Synthesis and Surface Chemistry of Spherical Mesoporous Organic−Inorganic Hybrid Particles with an Integrated Alcohol Functionality on the Pore Surface

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Novel mesoporous organic−inorganic spherical hybrid particles are described that contain a 3-hydroxypropyl organic functionality which is integral to the pore surface. The 3-hydroxypropyl hybrid particle is synthesized in three steps starting from a 4:1 (mol/mol) mixture of tetraethoxysilane and [3-(methacryloxy)propyl]trimethoxysilane, where the monomers are polymerized to a poly(organoalkoxysilane) oil, followed by sol−gel reaction to the hybrid silicate bead, which is finally subjected to an alkaline hydrothermal treatment to liberate the alcohol from the ester protecting group. The silicate precursor and final product were characterized by NMR spectroscopy and nitrogen sorption analysis. The heterogeneous surface chemistry of the hybrid's alcohol functionality was explored by running a series of classical alcohol reactions including bromination, esterification (carbamic and carbonic), and etherification (Williamson, epoxide ring opening). The brominated analogue was further converted via cyanation and Grignard couplings. Nuances to the heterogeneous surface chemistry are discussed as well as product characterizations by NMR spectroscopy and combustion analysis. A stability study was further conducted on the 3-hydroxypropyl hybrid silicate using an alkaline resistance test under HPLC packed column conditions. The hybrid material was found to be over 10-fold more stable than a comparable silica gel material. In a second HPLC test, the cyano derivatized hybrid material was found to be more resistant to acid-induced siloxane cleavage vs a comparable (3-cyanopropyl)silane grafted silica gel.

Introduction

Porous organic−inorganic hybrid silicates have been the subject of intense research activity in the past decade. The driving forces behind these activities are these materials' novel properties, which are not accessible by traditional macroscale composites or conventional inorganic and organic materials. Specifically, the integration of organic groups into an inorganic network leads to many new hybrid materials with unique physical and chemical properties. For example, materials with electron acceptor abilities can be achieved by incorporating 4,4′-bipyrindinium units into an MCM-41 type periodic mesoporous organosilica (PMO).[1] Often, organic moieties are introduced into the silica network through organosilane precursors in a one-pot reaction. Hydrolytic co-condensations among organosilanes or between organosilanes and tetraalkoxysilanes have lead to many hybrid materials with homogeneous combinations of inorganic and organic moieties in a single, integrated structure. Examples of hybrid products created by this method include hybrid silicates with embedded organic groups such as methyl,[2] ethyl,[3] and bridging organics.[4] Bridging organic hybrids can have unique features in their own right. For example, a hybrid material made from a benzene-bridged organosilane monomer $(H_5C_2O)_3SiC_6H_4Si(OC_2H_5)_3$ was recently found to consist of crystal-like pore walls associated with ordered mesoporous channels.[5] For this example and many other applications, further surface modification is required to introduce specific binding sites or functionality to the pore surface. Unfortunately, many desirable modifications are impeded by the limited reactivity of the hybrid's organic moiety, a limited choice of organic silanes, and/or the often poor chemical stability of the surface grafted siloxane ligands. Functional groups introduced via silane grafting include alkylamines,[6] epoxides,[7] alkyl halides,[8] and alkylthiols.[9]

In an effort to overcome the above limitations, hybrid materials have recently been prepared in the one-pot reaction through the co-condensation of a tetraalkoxysilane and one or more organosilane precursors with organo-reactive groups. These organo-reactive groups

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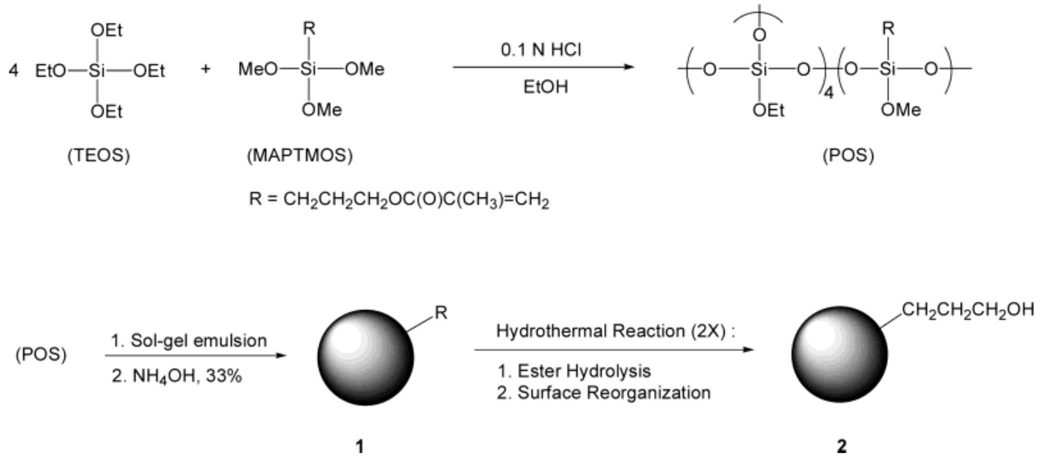
Scheme 1. Overview of Hybrid Silicate Particle Synthesis



are significantly more amenable and versatile toward further modification. Stein and co-workers prepared a vinyl-functionalized MCM-41 by co-condensation of vinyltriethoxysilane and TEOS.[10] They found that the vinyl groups appeared to be more uniformly distributed throughout the channels in comparison to vinyl groups introduced by a silylation process, where a large portion of the vinyl groups are on the external surface and near the channel openings.[11] Many other organo-reactive hybrid products have been prepared in a similar method, including thiol-,[12] phenyl-,[13] and aminopropyl[14]-functionalized porous silicates.

To our knowledge, there have been no examples of spherical, mesoporous hybrid materials with an integrated surface alcohol functionality, despite the alcohol group being one of the most studied and versatile functionalities known in synthetic chemistry. Herein, we report the synthesis and characterization of novel 3-hydroxypropyl-functionalized amorphous hybrid particles obtained through the co-condensation of [3-(methacryloxy)propyl]trimethoxysilane and tetraethoxysilane.[15] Due to our particular interest in hybrid materials that are useful for HPLC, the 3-hydroxypropyl-functionalized hybrid is spherical and is purposefully designed to have low micropore surface areas and larger pore diameters, which distinguishes it from most previously reported hybrid materials. In addition, we will describe a number of hydroxyl group transformations as well as demonstrate significantly improved hydrolytic stability for a 3-cyanopropyl ligand prepared in two steps from the 3-hydroxypropyl hybrid in comparison to an analogous structure prepared by post surface silylation reaction.

Results and Discussion

Synthesis of Alcohol-Functionalized Hybrid Silicate Particles. The alcohol-functionalized particles were synthesized as outlined in Scheme 1. Monomers tetraethoxysilane (TEOS) and [3-(methacryloxy)propyl]trimethoxysilane (MAPTMOS) were dissolved in ethanol and then cohydrolyzed and condensed by addition of 0.1 N HCl to form poly(organoalkoxysilane) oligomers (POS). The mole ratio of TEOS:MAPTMOS was 4:1, and the degree of polymerization and hence viscosity of the POS were controlled by the amount of 0.1 N HCl added to the reaction. ^{1}H, ^{13}C, and ^{29}Si NMR spectra were indicative of a random copolymer structure, which is consistent with the work of Colon.[16]

The precursor particles (**1**) to the 3-hydroxypropyl-functionalized hybrid particles (**2**) were prepared by sol−gel emulsification chemistry. In one vessel, the POS and toluene (a porogen) were stirred at room temperature to create a homogeneous liquid. In a second vessel, a combination of two surfactants, ethanol and water, was stirred at 55 °C to create a white mixture. The two vessel's contents were then combined under high shear mixing to form oil droplets in a continuous water/ethanol phase. The size of the droplets could be controlled by the emulsification speed and the amount of surfactant. The POS oil droplets were gelled to hybrid silicate particles by adding concentrated ammonium hydroxide to the emulsion at an elevated temperature. The gelled hybrid particles **1** were washed with water and methanol and then dried. Similar to silica gels made in the same way, the final particles were amorphous yet very spherical as measured by SEM (see Supporting Information).

Characterization data are shown in Table 1 for the particles **1**. The particles were porous as measured using nitrogen sorption, with a specific surface area (SSA) of 550 m^2/g and a narrow pore size distribution with a modal pore diameter (MPD) of 3.5 nm. As shown in

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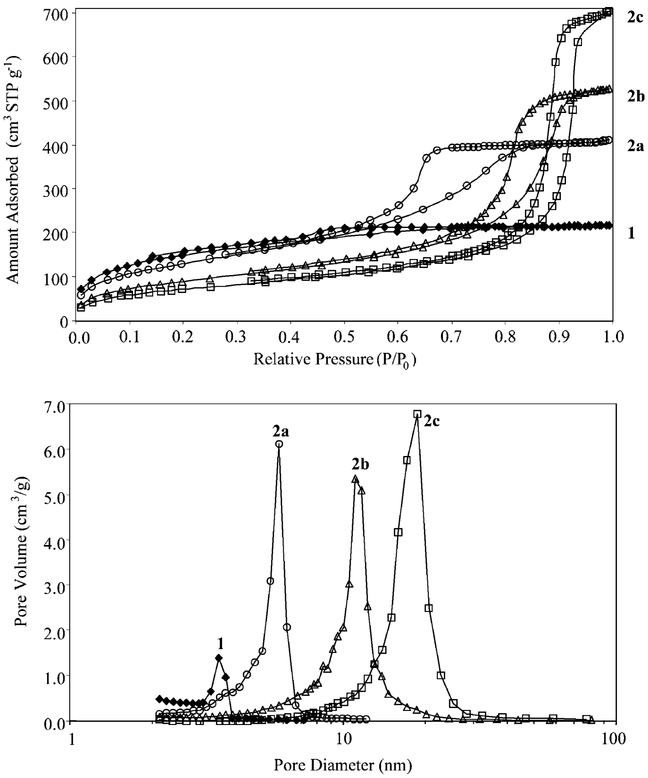

Figure 1. Nitrogen sorption isotherm (top) and differential pore volume/diameter (bottom) plots for materials **1**−**2c**.

Table 1. Characterization Data for Hybrid Organic−Inorganic Silicate Materials 1 and 2

material	Tris concn (M)	pH start	pH final	^{13}C NMR ratio alcohol/ester	SSA (m^2/g)	PV (cm^3/g)	MPD (nm)
1	NA	NA	NA	13/87	551	0.34	*3.5*
2a	0.3	10.0	8.5	67/33	483	0.64	*5.9*
2b	1.2	10.8	9.5	>99/1	335	0.82	*11.1*
2c	1.2	10.8	10.5	>99/1	267	1.09	*18.8*

Figure 1, an isotherm most closely resembling a Type I curve was observed, which is characteristic of a microporous material. At the same time, elements of mesoporosity were also observed.[17] The mesoporous size distribution of the material was found to be quite narrow, as evidenced by the differential pore volume over the pore size plot (Figure 1). Applying the arguments set forth by Boury and Corriu,[18] the observed narrow pore size distribution may be attributed to structural organization caused by the POS organic group interaction with toluene at its interface during the emulsion formation and sol−gel stages. Additionally, the 3-(methacryloxy)propyl substituent could sterically disrupt the silanol condensation process to inhibit any silicate encapsulation and thereby give a surface preferentially enriched in 3-(methacryloxy)propyl groups.

^{13}C and ^{29}Si CP-MAS NMR spectra of **1** are shown in Figure 2a,b. The ^{13}C spectrum is consistent with the methacrylate group being largely intact; however, approximately 13% of the methacrylate groups has been converted to the 3-hydroxypropyl unit, arguably due to the ammonium hydroxide-initiated hydrolysis during the gel-setting stage. Resonances at ca. 45 and 175 ppm (marked with an *x* in the figures) are assigned to a small amount of oligomeric poly(methacrylic acid) presumed to have formed by oligomerization of hydrolyzed methacrylic acid or possibly derived from a radically polymerized MAPTMOS contaminant in the starting material. The ^{29}Si spectrum indicates material **1** was fairly well condensed. The T^3 silicon sites are the major T species (~46%), followed by the T^2 sites (~11%) and virtually no T^1 sites (<0.1%). The Q^4 site was the major Q species, again followed by the Q^3 sites (~39%) and the Q^2 sites (~4%). It should be noted that the spectral contribution from lattice (Q^4) silicon environments are under-represented in the ^{29}Si CPMAS spectra due to their prohibitively long Si−H bond distances and therefore were not considered for semiquantitative comparisons.[19]

The 3-hydroxypropyl-functionalized hybrid particles (**2**) were next prepared by concurrent base-catalyzed ester hydrolysis and further hydrothermal conditioning of the silicate structure. The reaction was performed by preparing a suspension of particles in a tris(hydroxymethyl)aminomethane (TRIS) water solution and heating the mixture in a stirred bomb at elevated temperature and pressure. Methacrylic acid was generated in the hydrolysis step, resulting in an immediate pH drop at the beginning of the reaction that retarded further hydrolysis and reorganization.[20] The completion of hydrolysis could be achieved by increasing the TRIS concentration (Table 1, **2a** vs **2b**) to compensate for methacrylic acid sequestration. A larger pore diameter version of **2b** was achieved by subjecting the material to second hydrolysis (Table 1, **2b** → **2c**).

As shown in Table 1, in reacting particle **1** to form particles **2a**−**2c**, the pore volume (PV) increased, which is attributed to removal of the methacrylic acid moiety from the particle and removal of solubilized silicates. In going from **1** to **2c**, the nitrogen sorption isotherm was transformed from a Type I to a Type IV with a shift from an H2- to an H1-type hysteresis. The MPD increased from 3.5 to 18.8 nm, and the SSA decreased from 551 to 267 m^2/g, consistent with past hydrothermal treatment trends for amorphous silica.[21] Recognizing the difficulties in interpreting nitrogen isotherms and hysteresis loops as set forth by Kruk and Jaroniec,[22] these changes are consistent with reorganization of the structure where silicates dissolve more rapidly from a high radius of curvature regions (especially positive curvature) of the particle and then redeposit onto a smaller radius of curvature regions (especially negative curvature).[20] In the course of the dissolution/redeposition process, the 3-hydroxypropylsilicate may be less prone to dissolve from the surface due to its lower solubility in the TRIS solution. Dissolved inorganic silicates would be sterically encumbered from redepositing around the 3-hydroxypropyl group for the reasons discussed above for material **1**. Further evidence for enrichment of the 3-hydroxypropyl groups at the surface of the particle

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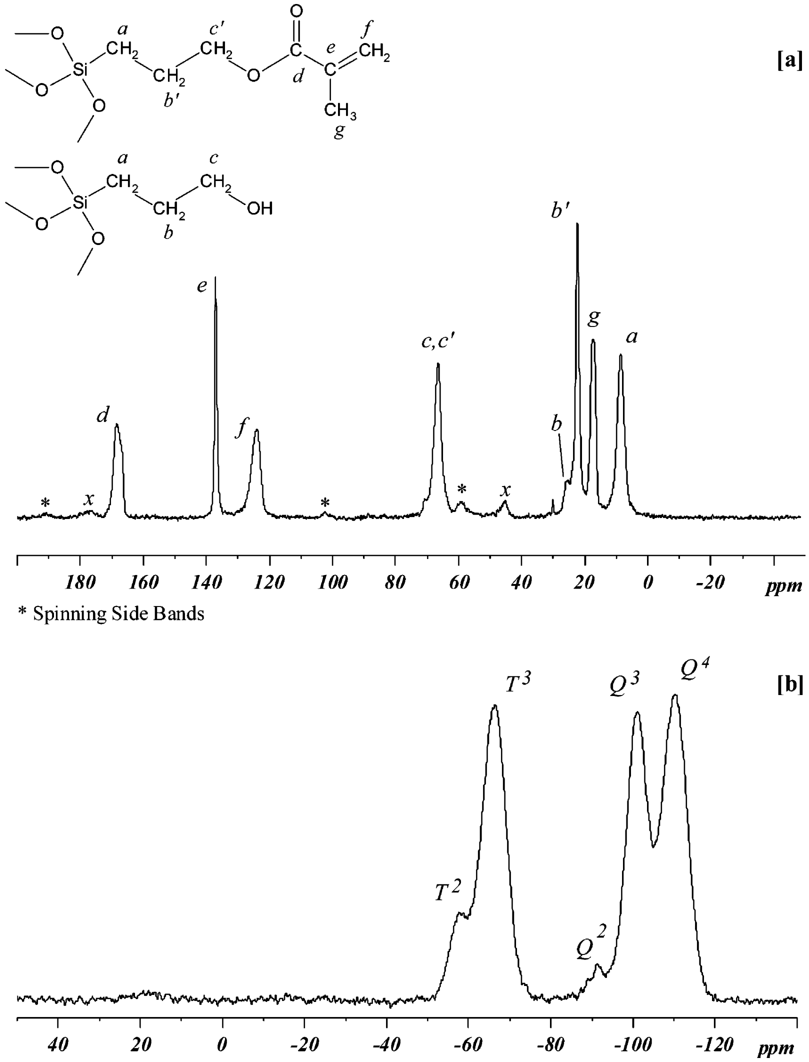


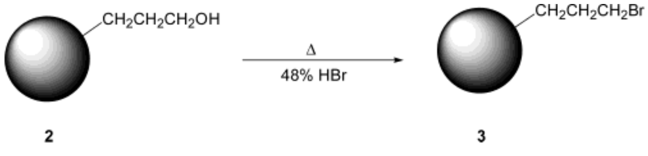
Figure 2. ^{13}C NMR (a) and ^{29}Si NMR (b) CPMAS spectra of 3-(methacryloxy)propyl hybrid silica.

are found in the surface chemistry and alkaline resistance studies below. Hydrothermal treatment left the particle's sphericity intact (see Supporting Information for SEM).

On the basis of the ^{13}C CPMAS NMR spectra, the 3-(methacryloxy)propyl ester groups were effectively hydrolyzed with the high-concentration TRIS solution (**2a** vs **2b**). The resonance assigned to poly(methacrylic acid) could not be removed by washing. With the expectation that this polymer will be exceptionally soluble in an alkaline solution, the inability to remove it suggests it is entrapped in the silicate matrix. The ^{29}Si spectra of materials **2a**−**2c** showed increased degrees of condensation with the first hydrothermal treatment (**1** → **2a**). The T silicon populations were T^3 (∼59%), T^2 (∼13%), and T^1 (<0.1%), and the Q populations were Q^3 (∼27%) and the Q^2 sites (∼1%). More aggressive treatments (**2b** and **2c**) lead to little change in degree of condensation within experimental error. ^{13}C and ^{29}Si CPMAS spectra for the 3-hydroxypropyl hybrid silica (**2b**) are shown in Figure 3.

Alcohol Surface Chemistry of Hybrid Silicate Particles. In an effort to better characterize the 3-hydroxypropyl hybrid silicate particles, a series of alcohol group transformations were surveyed. The reactions were selected for their apparent simplicity in terms of mechanism and characterization, as well as for any guidance which might be derived from similar heterogeneous experimentation. The degree of alcohol group transformation and hence level of new substituent derivatization was determined by the increase in %C and/or %Br for the product vs unreacted alcohol particle as well as by ^{13}C CP-MAS NMR spectroscopy. A summary of elemental results and the corresponding surface concentrations are shown in Table 2.

Bromination. The first surface reaction was designed to further probe the location of the alcohol group. The 3-hydroxypropyl groups were converted into 3-bromopropyl groups via reaction with concentrated hydrobromic acid solution.



Stein and co-workers used a similar approach to measure the accessibility of vinyl groups in a MCM-type material using bromine (Br$_2$).[10] Maximum conversion was achieved by refluxing in a 48% HBr aqueous solution at 105 °C overnight. The product particles (**3**)

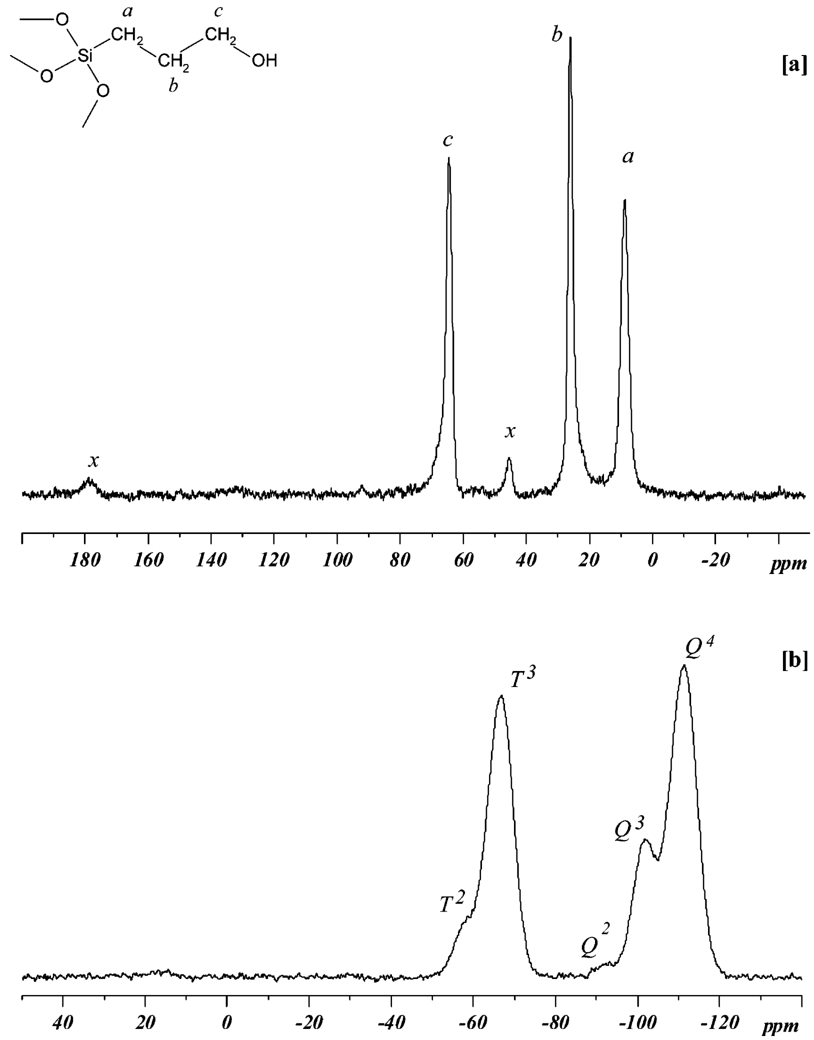


Figure 3. ^{13}C NMR (a) and ^{29}Si NMR (b) CPMAS spectra of 3-hydroxypropyl hybrid silica **2b**.

Table 2. Elemental and Surface Concentration Data for Surface Derivatized Hybrid Products 3−11[a]

	element analysis		surface concn
material	element	%	(μmol/m^2)
2b	C	11.47	NA
3	Br	13.72	5.75
	C	10.44	NA
4	C	23.07	3.63
5	C	22.16	3.29
6	C	14.70	1.36
7	C	14.81	1.67
8	C	15.19	0.96
9	C	14.20	2.93
10	Br	0.70	NA
	C	12.40	2.73
11	Br	6.13	NA
	C	12.48	0.91

[a] See Experimental Section for details of surface concentration calculation.

had a 3-bromopropyl surface concentration of 5.75 μmol/m^2 as calculated from the increase in %Br. The SSA and PV dropped by 60 m^2/g and 0.08 cm^3/g, respectively, with bromination. A similar phenomenon was observed with the bromination of vinyl materials[10] and is attributed here to the increase in weight achieved by replacing the hydroxyl substituent with the heavier bromo substituent. The ^{13}C CPMAS NMR spectrum indicated approximately 77% conversion of hydroxyl into bromo groups, and there was no elimination product detected (Figure 4). The *c*′ peak at 35 ppm is assigned to the bromo methylene group, and the *c* peak at 65 ppm is assigned to the hydroxy methylene group. The ^{29}Si CPMAS NMR spectrum was relatively unchanged versus the starting particle.

Silica particles are typically assigned a silanol surface concentration of about 8 μmol/m^2 (4.6 groups/nm^2) for a fully hydroxylated surface.[23] If the organosilicon repeat units were homogeneously dispersed within the hybrid formulation, then 1.6 μmol/m^2 of 3-hydroxypropyl groups (i.e., 1/5 of 8 μmol/m^2) would be expected on the particle surface. Therefore, a 3-hydroxypropyl surface concentration of ca. 7.5 μmol/m^2 (i.e., 5.75 μmol/m^2/0.77) is supportive of a material where there is an enrichment of alcohol groups on the pore surface. Further evidence for organic group location at the pore surface is found in hydrolytic stability studies (vide infra).

Esterification. 3-Hydroxypropyl particles **2** were reacted with dodecyl isocyanate in refluxing toluene to form a C_{12} carbamate on the particle surface. The hybrid particles and toluene were carefully dried before the reagent was added for surface coupling. Despite these precautions, excess isocyanate was hydrolyzed to the corresponding dodecylamine. The amine could be re-

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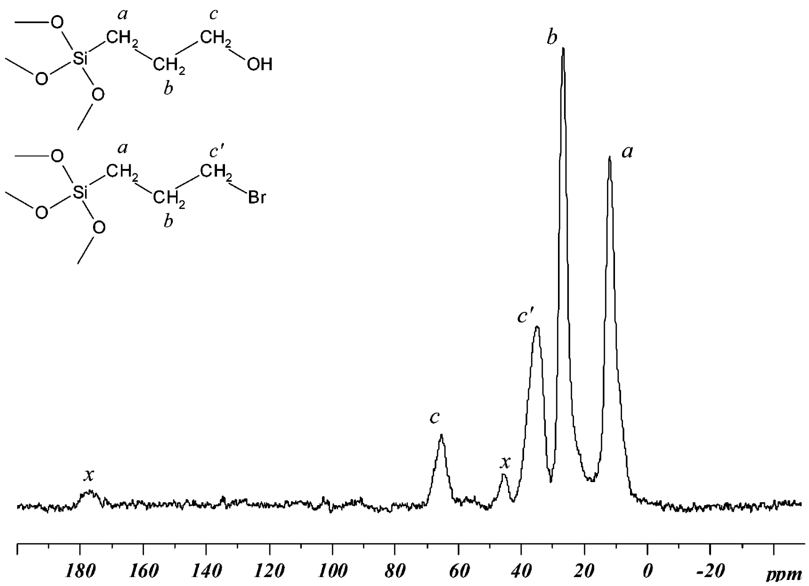
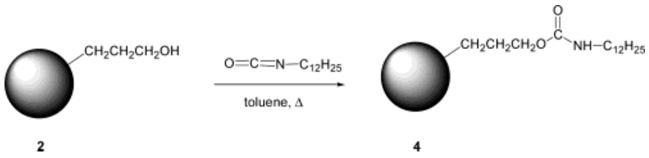


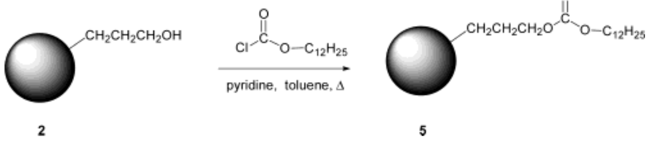
Figure 4. ^{13}C CPMAS NMR spectrum of brominated 3-hydroxypropyl hybrid particles **3**.

moved by acidifying a suspension of **4** in a 50:50 solution of 1% TFA:acetone at 50 °C followed by washing with >75 °C toluene. The resulting product was free of amine as measured by FTIR and ^{13}C CPMAS NMR spectroscopy. The surface concentration of product **4** was 3.63 μmol/m^2 as measured by the %C increase. This leaves about two-thirds of the alcohol groups unreacted, consistent with the analysis of the ^{13}C CPMAS NMR data (Figure 5a). For the NMR data analysis, the integrated peak areas from the spectral deconvolution were used to solve simultaneous equations to arrive at a semiquantitative ratio of unreacted propanol groups to reacted ligands.

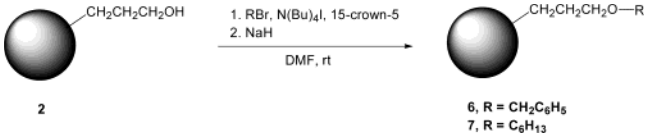


A similar surface concentration has been reported for the analogous structure derived by silane coupling to silica gel.[24]

In an analogous reaction to the synthesis of **4**, the corresponding dodecyl carbonate-derivatized particle **5** was prepared from **3** with dodecyl chloroformate and pyridine. In the present case, pyridine hydrochloride salts were efficaciously removed by washing with a 50:50 solution of 1% HCl:acetone at 50 °C followed by washing with >75 °C toluene. The surface concentration of the carbonate group was 3.29 μmol/m^2 based on the increase in %C for the product vs starting material. Semiquantitative analysis of the ^{13}C CPMAS NMR data, as in the previous case, indicates about two-thirds of the alcohol groups was unreacted (Figure 5b).



Etherification. One of the most common procedures for the solution-based synthesis of unsymmetrical ethers is the Williamson reaction.[25] To the best of our knowledge, its application on solid supports has been limited to benzyl halide substitution and methylation via alkylation of a secondary alcohol with methyl iodide in the presence of NaH and 15-crown-5 in DMF at 23 °C for 18 h.[26,27] In a first attempt to make a benzyl ether, particle **2** was combined with NaH and catalysts 15-crown-5 and tetrabutylammonium iodide in DMF, followed by benzyl bromide addition. A disappointingly low benzyl ether coverage was achieved (0.38 μmol/m^2) based on the increase in %C.



For a solution-phase Williamson reaction, one usually deprotonates the alcohol with NaH prior to the addition of alkyl halide. In the present case for **2**, we hypothesize that the deprotonated hydroxide may form a stabilized intermediate or secondary structure, with possible hydroxide backbiting onto a surface silicon to form a stable five-membered ring. Subsequent reaction with the alkyl halide would then be impeded. Improved coverage was achieved when NaH was added after combining particle **2** with benzyl bromide. In this order of addition, the ether-forming reaction appears to become more competitive. A coverage of 1.36 μmol/m^2 was found for product **6** made this way with benzyl bromide. A similar surface concentration of 1.67 μmol/m^2 was found for the product made this way with 1-bromohexane to form product **7**, albeit a 5-fold increase in alkyl bromide was used to drive the reaction

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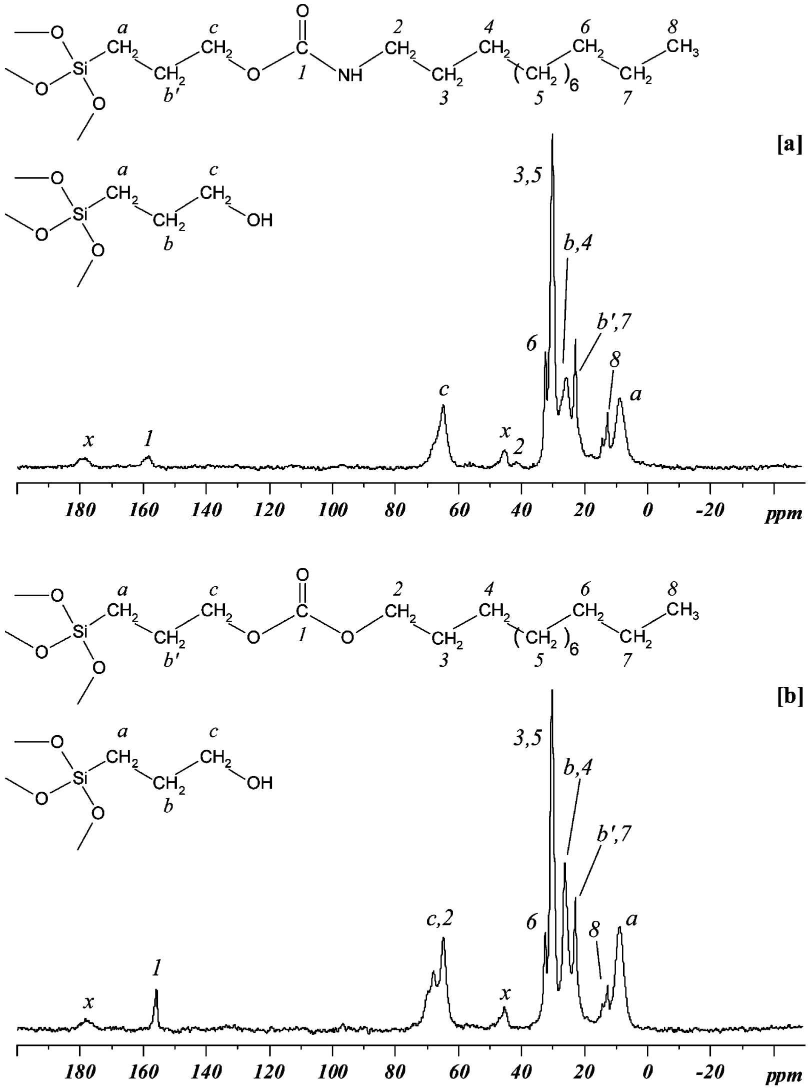
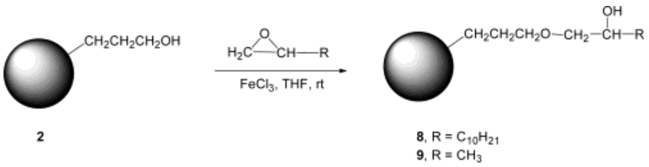


Figure 5. ^{13}C CPMAS NMR spectrum of ester-derivatized 3-hydroxypropyl hybrid Particles **4** (a) and **5** (b).

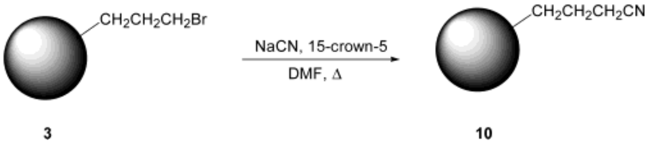
kinetics. The ^{13}C CPMAS NMR spectra in both cases were consistent with partial etherification (Figure 6).

In an effort to probe the ether transformation further, we turned from nucleophile activation (alcohol deprotonation) to electrophile activation. Specifically, 1,2-epoxyalkanes were used as the electrophile in an Fe(III) chloride-catalyzed ring opening of the epoxide via alcohol attack. An Fe(III)-catalyzed ring opening of epoxides has been shown to afford clean addition at the primary carbon for reactions in solution.[28]



When 3-hydroxypropyl particles **2** were reacted with an equivalent of the 1,2-epoxydodecane and 0.1 equiv of ferric chloride catalyst in THF at room temperature, a β-hydroxy C_{12} ether surface product **8** was formed as determined by ^{13}C CPMAS NMR spectroscopy (Figure 7). The surface concentration of the ether was 0.96 μmol/m^2 based on the increase in %C. An increase in surface concentration to 2.93 μmol/m^2 was achieved by using the smaller 1,2-epoxypropane in place of the dodecyl analogue and doubling the reagent's equivalents (product **9**). The increase in coverage is consistent with less steric congestion and accelerated reaction kinetics. The catalytic amounts of iron could be removed by washing with 1% HCl solution.

*Cyanation of Particle **3***. Brominated particle **3** was next studied as a means to explore surface-bound electrophiles as reactants in S_N2-type reactions. Cyanide was selected as the first reagent for study because of its good nucleophilicity. 15-Crown-5 ether was used to increase the solubility of NaCN as well as the nucleophilicity of the cyanide ion, and DMF was used to further promote the reaction.



When the particles **3** were thus reacted at 110 °C overnight, substantial conversion of the bromo to cyano substituent was achieved as measured by ^{13}C CPMAS

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[28] Iranpoor, N.; Salehi, P. *Synthesis* **1994**, 1152−1154.

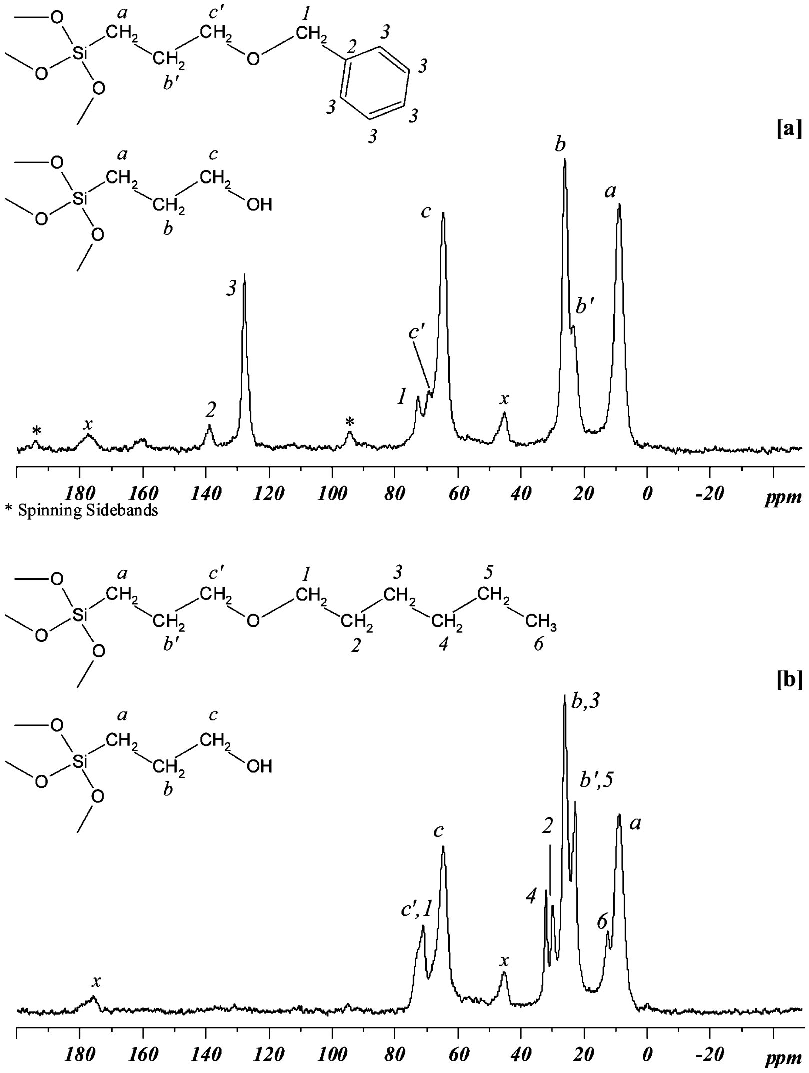


Figure 6. ^{13}C CPMAS NMR spectroscopy of Williamson ether products **6** (a) and **7** (b).

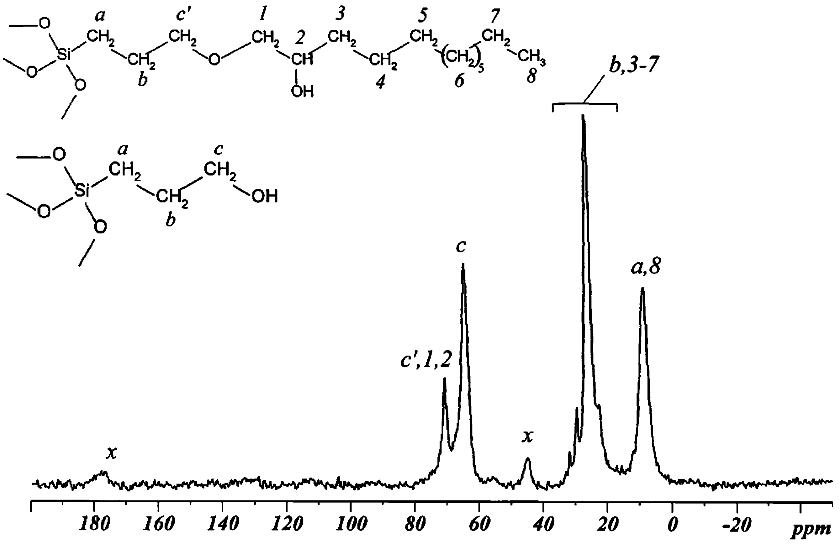


Figure 7. ^{13}C CPMAS NMR spectroscopy of β-hydroxy ether product **8**.

NMR spectroscopy (Figure 8) to form particles **10**. The bromo methylene resonance (35 ppm) is no longer seen, and a new resonance appears at 119 ppm, which is assigned to the nitrile carbon. The %Br in the product dropped to 0.70% from the starting material 13.72%, suggesting ca. 95% conversion. At the same time, the surface concentration (2.73 μmol/m^2) calculated from the increase in %C indicated a lower conversion of ca. 45%. Some but not all of the %C discrepancy with the NMR spectrum and %Br data may be attributed to the error involved in measuring the small increase in %C that occurs in adding the nitrile group to the particle's

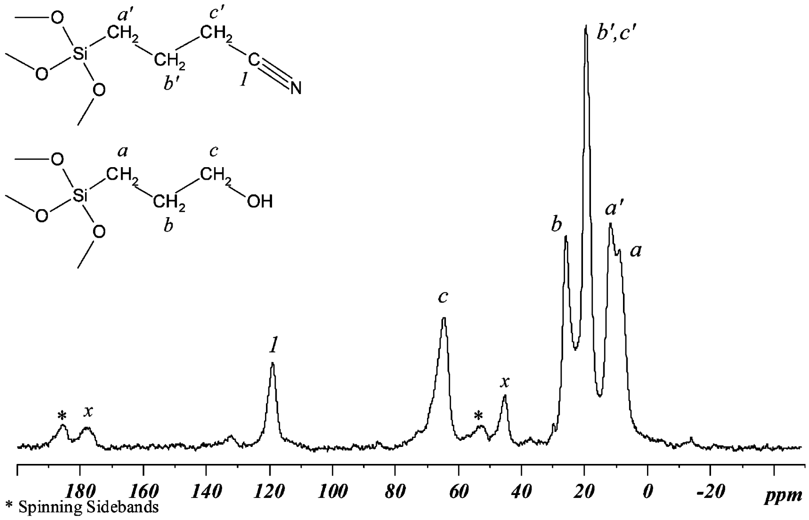
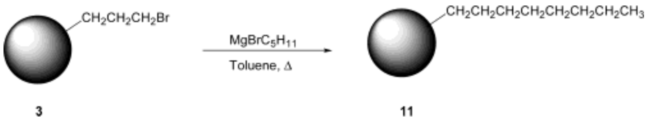


Figure 8. ^{13}C CPMAS NMR spectroscopy of cyanated 3-hydroxypropyl hybrid particles **10**.

surface. An absolute error of 0.15%C exists for the carbon analyzer, which if applied to the present case would increase the conversion to ca. 60% (3.43 μmol/m^2). As an alternative explanation, if the %Br measured for product **3** was in part derived from nonbromopropyl species, that is, residual HBr, the calculated surface concentration of 3-bromopropyl groups would be less than 5.75 μmol/m^2. As a result, the discrepancy would lessen between the %C vs NMR and %Br determinations.

*Grignard Coupling of Particle **3***. Encouraged by the relative success of the cyano substitution, a Grignard coupling was next attempted between particle **3** and pentylmagnesium bromide. The Grignard reagent was only added after careful drying of the particle and toluene, and a 3-fold excess of the reagent was refluxed in toluene for 2 h.



A C_5 group coverage of about 0.91 μmol/m^2 was achieved based on the increase in %C (product **11**). However, residual Mg salts (1.1 wt %) were not removed from the particles, despite copious washing with 1% HCl. The additional weight of the salts is ignored in the calculation of coverage, thereby making the calculated value of 0.91 μmol/m^2 approximate. The ^{13}C CPMAS NMR spectrum was also consistent with partial coupling. As cited above, the low surface concentration is attributed to the steric bulk that ensues as groups are added to the surface. Metal catalysts such as Cu(I) salts were not pursued to drive conversion for fear of inadequate removal in light of our particular interest in chromatographic media.

Hydrolytic Resistance Studies. *Alkaline Resistance of Particle **2b***. In an effort to further support the enrichment of the particle's surface with 3-hydroxypropyl groups, a measure of the particle's resistance to dissolution in an alkaline mobile phase under HPLC test conditions was conducted in the manner described previously.[29] In brief, HPLC columns were packed under slurry conditions with the particles **2** or underivatized silica gel with a similar surface area (both sized to nominal 5-μm diameters). Under a flow of a 50 mM TEA buffer (pH 10.0) at 50 °C, silicate dissolution is initiated, where the silicates are flushed from the column. As the silicates are removed from the spherical particle wall, the particle skeletal strength weakens and the packed particle bed shifts, resulting in a loss in column efficiency (N) due to peak fronting. In many cases, the particles collapse, which leads to a column pressure increase that eventually exceeds the limit of the HPLC system. In cases where the virgin column has a tailing peak, an increase in efficiency may be observed prior to efficiency loss and/or column failure. As the particles degrade and the bed shifts, the peak begins to front, which offsets the original tailing, thereby creating an apparent increase in efficiency. Over multiple runs, the ultimate failure point is reproduced by the test (±5%).

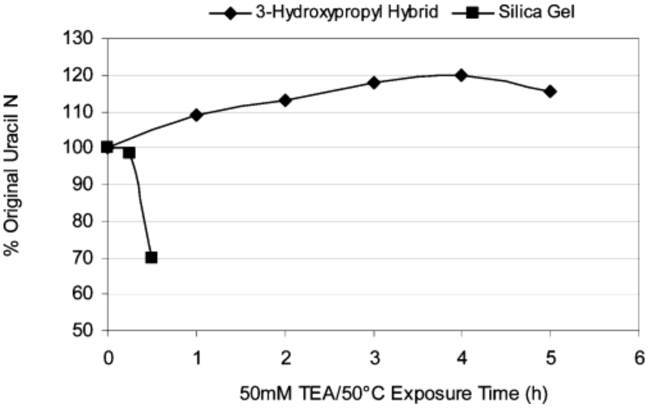


Figure 9. Alkaline resistance of 3-hydroxypropyl hybrid **2b** vs underivatized silica gel.

As shown in Figure 9, hybrid particle **2b** survived 5 h of exposure before the column failed due to high system backpressure. At the same time, the underivatized silica gel lasted only one-tenth the exposure time before failing due to high backpressure. The underivatized silica gel also showed a significant loss of efficiency, while the hybrid material did not. The result strongly supports that the hybrid's pore surface has a

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(29) O'Gara, J. E.; Alden, B. A.; Gendreau, C. A.; Iraneta, P. C.; Walter, T. H. *J. Chromatogr. A* **2000**, *893*, 245−251.

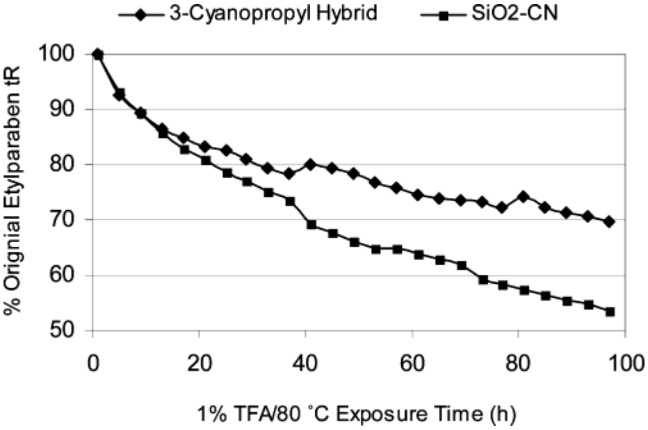

Figure 10. Acidic resistance of 3-cyanopropyl-derivatized particle **10** vs trifunctional cyanopropyl-derivatized silica gel (SiO_2−CN).

large population of 3-hydroxypropyl groups, which protects the underlying silicate substrate from hydroxyl anion attack. As the organic surface coat is breached, the underlying silicate is rapidly dissolved, and particle collapse occurs as for silica gel.

Acidic Resistance of Derivatized Particle ***10***. The surface modification of silica gel via grafting with siloxane ligands provides the basis for many catalytic and reversed-phase (RP) HPLC materials. Despite the import of RP HPLC in a variety of chemical and biological disciplines, this analytical technique is rarely used at a pH below 2 because of fast degradation in the separation caused by hydrolytic cleavage of the siloxane bond connecting the alkyl group to the inorganic oxide's surface.[23] This problem holds true especially for short-chain siloxanes with polar functional group substituents and is exemplified by the 3-cyanopropyl siloxane ligand.[29]

Cyano-derivatized particles **10** were sized to a nominal 5-μm diameter and then tested for resistance to siloxane bond cleavage in an acidic mobile phase in an effort to probe how well the siloxane moiety of the organosilane is integrated into the skeletal structure. For comparison, a 5 μm silica gel was surface modified using (3-cyanopropyl)trichlorosilane (SiO_2−CN). Both materials were tested for resistance to acid-catalyzed hydrolysis under HPLC test conditions in the manner described previously.[29] As before, HPLC columns were packed under slurry conditions. Under a flow of 1% TFA (pH 1.0) at 80 °C, siloxane hydrolysis is initiated, where the (3-cyanopropyl)trihydroxysilane groups are flushed from the column. As the bonded groups are removed from the particle surface, the retention of the analyte ethylparaben decreases. The degree of retention loss in a given time is then taken as a measure of 3-cyanopropyl group stability.

3-Cyanopropyl hybrid particles **10** were found to maintain about 70% (i.e., lost 30%) of its retention over 97 h of testing. By comparison, the 3-cyanopropyl silica gel phase maintained about 50% of its retention in the same time (Figure 10). The improved resistance to low pH hydrolysis for **10** is attributed to the connecting siloxane bonds being better integrated or embedded into the particle's surface from both increased connectivity (thermodynamic) or possibly steric congestion (kinetic).[30] From a practical standpoint, an organo-functionalized material with improved chemical stability at low pH has been demonstrated by the hybrid route.

Experimental Section

Characterization. Elemental analyses (CHN) were performed using an Exeter Analytical Inc. combustion analyzer model CE-440. %Br analyses were performed by Atlantic Microlabs, Inc. (Norcross, GA). The specific surface areas (SSA), pore volumes (PV), and modal pore diameters (MPD) were measured using the multipoint nitrogen sorption method (Micromeritics ASAP 2405) as follows: the SSA was calculated using the BET method, the PV was determined at a single point for $P/P_o > 0.98$, and the MPD was calculated from the desorption leg of the nitrogen isotherm using the BJH method. Multinuclear (^{13}C, ^{29}Si) CP-MAS NMR spectra were obtained using a Bruker Instruments Avance-300 spectrometer (7-mm double broadband probe). The spinning speed was typically 5.0−6.5 kHz, recycle delay was 5 s, and the cross-polarization contact times were ~6 and 8 ms for ^{13}C and ^{29}Si, respectively. Reported ^{13}C and ^{29}Si CP-MAS NMR chemical shifts were recorded relative to tetramethylsilane using external standards: adamantane (^{13}C CP-MAS NMR, δ 38.55) and hexamethylcyclotrisiloxane (^{29}Si CP-MAS NMR, δ −9.62). Populations of different silicon environments were evaluated by spectral deconvolution using DMFit software.[31] Cross-polarization efficiencies are dependent on individual spin−lattice and cross-relaxation rates, which for silicon species attached to hydroxyl groups (i.e., Q^2 and Q^3 environments) are very similar. Optimizing cross-polarization experimental parameters relative to these relaxation characteristics allowed semiquantitative analysis of silicon environments with similar relaxation behavior via spectral deconvolution and integration. Solution-phase ^1H and ^{13}C spectra were recorded in chloroform-*d* with chloroform as an internal standard at 7.24 and 77.7 ppm, respectively. Liquid-phase ^{29}Si spectra were recorded as neat samples with TMS as an external standard at 0.00 ppm. Thermogravimetric analysis (TGA) was performed using a Perkin-Elmer TGA 7 instrument (N_2 atmosphere, 25−200 °C, ramp rate = 40 °C min^{-1}) using Pyris software (v. 2.04). IR spectra were recorded on a Mattson Polaris FT-IR spectrometer. Viscosity data were collected at 25.0 °C using a Brookfield Digital Viscometer with a No. 18 spindle. HPLC testing was run on an Alliance 2690 XE separations module, a model 996 photodiode array detector, a Millennium[32] v. 2.15.01 data management system (all from Waters Corporation), and a NESLAB RTE-111 circulating water bath for column temperature control (NESLAB Instruments, Inc.).

Synthesis. All reagents were used as-received unless otherwise noted. All silanes were obtained from Gelest, Inc. All solvents, acids, and bases were obtained from J.T. Baker, Inc. All other reagents were obtained from Aldrich. Glassware used for moisture-sensitive reactions was flame-dried and then cooled under a stream of argon. All particle products were dried under vacuum at 80 °C for a minimum 16 h prior to characterization and had less than 2% volatiles as measured by TGA.

POS Preparation. A solution of [3-(methacryloxy)propyl]-trimethoxysilane (671 g, 2.7 mol) and tetraethoxysilane (2250 g, 10.8 mol) was prepared in ethanol (788 mL), and then 0.1 N hydrochloric acid (304 mL) was added with stirring. The resulting solution was refluxed for 16 h in an atmosphere of nitrogen. Ethanol and methanol were then removed via distillation at atmospheric pressure. Residual alcohol and volatile species were next removed by heating at 130 °C for 0.5 h in a sweeping stream of nitrogen. The resulting POS was a

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[30] Guo, Y.; Colón, L. A. *Anal. Chem.* **1995**, *67*, 2511−2516.

[31] Massiot, D.; Fayon, F.; Capron, M.; King, I.; Calvé, S. Le; Alonso, B.; Durand, J. O.; Bujoli, B.; Gan, Z.; Hoatson, G. *Magn. Reson. Chem.* **2002**, *40*, 70−76.

[32] Berendsen, G. E.; de Galan, L. *J. Liq. Chromatogr.* **1978**, *1*, 561−586.

colorless, viscous oil (1804 g): viscosity, 68 Cp. ^{1}H NMR (CDCl$_3$, δ): 0.67 (2H, Si−CH$_2$−), 1.76 (2H, −CH$_2$−), 1.88 (3H, −CH$_3$), 4.06 (2H, −CH$_2$−O−), 5.49 and 6.04 (1H each, =CH$_2$), 3.81 and 1.18 (CH$_2$ and CH$_3$ from ethoxy silane). ^{13}C NMR (CDCl$_3$, δ): 7.7 (Si−CH$_2$), 17.7 (−CH$_3$), 21.7 (−CH$_2$−), 66.0 (−CH$_2$−O−), 124.6 (=CH$_2$), 136.0 (−C(CH$_3$)=CH$_2$), 188.8 (−O−C(=O)−), 58.6 and 17.5 (CH$_2$ and CH$_3$ from ethoxy silane). ^{29}Si NMR (CDCl$_3$, δ): −50 to −55 (T^1), −58 to −62 (T^2), −63 to −68 (T^3), −85 to −91 (Q^1), −92 to −99 (Q^2), −100 to −105 (Q^3), −106 to −113 (Q^4). IR (neat): 2977.4, 2929.9, 2895.1 ($\nu_{\mathrm{C-H}}$), 1721.2 ($\nu_{\mathrm{C=O}}$), 1638.2 ($\nu_{\mathrm{C=C}}$), 1161.9 ($\nu_{\mathrm{Si-O-C}}$), and 1089.3 cm^{-1}($\nu_{\mathrm{Si-O-Si}}$). Anal.: C, 34.25; H, 6.52.

3-(Methacryloxy)propyl-Functionalized Hybrid Particles (1). A mixture of surfactants Triton X-45 (1.5 g), TRIS lauryl sulfate (0.24 g), anhydrous ethanol (60 mL), and deionized water (280 mL) was heated at 55 °C for 0.5 h, resulting in a white liquid. Under rapid agitation, a solution of toluene (2 mL) in poly(organalkoxysiloxane) (30 g) was added into the ethanol/water/surfactant mixture and then emulsified in the aqueous phase using a Ross Model 100L High Shear Mixer. After 3 min, 30% NH$_4$OH (8 mL) was added into the emulsion to gel the emulsion beads. Suspended in the solution, the gelled product was transferred to a flask and stirred at 55 °C for 17 h. The resulting particles were collected on 0.5-μm filtration paper and washed successively with copious amounts of water and methanol. IR: 2956.9, 2931.9, 2895.7 ($\nu_{\mathrm{C-H}}$), 1718.6 ($\nu_{\mathrm{C=O}}$), 1636.6 ($\nu_{\mathrm{C=C}}$), and 1091.9 cm^{-1} ($\nu_{\mathrm{Si-O-Si}}$). Anal. Calcd for C$_7$H$_{11}$O$_{11.5}$Si$_5$: C, 20.03; H, 2.65. Found: C, 21.10; H, 3.00.

3-Hydroxypropyl-Functionalized Hybrid Particles (2b). Particles **2a** (2.7 g) were suspended in a 1.2 M tris(hydroxymethyl)aminomethane solution (135 mL, pH 10.8). The suspension was then enclosed in a stainless steel Parr autoclave and heated to 165 °C for 21 h. Upon cooling, the particles were collected on 0.5-μm filtration paper and washed using copious amounts of water and methanol. IR: 3374.2 ($\nu_{\mathrm{O-H}}$), 2934.1, 2892.4 ($\nu_{\mathrm{C-H}}$), and 1100.0 cm^{-1} ($\nu_{\mathrm{Si-O-Si}}$). Anal. Calcd for C$_3$H$_7$O$_{10.5}$Si$_5$: C, 10.25; H, 2.01. Found: C, 11.47; H, 2.18.

3-Bromopropyl-Derivatized Hybrid Particles (3). 3-Hydroxypropyl particles **2b** (10 g) were suspended in 100 mL of 48% HBr aqueous solution. The suspension was heated to 105 °C for 24 h and then cooled. The particles were collected on 0.5-μm filtration paper and washed using copious amounts of water and acetone. IR: 2945.5, 2896.6 ($\nu_{\mathrm{C-H}}$), 1090.9 ($\nu_{\mathrm{Si-O-Si}}$), and 688.8 cm^{-1} ($\nu_{\mathrm{C-Br}}$). Anal.: C, 10.44; H, 1.70; Br, 13.72.

Dodecylcarbamic Acid Ester-Derivatized Hybrid Particles (4). Dried 3-hydroxypropyl particles **2b** (15 g) were added into 75 mL of dry toluene under argon, and then dodecylisocyanate (9.16 g, 43.3 mmol) was added to the suspension. The suspension was heated to reflux for 16 h and then cooled. The particles were collected on 0.5-μm filtration paper and washed using copious amounts of water and acetone. The particles were then resuspended in a 150-mL solution of acetone:1% TFA (50:50 v/v) at 50 °C for 1 h. Upon cooling, the particles were collected on 0.5-μm filtration paper and washed using copious amounts of heated toluene (>75 °C) and room-temperature acetone. IR: 2924.6, 2853.9 ($\nu_{\mathrm{C-H}}$), 1694.6 ($\nu_{\mathrm{C=O}}$), and 1537.8 cm^{-1} ($\delta_{\mathrm{N-H}}$). Anal.: C, 23.07; H, 4.03; N, 1.08.

Dodecylcarbonic Acid Ester-Derivatized Hybrid Particles (5). Dried 3-hydroxypropyl particles **2b** (15 g) were added into 75 mL of dry toluene under argon, and then dodecyl chloroformate (8.60 g, 34.6 mmol) and dry pyridine (3.42 g, 4.32 mmol) were added to the suspension. The suspension was heated to reflux for 16 h and then cooled. The particles were collected on 0.5-μm filtration paper and washed using copious amounts of water and acetone. The particles were then resuspended in a solution of acetone/1% HCl (50:50 v/v, 150 mL) at 50 °C for 1 h. Upon cooling, the particles were collected on 0.5-μm filtration paper and washed using copious amounts of heated toluene (>75 °C) and room-temperature acetone. IR: 2924.5, 2854.5 ($\nu_{\mathrm{C-H}}$), and 1744.4 cm^{-1} ($\nu_{\mathrm{C=O}}$). Anal.: C, 22.16; H, 3.77.

Ether-Derivatized Hybrid Particles (6 and 7). Sodium hydride was isolated from mineral oil by washing twice with 30 mL of pentane and then drying under a stream of argon. The dried NaH (**6** 0.24 g, 10 mmol; **7** 0.59 g, 24.5 mmol) was suspended in dry DMF (**6** 15 mL, **7** 40 mL). In a separate flask, 3-hydroxypropyl particles **2b** (2 g) were combined with an alkyl bromide (**6** benzyl bromide, 1.7 g, 10 mmol; **7** 1-bromohexane, 8.06 g, 48.8 mmol) in 20 mL of dry DMF under argon. The NaH suspension was slowly added dropwise to the particle/alkylbromide mixture over 20 min, and then the mixture was stirred at room temperature for 16 h. The NaH was then quenched by slow addition of 1% acetic acid solution. The particles were collected on 0.5-μm filtration paper and then washed using copious amounts of 1% acetic acid solution, water, and acetone. **6**: IR: 3070.3, 3034.3 ($\nu_{\mathrm{C-H(aromatic)}}$) and 2940.2, 2885.9 cm^{-1} ($\nu_{\mathrm{C-H}}$). Anal. C, 14.70; H, 2.32. **7**: IR: 2937.6, 2876.3 cm^{-1} ($\nu_{\mathrm{C-H}}$). Anal.: C, 14.81; H, 2.77.

***β*-Hydroxy Ether-Derivatized Hybrid Particles (8 and 9).** 3-Hydroxypropyl particles **2b** (2 g) were combined with an epoxyalkane (**8** 1,2-epoxydodecane, 1.07 g, 5.8 mmol; **9** 1,2-epoxypropane, 1.06 g, 12.4 mmol), and FeCl$_3$ (0.094 g, 0.58 mmol) in 50 mL of dry THF under argon. The mixture was stirred at room temperature for 4 h. The particles were collected on 0.5-μm filtration paper and then resuspended in a solution of acetone/1% HCl (50:50 v/v, 100 mL) at 50 °C for 1 h. Upon cooling, the particles were collected on 0.5-μm filtration paper and washed using copious amounts of acetone/water (50:50 v/v) and acetone. **8**: IR: 2939.2, 2880.8 cm^{-1} ($\nu_{\mathrm{C-H}}$). Anal. C, 15.19; H 2.77. **9**: IR: 2940.0, 2878.1 cm^{-1} ($\nu_{\mathrm{C-H}}$). Anal.: C, 14.20; H, 2.50.

Cyano-Derivatized Hybrid Particles (10). 3-Bromopropyl particles **3** (1 g), 15-crown-5 ether (1.2 mL, 6.0 mmol), and sodium cyanide (0.33 g, 6.7 mmol) were combined with 20 mL of dry DMF under argon. The suspension was heated to reflux for 20 h and then cooled. The particles were collected on 0.5-μm filtration paper and washed using copious amounts of toluene, acetone, acetone/water (50:50 v/v), and acetone. IR: 2943.6, 2890.9 ($\nu_{\mathrm{C-H}}$), 2251.0 ($\nu_{\mathrm{C\equiv N}}$), and 1084.7 cm^{-1} ($\nu_{\mathrm{Si-O-Si}}$). Anal.: C, 12.40; H, 1.96; N, 1.41.

Pentyl-Derivatized Hybrid Particles (11). Pentylmagnesium bromide was isolated from diethyl ether by drying under a stream of argon and then taken back up in dry toluene to prepare a 2 M solution. Dried 3-bromopropyl particles **3** (14 g) were added to 75 mL of dry toluene under argon, and then 43 mL of the 2.0 M pentylmagnesium bromide (86 mmol) toluene solution was added dropwise. The mixture was then refluxed for 4 h. Upon cooling, the particles were collected on 0.5-μm filtration paper and washed using copious amounts of toluene, acetone, acetone/water (50:50 v/v), and acetone. IR: 2956.7, 2928.3, and 2858.7 cm^{-1} ($\nu_{\mathrm{C-H}}$). Anal.: C, 12.48; H, 2.29.

Calculation of Functional Group Surface Concentration for One-Step Transformations. The equation shown below was used to determine the surface concentration of groups derived from the 3-hydroxypropyl particle,

$$\text{surface concentration } (\mu\text{mol/m}^2) = \frac{10^6\,(P_{x1} - P_{x0})}{\mathrm{SSA}(100 W_x N_{x1} - P_{x1} M_{e1})}$$

where P_{x1} is the % element measured for the derivatized material (e.g., %C or %Br), P_{x0} is the % element measured for the underivatized material (e.g., %C or %Br), SSA is the the specific surface area (m^2/g) of the underivatized material, W_x is the atomic weight (g/atom) of the element measured (e.g., 12.01 for C and 79.91 for Br), N_{x1} is the number of atoms added in the process of derivatization, and M_{e1} is the effective molecular weight (g/mol) of the added ligand, where the effective molecular weight is the molecular weight of what is added on the surface minus the molecular weight of the leaving group from the underivatized surface.

It is important to note that the equation is based on several assumptions and/or limitations: (1) all of the carbon on the particle, for which the SSA was derived, remains on the particle during the process. (2) Washing steps and adequate drying remove unbonded reactant, side products, solvents, and so forth, prior to elemental analysis. If the %C on the underivatized particle is reduced to zero in the above equation, the equation reduces to the established Berendsen–de Galan equation used for calculating surface concentrations for silica gel derivatizations.[32]

Calculation of Functional Group Surface Concentration for Two-Step Transformations. The equation shown below was used to determine the surface concentration of groups derived from the 3-bromopropyl particle (first derivatized) via the 3-hydroxypropyl particle (underivatized),

$$\text{surface concentration } (\mu\text{mol/m}^2) = \frac{106(100W_xN_{x1} - P_{x0}M_{e1})(P_{x2} - P_{x1})}{\text{SSA}(100W_xN_{x1} - P_{x1}M_{e1})(100W_xN_{x2} - P_{x2}M_{e2})}$$

where P_{x0} is the % element measured for the underivatized material (e.g., %C or %Br), P_{x1} is the % element measured for the first derivatized material (e.g., %C or %Br), P_{x2} is the % element measured for the second derivatized material (e.g., %C or %Br), SSA is the specific surface area (m^2/g) of the underivatized material, W_x is the atomic weight (g/atom) of the element measured (e.g., 12.01 for C and 79.91 for Br), N_{x1} is the number of atoms added in the process of first derivatization, N_{x2} is the number of atoms added in the process of second derivatization, M_{e1} is the effective molecular weight (g/mol) of the added ligand in the first derivatization, where the effective molecular weight is the molecular weight of what is added on the surface minus the molecular weight of the leaving group from the underivatized surface, and M_{e2} is the effective molecular weight (g/mol) of the added ligand in the second derivatization, where the effective molecular weight is the molecular weight of what is added on the surface minus the molecular weight of the leaving group from the first derivatized surface.

The same assumptions and/or limitations apply as for the above one-step transformations.

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Supporting Information Available: Scanning electron microscope (SEM) views of particles **1** and **2c** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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