Primary Amine Confinement at the Interface of Grafted Calixarenes and Silica

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Materials consisting of covalently anchored primary amines on the surface of silica have been widely used as active sites for heterogeneous base catalysis[1] as well as adsorption of organic molecules,[2] organometallic complexes,[3] nanoparticles,[4] and enzymes.[5] Yet despite demonstrations that the environment surrounding anchored primary amines on silica controls resulting adsorptive and catalytic properties via mechanisms that involve cooperativity between the amine and adjacent surface,[1,6] the predominant atomic connectivity between amine and silica in these materials has relied almost exclusively on a propyl tether between nitrogen and silicon, with subsequent immobilization strategies that typically consist of forming additional bonds to the primary amine via either alkylation,[7] or formation of either Schiff base,[8] amide,[9] or urea linkages.[10] In particular, in view of emerging correlations between confinement and enantioselectivity in biological,[11] homogeneous,[12] and heterogeneous catalytic systems,[9a,13] it is highly desirable to confine primary amine functionality without the use of a microporous material as the confinement entity,[13h,14,15] which inevitably results in mass transport limitations and an inability to control the degree of confinement using organic synthesis as a powerful tool to tailor material architecture on the molecular level. Current amine on silica anchoring strategies do not permit this type of confinement because the ubiquitous propyl tether leads to an open and accessible primary amine anchored surface site.

This manuscript reports new materials consisting of confined and site-isolated primary amine functionality covalently immobilized on the surface of silica. The confinement approach relies on the attachment of primary amine functionality to the lower rim of a grafted calixarene on silica.[16,17] The calixarene serves the purpose of rigorously isolating primary amine functionality, and in principle provides a synthetically versatile scaffold for anchoring a variety of functional groups and tether combinations within confined environments. Scheme 1 demonstrates the synthetic approach, beginning with monoalkylation of parent *tert*-butylcalix[4]arene with a protected amine using Mitsunobu coupling procedures, as reported previously,[1,18] to synthesize compounds **1a**−**1d**, with **1a** notably consisting of an asymmetric center directly connected to nitrogen. The resulting monoalkylcalixarenes are treated with ethoxy-trichlorosilane, yielding graftable **2a**−**2d** as well as N-deprotected analogs **3a**−**3d**. Subsequent treatment with silica in a dry nonpolar solvent efficiently grafts the aminocalixarene under neutral conditions to synthesize materials **4a**−**4d**. Schiff bases are synthesized by either of two contrasting approaches using the building blocks above involving: (i) treatment of materials **4a**−**4d** with salicylaldehyde to synthesize **5a**−**5d** (heterogeneous approach) or (ii) treatment of homogeneous **3a**−**3d** with salicylaldehyde to synthesize Schiff base calixarenes **6a**−**6d** (homogeneous approach).

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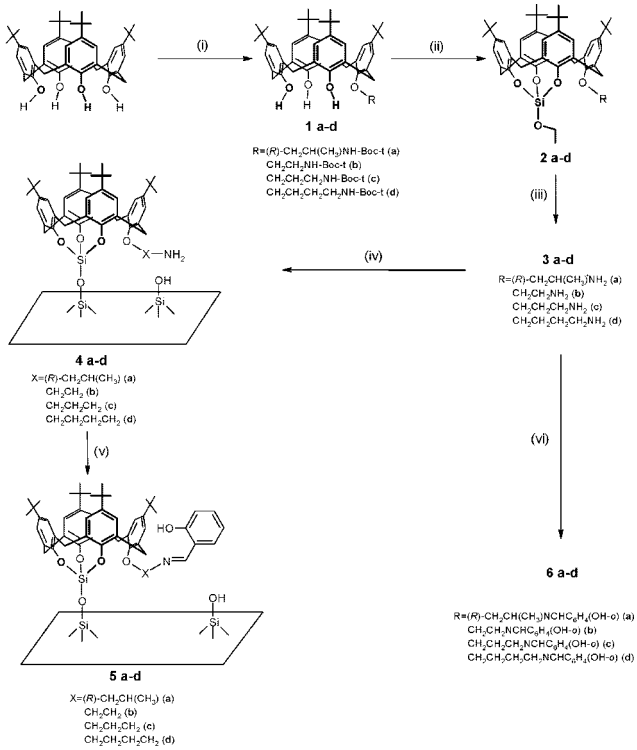
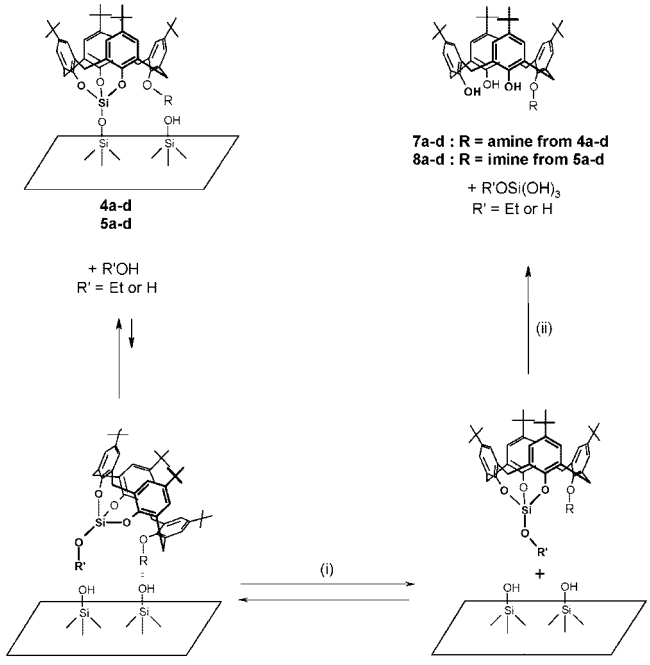
Scheme 1



(i) ROH, DEAD, TPP, toluene, 70 °C, 2h. (ii) $Cl_3SiOC_2H_5$, NEt_3, DMAP (cat), benzene, r.t., 12 h. (iii) $(CH_3)_2SiI$, CH_2Cl_2 r.t., 15 min. (iv) Selecto silica gel, benzene, r.t. overnight. (v) Low coverage material (~ 40 micromole/g) and salicylaldehyde, toluene, reflux, 8 h. (vi) Salicylaldehyde, toluene, reflux, 3 h.

Scheme 2



(i) Benzene or toluene solvent (ii) Wet acetonitrile.

The grafting of **3a**−**3d** onto the silica surface is driven by the reversible partitioning of functionalized calixarene to the silica surface in nonpolar solvents as shown in Scheme 2.

In nonpolar solvents such as toluene and benzene used for binding experiments and materials synthesis, this partitioning is favored in the direction of covalently anchored material; however, in the presence of polar solvents containing water, partitioning to

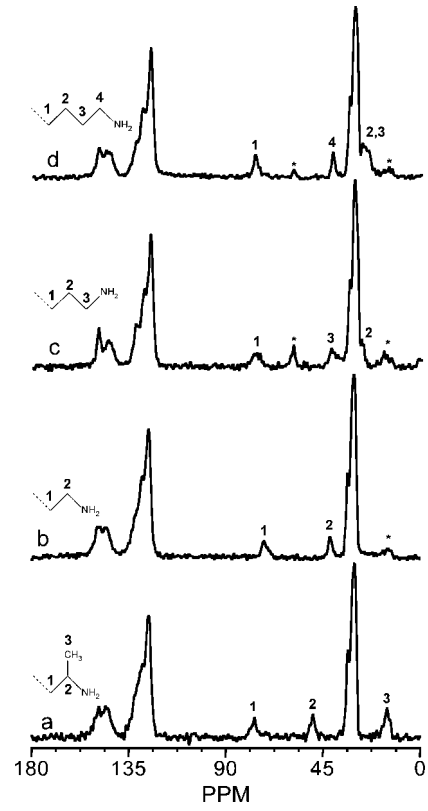


Figure 1. ^{13}C CP/MAS NMR spectra of (a) **4a**, (b) **4b**, (c) **4c**, and (d) **4d** acquired at 14 kHz rotation speed. The functional group substituent attached to the calixarene lower rim oxygen is shown and resonances corresponding to it are numbered. Asterisk denotes either a spinning sideband or a trace of residual surface ethoxy resonances.

silica is less favorable and, instead, calixarene desilylation ultimately results in leached triols **7a**−**7d** (for anchored amines) and **8a**−**8d** (for anchored Schiff bases). This route leading to leaching of grafted calixarene sites from the surface has been exploited in this manuscript for the purpose of characterizing the quantity of anchored iminocalixarene formed using liquid-phase spectroscopic methods.[19] The slow kinetics of this leaching process relative to mass transport (leaching after 1 min at room temperature in excess wet acetonitrile solvent produces less than 35% of sites leached) are consistent with covalent calixarene attachment. Solid-state ^{13}C CP/MAS NMR spectra of grafted aminocalixarenes, shown in Figure 1, demonstrate that silicon ethoxide hydrolysis occurs during anchoring via the general reduction of ethoxy resonance intensity, and that the tether connecting the amine to anchored calixarene is maintained intact. Nitrogen physisorption at 77 K measures a decrease in total pore volume corresponding to the expected molecular volume of the grafted calixarene fragment. Other solid supports can also be used for calixarene anchoring and have been previously shown to result in similar absorption properties, such as MCM-41S type materials,[20] alumina,[21] and titania.[21,22]

Confinement of anchored amines in **4a**−**4d** is assessed by using salicylaldehyde as a probe molecule that covalently binds to form a Schiff base in toluene at 100 °C for a duration of 8 h. These conditions lead to a complete conversion of conventional primary aminopropyl functional groups on the surface of silica. As an additional control, conversion of unconfined homoge-

(19) Surface sites have been leached in wet acetonitrile to give greater than 85% removal of sites from the surface as verified thermogravimetrically.

Table 1. Materials and Shape-Selective Salicylaldehyde Binding

material	molecular precursor	coverage (nm^2/calix)[1]	Schiff base (%)[2]
4a	**3a**	21.3	21
4b	**3b**	20.4	53
4c	**3c**	18.2	81
4d	**3d**	20.0	91

[a] Calixarene site surface coverage from carbon elemental analysis data. [b] Calixarene site fraction converted to Schiff base after treatment with salicylaldehyde as determined spectrophotometrically after leaching.

neous **3a**−**3d** to corresponding iminocalixarenes **6a**−**6d** was accomplished under similar conditions in uniformly high isolated yields of 73% (for **6a**), 77% (for **6b**), 74% (for **6c**), and 81% (for **6d**) after column chromatography.

Table 1 summarizes the effect of tether length on amine confinement in **4a**−**4d**, in the limit of low surface density (∼20 nm^2/calixarene), in which the relative fraction of calixarene sites bound with salicylaldehyde does not vary as calixarene surface density is further reduced. The relative proportion of aminocalixarene sites in **4a**−**4d** converted to anchored Schiff base after treatment varies systematically according to the length of the tether connecting amine to calixarene. The short and sterically bulky tether in **4a** leads to a low of 21% of sites bound with salicylaldehyde. In contrast, the long and flexible tethers in **4c** and **4d** afford greater than 80% binding, with the two methylene tether in **4b** leading to an intermediate amount of 53% of sites bound with salicylaldehyde, under the same conditions. Experiments with materials at much higher grafted calixarene surface densities (synthesized at a coverage of ∼5.5 nm^2/calixarene) demonstrate a significantly reduced ability to bind salicylaldehyde for all tether lengths, presumably as a result of intersite confinement that results from restricted accessibility in spaces between anchored calixarene sites on the silica surface.[20] This is in stark contrast to the intrasite confinement observed for all materials in Table 1. When the results above are considered in conjunction with the uniformly high binding of salicylaldehyde observed in homogeneous controls **3a**−**3d** (vide supra), the essential role of the two-dimensional silica surface in **4a**−**4d** for confinement becomes readily apparent. We propose that the silica surface serves to confine primary amine functionality from below in a cooperative fashion with calixarene, which confines from above, with calixarene and silica forming an inverted wedge-type of pocket that surrounds each primary amine functional group. On the basis of the observed shape-selective binding of salicylaldehyde above, the size of this pocket must be on par with the ∼5 Å dimension of salicylaldehyde for the most confined amine in **4a**. This pocket size is slightly smaller than the hydrophobic binding pocket surrounding isolated primary amine Lys H93 in catalytic antibody 33F12, which measures to be ∼8 Å in diameter according to single-crystal X-ray diffraction.[21]

The confinement approach demonstrated above for primary amine functionality is generalizable to other functional groups, such as carboxylic acids, and in principle permits the arrangement of orthogonal chemical functionalities on the surface. This could be potentially applied to organize pairs of isolated functional groups in close proximity to each other on the surface,

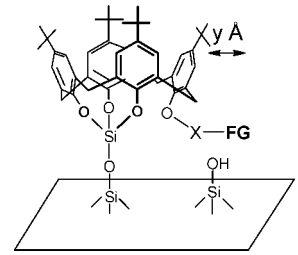


Figure 2. Schematic control of general functional group (**FG**) isolation using the class of materials described in this manuscript, relying on biasing the protrusion distance *y* relative to upper-rim substituent, using spacer X.

which demonstrate useful function as bifunctional catalysts, such as Bronsted acid−base pairs invoked in the active site of catalytic antibody 33F12[22] and synthetic heterogeneous catalysts[23] previously.

Because the steric bulk of the calixarene cone upper-rim substituents controls closest approach distance between grafted sites, confinement in the class of materials described in this manuscript is expected to facilitate site isolation and prevent undesired close-range interactions between grafted sites, which often carry detrimental catalytic consequences in bifunctional catalysis (i.e., functional group coordination to Lewis acid metal center[23,27]). The degree of site isolation and accessibility of a functional group tethered to the calixarene lower rim is inevitably controlled by the horizontal distance that the group protrudes relative to the calixarene upper-rim substituents. This in-turn can be controlled with extremely fine resolution through design and synthesis of the calixarene as schematically illustrated in Figure 2. The ability to rigorously isolate anchored functional groups within an enclosed and confined space cannot be achieved when using flexible tethers as in aminopropyl groups on the surface of silica.[28] We are currently extending the confinement studies described in this manuscript to other functional groups and are further characterizing the confinement in these systems using spectroscopy and probe molecule binding studies. These results will be presented in due course.

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Supporting Information Available: TGA spectra, ^{1}H and ^{13}C NMR spectra, extinction coefficients, and nitrogen adsorption/desorption isotherm (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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