting from the formation of the bound chromophore, whereas the material deprotected via TMSI shows virtually no absorbance in the same wavelength region (-----). Both materials are derived from the same microporous material imprinted with **1**.

Ether (EM Science) was dried by distillation over sodium/benzophenone. Water was distilled, purified with a Barnstead Nanopure Infinity system to at least 18 MΩ purity, and passed through a 0.2 $-\mu$m filter. 3-(Triethoxysilylpropyl)-*tert*-butylcarbamate was purchased from Gelest. The surface-functionalized control material, 3-aminopropyl functionalized silica gel, was purchased from Aldrich and used as received. All other reagents, unless otherwise reported, were purchased from Aldrich and were used as received.

(3-Triethoxysilylpropyl)-carbamic Acid 1-Methyl-cyclohexyl Ester (2). To a solution of 1-methylcyclohexanol (5.06 mL, 40.44 mmol) in ether (140 mL) at room temperature under N_2 was added methyllithium (1.4 M in ether, 1.64 mL, 2.3 mmol) dropwise. After 1 h, the mixture was cooled to −40 °C in an acetonitrile/CO_2 bath, and 3-(triethoxysilyl)propyl isocyanate (8.3 mL, 35.17 mmol) was added. After 2.5 h, the solution was allowed to warm to room temperature. The mixture was concentrated to an oil and purified by silica chromatography (Silica Gel 60 and 6.0:1.0 v/v hexanes/ethyl acetate) to yield a clear oil (7.31 g, 20.2 mmol, yield 58%). ^{1}H NMR ($CDCl_3$): 0.614 (2H, t, $J = 8.0$ Hz, CH_2); 1.209 (9H, t, $J = 6.8$ Hz, $Si(OCH_2CH_3)_3$); 1.36−1.55 (8H, m, CH_2); 1.45 (3H, s, CH_3); 1.589 (2H, m, CH_2); 2.08 (2H, m, CH_2); 3.108 (2H, q, $J = 6.4$ Hz, CH_2); 3.803 (6H, t, $J = 6.8$ Hz, $Si(OCH_2CH_3)_3$); 4.768 (1H, m, N*H*). ^{13}C NMR ($CDCl_3$): 7.61 (CH_2); 18.24 (CH_3); 22.14 (CH_2); 23.33 (CH_2); 25.46 (CH_3); 25.85 (CH_2); 36.97 (CH_2); 43.00 (CH_2); 58.38 (CH_2); 80.13 (*C*); 155.87 ($C{=}O$). Mass spectrum (FAB ^{1}H): *m/z* 362.237115 ($^1HC_{17}H_{35}NO_5Si$, 362.236277).

(3-Triethoxysilylpropyl)-carbamic Acid 1,1,3-Trimethyl-3-(3-triethoxysilylpropylcarbamolyloxy)-butyl Ester (3). To a solution of 2,4-dimethylpentane-2,4-diol (1.5 mL, 10.5 mmol) in ether (80 mL) at room temperature under N_2 was added methyllithium (1.4 M in ether, 0.5 mL, 0.7 mmol). After approximately 1 h the mixture was cooled to −77 °C, and 3-(triethoxysilyl)propyl isocyanate (8.3 mL, 35.17 mmol) was added dropwise. The solution was allowed to warm to −40 °C in an acetonitrile/CO_2 bath. After approximately 8 h, the solution was slowly warmed to room temperature, with stirring, overnight. The mixture was concentrated to an oil and purified by silica chromatography (Silica Gel 60 and 8.0:1.0

v/v hexanes/ethyl acetate) to yield a clear oil (1.33 g, 2.12 mmol, yield 20%). ^{1}H NMR ($CDCl_3$): 0.608 (4H, t, $J = 8.1$ Hz, $\mathrm{C}H_2$); 1.219 (18H, t, $J = 6.9$ Hz, $\mathrm{Si(OCH_2C}H_3)_3$); 1.467 (12H, s, $\mathrm{C}H_3$); 1.585 (4H, m, $\mathrm{C}H_2$); 2.461 (2H, s, $\mathrm{C}H_2$); 3.109 (4H, q, $J = 6.6$ Hz, $\mathrm{C}H_2$); 3.811 (12H, t, $J = 6.9$ Hz, $\mathrm{Si(OC}H_2\mathrm{CH_3)_3}$); 4.723 (2H, m, $\mathrm{N}H$). ^{13}C{^{1}H} NMR ($CDCl_3$): 7.57 ($C\mathrm{H_2}$); 18.26 ($C\mathrm{H_3}$); 23.34 ($C\mathrm{H_2}$); 27.91 ($C\mathrm{H_3}$); 42.97 ($C\mathrm{H_2}$); 46.96 ($C\mathrm{H_2}$); 58.40 ($C\mathrm{H_2}$); 81.14 (C); 155.73 (C=O). Mass spectrum (FAB ^{7}Li): m/z 633.379430 ($^7\mathrm{LiC_{27}H_{58}N_2O_{10}Si_2}$, 633.379008).

Silica Synthesis. Microporous imprinted silica was prepared according to procedures reported previously.[2] Mesoporous imprinted materials were prepared via the following procedure. In a typical synthesis, a mixture of tetraethyl orthosilicate (30 mL, 134.4 mmol), (3-triethoxysilylpropyl)-*tert*-butylcarbamate (0.87 g, 2.7 mmol), and absolute ethanol (94.5 mL) was brought to reflux in a 250-mL round-bottom two-necked flask equipped with a condenser. The solution was brought to reflux and the following aliquots were added at 1-h intervals: 0.6 mL of pH 2.0 *p*-toluenesulfonic acid in water, 0.6 mL of pH 2.0 *p*-toluenesulfonic acid in water, 4.73 mL of water, and 4.73 mL of water. The solution was refluxed for 1 h after the last water addition, and then added hot to a 16-oz jar containing 5.32 mL of a pH 12.4 solution of aqueous ammonium hydroxide. Upon subsequent gelation, the clear solid was placed in a 40 °C oven and allowed to dry for 10 days. The resulting silica monoliths were ground into particles with diameter less than 10 μm using a planetary mill and repetitive wet-sieving in absolute ethanol. The material was then dried in air overnight and stored in a desiccator.

High-Resolution Thermogravimetric Analysis (Imprint Deprotection). Analysis was performed using samples (from 10 to 300 mg) in a N_2 environment (30 mL/min) and an alumina or Pt pan. For imprint deprotection, samples were first purged of O_2 over a 10-h period at room temperature before temperature-programmed heating at a rate of 1 °C /min to a final temperature of 240 °C.

Potentiometric Titration. In a typical procedure,[33] 15−150 mg of silica was suspended in glacial acetic acid (approximately 40 mL) until the voltage stabilized. The mixture was titrated with a 0.1 N solution of perchloric acid in glacial acetic acid using 5−20-μL doses every 300−720 s.

Fluorescence Investigation Procedures. To a solution of 4-pyrenebutyraldehyde in methanol was added a sufficient amount of silica material as to achieve binding of 0.15 mmol aldehyde/g material. Thus, 3 mL of a 3 mM aldehyde solution was mixed with 50 mg of surface-functionalized material (0.065 mmol amine, 0.14 equiv), and, separately, 1.7 mL of a 12.7 mM solution was mixed with 50 mg of imprinted silica (0.011 mmol amine, 2 equiv). The solutions were stirred for 18 h at room temperature, and uptake was monitored by UV/Vis spectrophotometry at $\lambda = 342$ nm ($\epsilon = 42{,}200\ \mathrm{M^{-1}}$). Materials were then filtered, washed with a combination of acetonitrile (60 mL), chloroform (30 mL), and pentane (60 mL), and Soxhlet extracted in chloroform for 16 h. Measurements used a 700-V excitation voltage, a 15-nm/min scan rate, 2.5-nm excitation/emission slit widths, and a 340-nm excitation wavelength.

Salicylaldehyde Binding. For solid-state UV/Vis experiments, a solution of salicyladehyde (2.65 mL, 0.005 M, 2 equiv) in acetonitrile was added to 30 mg of imprinted silica under constant stirring at room temperature. After at least 2.5 h, the materials were filtered, washed with a combination of 100 mL of acetonitrile, 100 mL of chloroform, and 50 mL of pentane, and subsequently Soxhlet extracted in chloroform for 16 h. Samples prepared for quantitative binding experiments used 1,3,5-trimethoxybenzene as an internal standard, with binding monitored via GC using syringe-filtered samples.

TNBS Binding. Imprinted Material (300 mg) was treated with a 1.0 wt % solution of TNBS in DMF (8 mL, 0.260 mmol) at room temperature and stirred for 20 h. The silica was filtered, washed with DMF (20 mL) and chloroform (30 mL), Soxhlet extracted in chloroform for 24 h, and dried under vacuum overnight.

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