

Energetics of Small Molecule and Water Complexation in Hydrophobic Calixarene Cavities

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Calixarenes grafted on silica are energetically uniform hosts that bind aromatic guests with 1:1 stoichiometry, as shown by binding energies that depend upon the calixarene upper rim composition but not on their grafted surface density ($0.02\text{--}0.23\text{ nm}^{-2}$). These materials are unique in maintaining a hydrophilic silica surface, as probed by H_2O physisorption measurements, while possessing a high density of hydrophobic binding sites that are orthogonal to the silica surface below them. The covalently enforced cone-shaped cavities and complete accessibility of these rigidly grafted calixarenes allow the first unambiguous measurements of the thermodynamics of guest interaction with the same calixarene cavities in aqueous solution and vapor phase. Similar to adsorption into nonpolar protein cavities, adsorption into these hydrophobic cavities from aqueous solution is enthalpy-driven, which is in contrast to entropy-driven adsorption into water-soluble hydrophobic hosts such as β cyclodextrin. The adsorption thermodynamics of several substituted aromatics from vapor and liquid are compared by (i) describing guest chemical potentials relative to pure guest, which removes differences among guests because of aqueous solvation and van der Waals contacts in the pure condensed phase, and (ii) passivating residual guest binding sites on exposed silica, titrated by water during adsorption from aqueous solution, using inorganic salts before vapor adsorption. Adsorption isotherms depend only upon the saturation vapor pressure of each guest, indicating that guest binding from aqueous or vapor media is controlled by van der Waals contacts with hydrophobic calixarene cavities acting as covalently assembled condensation nuclei, without apparent contributions from $\text{CH}\text{--}\pi$ or other directional interactions. These data also provide the first direct quantification of free energies for interactions of water with the calixarene cavity interior. The calixarene–water interface is stabilized by $\sim 20\text{ kJ/mol}$ relative to the water–vapor interface, indicating that water significantly competes with the aromatic guests for adsorption at these ostensibly hydrophobic cavities. This result is useful for understanding models of water interactions with other concave hydrophobic surfaces, including those commonly observed within proteins.

Introduction

van der Waals interactions are ubiquitous in biological associations,^{1,2} synthetic small molecule capsules,³ and porous solids⁴ and are thought to control many molecular recognition phenomena in catalysis and adsorption. The relatively weak and nonspecific nature of these interactions complicates their study, which typically requires measuring small changes in heat capacity or vapor pressure⁵ of solutions or averaging measurements of interaction between two macroscopic surfaces.⁶ A promising approach to study highly cooperative van der Waals interactions is to form host/guest-type complexes⁷ accessible to characterization by using hydrophobic cavities in protein interiors,⁸ porous solids,⁹ or small molecule receptors.¹⁰ The characterization of host/guest complexes based solely on van der Waals interactions,

however, is made more difficult by (i) solvent effects that alter the structure of self-assembled hosts¹¹ or proteins,¹² (ii) competitive binding of the solvent within synthetic cavities, such as calixarenes,¹³ and (iii) the inability to define a specific host/guest geometry or stoichiometry for adsorption on solids¹⁴ or in resorcinarene self-assembled monolayers.¹⁵ Few systems consisting of host molecules immobilized on surfaces have proven and discrete host/guest stoichiometries.¹⁶ In efforts to understand the role of water solvation and the nature of the host/guest van der Waals interactions within open hydrophobic cavities, it is essential to assess the binding energies of host/guest van der Waals complexes, independent of solvent effects and for well-defined host/guest geometries and stoichiometries. These details and concepts will advance our understanding of many technological and fundamental processes that occur at water-accessible hydrophobic surfaces, while contributing to the design of effective synthetic host/guest systems stabilized by van der Waals forces.

Here, the energetics of van der Waals host/guest complexation are measured within rigid host cavities¹⁷ consisting of calixarenes covalently grafted on silica surfaces. These materials consist of

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isolated binding sites present at submonolayer surface densities, the number of which can be determined independently by elemental and thermogravimetric analyses. This synthetic approach ensures that all calixarene cavities exhibit identical functional group organization oriented away from the silica surface.^{18,19} These grafted calixarene materials enable the study of van der Waals host/guest complexation energetics in a variety of solvent environments because (i) the calixarene adsorption sites are constrained by synthesis to be identical and accessible regardless of solvent environment or surface density,²⁰ (ii) there is a large chemical diversity of calixarene upper rims possible²¹ that can provide for a variety of van der Waals environments, and (iii) calixarene host/guest complexes have been extensively characterized as stable structures in solids and solution. Previous data show that small aromatics form 1:1 stoichiometric complexes with calixarenes and are found preferentially within instead of outside the cavity. This stoichiometry is evident in solid-state complexes by X-ray crystallography^{22,23} and solution NMR titrations,^{13,24,25} but has been assumed, without rigorous demonstration, in functional materials involving calixarene self-assembled monolayers^{26,27} and chromatographic stationary phases.^{28,29} The data presented here verify that guests adsorb on grafted calixarene materials with a 1:1 stoichiometry and absolute enthalpies greater (more favorable) than those for guest condensation. This enhanced interaction reflects the cooperative effect of several phenolic groups within a single calixarene, but this interaction only introduces binding selectivity among various aromatic guests that arises from non-specific van der Waals interactions.

The interactions of water with small hydrophobic cavities and pores less than 1 nm in diameter, such as those in grafted calixarenes, are of significant interest because of the changes in the behavior of water at these length scales, which remain less clear than interactions of water with convex hydrophobic surfaces.³⁰ Crystallography and other structural probes have shown that water interacts at close range with ostensibly hydrophobic cavities, such as highly polar³¹ or amphiphilic³² calixarenes and carbon nanotubes,³³ but to the best of our

knowledge, none of these studies has measured the energetics of these interactions. The stability of grafted calixarene binding sites in aqueous solution and in contact with a vapor phase allows for a comparison of isotherms for guests adsorbing from solution and vapor. The difference in adsorption behavior from these two phases allows the nature of the interactions of water with the cavity of grafted calixarenes to be rigorously probed.

Experimental Procedures

General Methods. A Varian Cary 400 Bio UV/vis spectrophotometer with a Harrick Praying Mantis accessory was used for diffuse reflectance measurements on solids. N₂ physisorption was performed on a Quantachrome Autosorb-6 instrument using 20 adsorption and desorption data points after degassing the samples for at least 8 h at 393 K. Solid-state ¹³C cross-polarized magic-angle spinning (CP/MAS) NMR spectra were measured at the Caltech Solid-State NMR Facility using a 500 MHz Bruker DSX500 spectrometer. Elemental analysis was performed by the Berkeley Microanalytical Lab using a Perkin–Elmer 2400 Series II combustion analyzer. Thermogravimetry (TGA) studies were conducted on a TA Instruments TGA 2950 system using synthetic air (30% O₂ and 70% N₂) at 1 cm³ s⁻¹ and a Pt sample pan. A temperature ramp of 0.08 K s⁻¹ was used up to a final temperature of 1073 K. Grafted calixarenes combusted in a narrow temperature range near 650 K. The weight loss above 523 K was used to measure the number of calixarenes grafted and was within 1 wt % of estimates obtained from carbon contents measured by combustion analysis.

Synthesis of Grafted Calixarene Materials. Toluene, pyridine, and triethylamine were freshly distilled from CaH₂ under N₂ before use. Mesoporous silica gel (Selecto Scientific, 6 nm diameter pores, 37–62 μm particle size, N₂ BET surface area of 500 m²/g) and an MCM41-type ordered mesoporous silica (Sigma–Aldrich, 2.7 nm diameter pores, N₂ BET surface area of 1100 m²/g) were used as supports. All other synthesis reagents were obtained at their highest available purity and used as received.

Toluene solutions (15 mL/g of silica) of calixarenes **1**, **2**, **4**, or phenol **3** with 1.2 equiv of triethylamine were refluxed 24 h with SiCl₄-treated silica^{34,35} using standard Schlenk line techniques and procedures previously described.³⁶ Excess C₁₂ alcohol CH₃(CH₂)₁₀-CH₂OH (10 g/g of silica) was added to a synthesis solution of **4**(15) without intermediate washing and then refluxed for at least another 24 h to synthesize **4**(15)-C₁₂OH with 0.72 alkyl chains/nm². Other materials were modified with chlorosilanes (CH₃)₃SiCl (TMSCl) or CF₃(CF₂)₅(CH₂)₂Si(CH₃)₂Cl (R_fSiCl) by evacuation at 500 K at <5 Pa for 24 h and cooling to ambient temperature in N₂. R_fSiCl (1.1 g/g of silica) was grafted onto **4**(15) from dilute pyridine solutions (50 mL/g of silica) to prepare **4**(15)-R_fSiCl with 0.36 fluorocarbon chains/nm². Under similar conditions, 1.6 chains/nm² were deposited on unmodified silica. Trimethylsilyl groups were grafted onto **4**(06) from a 50 mol % solution of TMSCl and [(CH₃)₃Si]₂NH (12 mL/g of silica). After the materials were stirred overnight with the species to be grafted (calixarene, alcohol, or silyl chloride), they were washed with boiling toluene and with polar solvents at ambient temperature and then dried in vacuum at ambient temperature. Grafted calixarene materials were also modified with CsCl, CaCl₂, MgSO₄, and other salts (3–6 equiv nm⁻²) by incipient wetness impregnation with their aqueous solutions and drying at <5 Pa and 383 K for 4 h. Full

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synthesis and post-synthetic modification details are given in the Supporting Information. Grafted calixarene surface densities were verified to be unchanged by post-synthetic modification with chlorosilanes using ^{13}C NMR spectroscopy of samples prepared with ^{13}C -labeled methoxy calixarene **4**.

Adsorption Measurement Procedures. Water was purified to 18 M Ω using a Barnstead Nanopure Infinity system and passed through a 0.2- μm filter before use. Benzene, toluene, and xylenes were purified before adsorption measurements as recommended³⁷ by washing with cold concentrated H_2SO_4 and distilling from CaH_2 . Nitrobenzene was extracted into NaOH (aqueous) and distilled from CaH_2 under reduced pressure. Solution concentrations were measured by UV spectrophotometry using a Varian Cary 400 Bio UV/vis system equipped with a 1 \times 1 Peltier accessory for temperature control and stirring on both sample and reference beams. Before adsorption from solution, all materials were suspended in H_2O , passed over a 10 μm nylon sieve to remove fines, which would have led to diffuse light scattering in aqueous suspensions, and dried in a vacuum at <5 Pa and 423 K. Adsorption uptakes were determined from the difference in the concentration of the adsorbing species in the liquid phase before and after adding solids.

Adsorption uptakes of water and aromatics from their vapor were measured volumetrically using an in-house cell design. Exposed surfaces within the adsorption system contained only glass and perfluorinated polymer. Pressures were measured with a differential pressure gauge (MKS Instruments Baratron 223B, 10 Torr full scale, ± 0.01 Torr). Before adsorption, samples were held at 383 K for 1 h in dynamic vacuum (<0.1 Pa) using an oil diffusion pump backed by a rotary pump, both isolated from the adsorption system by traps cooled with liquid N_2 . Samples were held at constant temperature using a Nichrome glocoil (Eagle 415, 220 V, 660 W) jacketed by a flow of ice-cooled air, a Love self-tuning controller, and a K-type thermocouple. The entire adsorption unit was placed in an air bath maintained at ~ 313 K. All uptakes were estimated by assuming that adsorbates behave as an ideal gas.

Adsorption Modeling Procedures. A Born–Haber thermodynamic cycle describing aqueous adsorption^{8,38} on calixarene–silica materials is shown in Figure 1A. Adsorption from the aqueous phase ($\Delta G_{\text{ad, aq}}$) is described as a sequence of hypothetical steps that (1) remove bulk water from the proximity of the calixarene ($\Delta G_{\text{desolv, C}}$), the guest ($\Delta G_{\text{desolv, g}}$), and the calixarene cavity (ΔG_{w}), (2) adsorb the guest (ΔG_{g}), and (3) restore water around the guest–calixarene complex ($\Delta G_{\text{solv, C}}$) and recondense water liberated from the calixarene cavity ($\Delta G_{\text{cond, w}}$). The vaporization of guest molecules from pure liquid into an ideal gas phase ($\Delta G_{\text{vap, g}}$) and the transfer of guests from pure liquid into aqueous solution at the specified temperature and pressure (ΔG_{sat}) are also included as a reference in Figure 1A. It is reasonably assumed that all net changes to the water shell upon desolvation/solvation of the calixarene and the complex occur near the calixarene cavities; thus, they are formally described by ΔG_{w} . This requires that the sum of all remaining solvation terms be zero ($\Delta G_{\text{desolv, C}} + \Delta G_{\text{solv, C}} = 0$). It is also reasonably assumed that the free energy of adsorption of guest from the hypothetical vapor phase (ΔG_{g}) equals the free energy of the directly observed vapor-phase adsorption ($\Delta G_{\text{ad, vap}}$). Solutions of these nonpolar hydrocarbons in water obey a linear (Henry's law) relation between solution concentrations and guest pressure in the vapor; measured constants describing this equilibrium agree with the ratio of the vapor pressure (p_0) and aqueous solution mole fraction (x_0) in three-phase equilibrium with pure liquid at atmospheric pressure.^{39,40} In the Born–Haber cycle of Figure 1A, $\Delta G_{\text{desolv, g}}$ describes this Henry's law equilibrium between vapor-phase guest and the aqueous solution. Values for the temperature-dependent Henry's law coefficients, p_0 and x_0 , are obtained from tabulated references.^{39–42} The proportionality between

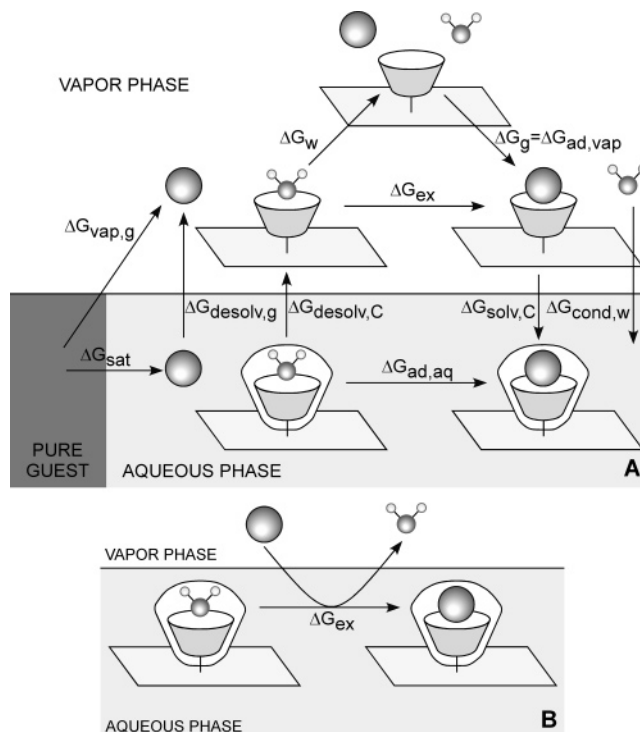


Figure 1. (A) Proposed Born–Haber thermodynamic cycle for adsorption of aromatic guests from an aqueous solution. All steps are described in the Experimental Procedures. (B) When adsorption uptakes are measured relative to a gaseous standard state and the host and complex solvation are assumed to be equal in magnitude, the Born–Haber cycle reduces to the exchange process shown.

the pressure of an ideal gas and the concentration of a solution exhibiting infinite dilution behavior results in the thermodynamic equivalence of p_0x_0/x_0 with pressure.^{39,40,43} For multilayer physisorption, x/x_0 (or the fractional concentration c/c_0) are thermodynamically equivalent to p/p_0 . Therefore, adsorption uptakes from vapor plotted against p/p_0 can be compared directly with those from aqueous solution as a function of c/c_0 . Using the assumptions described above and treating aqueous adsorption based on equivalent pressures, the thermodynamic cycle ultimately describes the exchange of water for a guest molecule (ΔG_{ex}), illustrated in Figure 1B. ΔG_{ex} is defined as

$$\Delta G_{\text{ex}} \equiv \Delta G_{\text{ad, aq}} - \Delta G_{\text{desolv, g}} = \Delta G_{\text{w}} + \Delta G_{\text{cond, w}} + \Delta G_{\text{ad, vap}} \quad (1)$$

Comparisons of adsorption free energies as ΔG_{ex} are based on a reference state of gas at standard temperature and pressure (STP), which removes effects of guest activity (solvation) known to dominate host/guest complexation processes in solution.^{44,45}

Adsorption data are described using multilayer Brunauer–Emmett–Teller (BET) isotherms, which, as in the case of Langmuir isotherms, require localized adsorption without lateral interactions on well-defined binding sites.⁴⁶ A modified BET equation, derived in the original study,⁴⁷ allows saturation surface densities and heats

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of adsorption to differ in the first, second, and subsequent adsorbed layers (eq 2)

$$\theta_A \equiv \frac{N_A}{N_C} = \frac{CX}{(1-X)} \left\{ \frac{1 + (\delta B - 1)(2X - X^2)}{1 + (C-1)X + (B-1)CX^2} \right\} \quad (2)$$

where C and B are given by

$$C = \exp\left(\frac{\Delta\Delta S_1}{R} - \frac{\Delta\Delta H_1}{RT}\right); \quad B = \exp\left(\frac{\Delta\Delta S_2}{R} - \frac{\Delta\Delta H_2}{RT}\right) \quad (3)$$

with differences in enthalpy and entropy between adsorption in the n th layer and in liquid-like multilayers denoted as $\Delta\Delta H_n$ and $\Delta\Delta S_n$, respectively. In what follows, these terms also carry subscripts “ex” or “vap” to denote adsorption from the aqueous phase (as a hypothetical vapor phase) or the vapor phase, respectively. For the materials studied, the first layer contains N_C calixarene adsorption sites described by the BET C constant and N_L is the capacity of the second and higher layers, exterior to the calixarenes and described by the BET B constant. N_A is the total number of adsorbed molecules, δ is the ratio of N_L/N_C , and X is the ratio c/c_0 or its thermodynamic equivalent p/p_0 . R is the ideal gas constant, and T is the adsorbent temperature in K.

For any given aqueous nitrobenzene concentration, the adsorption uptake on silica (per gram) is <5% of the uptake on grafted calixarenes [e.g., 1(23)]. Therefore, for aqueous adsorption, the constant C is much greater than B (≈ 1) and eq 2 becomes

$$\theta_A \equiv \frac{N_A}{N_C} = \frac{CX}{(1-X)} \left\{ \frac{1 + (\delta - 1)(2X - X^2)}{1 + (C-1)X} \right\} \quad (4)$$

For adsorption from vapor at $p/p_0 < 0.1$, background adsorption on passivated silica surfaces (*vide infra*) shows low heats of adsorption but large adsorption capacities ($\delta \gg 1$ and $C \gg B$) and eq 2 becomes

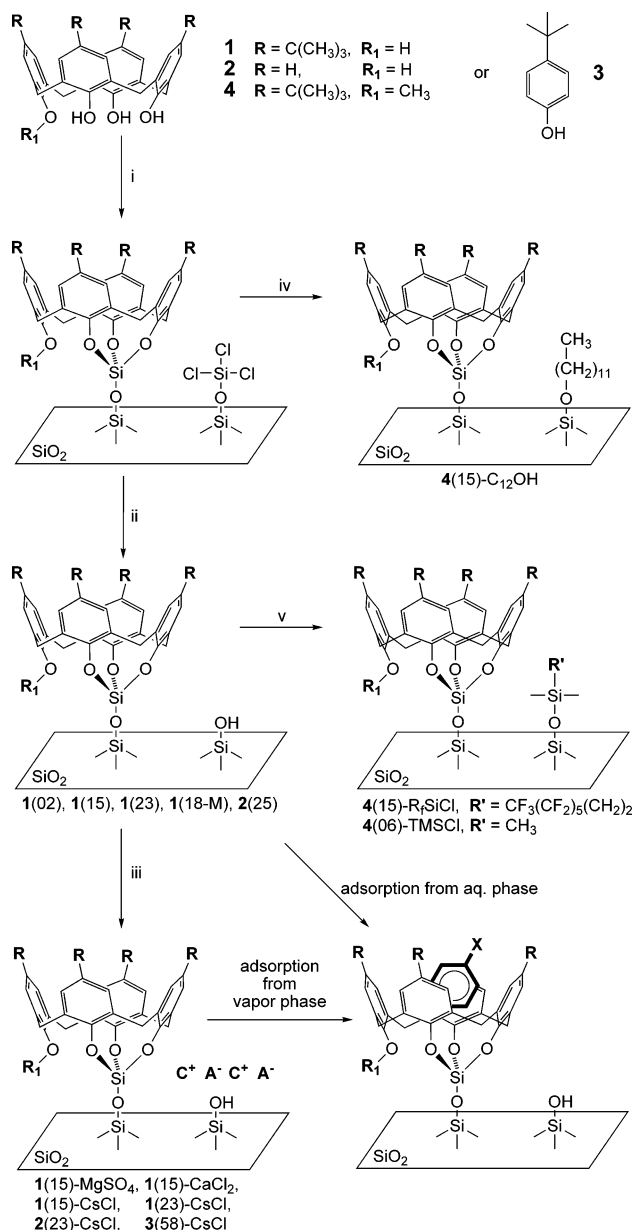
$$\theta_A \equiv \frac{N_A}{N_C} = \frac{CX}{1 + (C-1)X} + 2\delta BX \quad (5)$$

which includes additive contributions from strong binding on calixarene cavities at near-saturation coverages and adsorption on nonspecific surfaces that remain below saturation coverages throughout.

Results and Discussion

Structure of Grafted Calixarene Binding Sites. The grafting method in Scheme 1 leads to the rigid organization of calixarenes on silica surfaces up to ~ 0.25 calix nm^{-2} . This maximum surface coverage of grafted calixarenes is $\sim 40\%$ of that in compressed Langmuir–Blodgett monolayers¹⁹ or of that expected from calixarene single-crystal unit-cell dimensions.^{22,48–50} Experimental surface coverages at 40% of packed structures are consistent with random deposition without calixarene–calixarene interactions⁵¹ and are well below Si–OH surface densities (~ 1.7 OH nm^{-2})⁵² after treatment at 773 K. The method described in Scheme 1 leads to the highest reported immobilized calixarene surface densities³⁶ and exposes all immobilized calixarenes, in

Scheme 1. Materials Synthesis^{a,b}



^a Conditions: (i) add SiCl₄-treated silica to a toluene solution of calixarene and 1.2 eq of N(Et)₃ and reflux for 48 h; (ii) wash material with excess boiling toluene, MeOH, H₂O, MeOH, and Soxhlet extract in benzene; (iii) contact material with a minimum wetting volume of an aqueous solution of desired salt, for 24 h, and remove H₂O under 50 mTorr vacuum, at 383 K; (iv) without exposing the material to ambient atmosphere, add excess C₁₂H₁₇OH in toluene, reflux for 48 h, and wash as in (ii); (v) suspend the material in pyridine, add R'₃SiCl, reflux for 24 h under N₂ or suspend the material in 50:50 mol % TMSCl/HMDS solution, stir for 24 h at 323 K under N₂, and wash the material with toluene, MeCN, MeOH, H₂O, CHCl₃, and benzene Soxhlet. ^b Nomenclature and physical characterization of materials given in Table 1.

contrast with what may result in sol–gel co-condensation methods,⁵³ where calixarenes may reside in inaccessible regions.

Pore volumes and size distributions measured by N₂ physisorption at 77 K indicate that grafted calixarenes are evenly dispersed on the surface without detectable pore blocking in all samples. Calixarene grafting decreases silica pore volumes by ~ 1.1 nm³ per calixarene 1, consistent with calixarene dimensions

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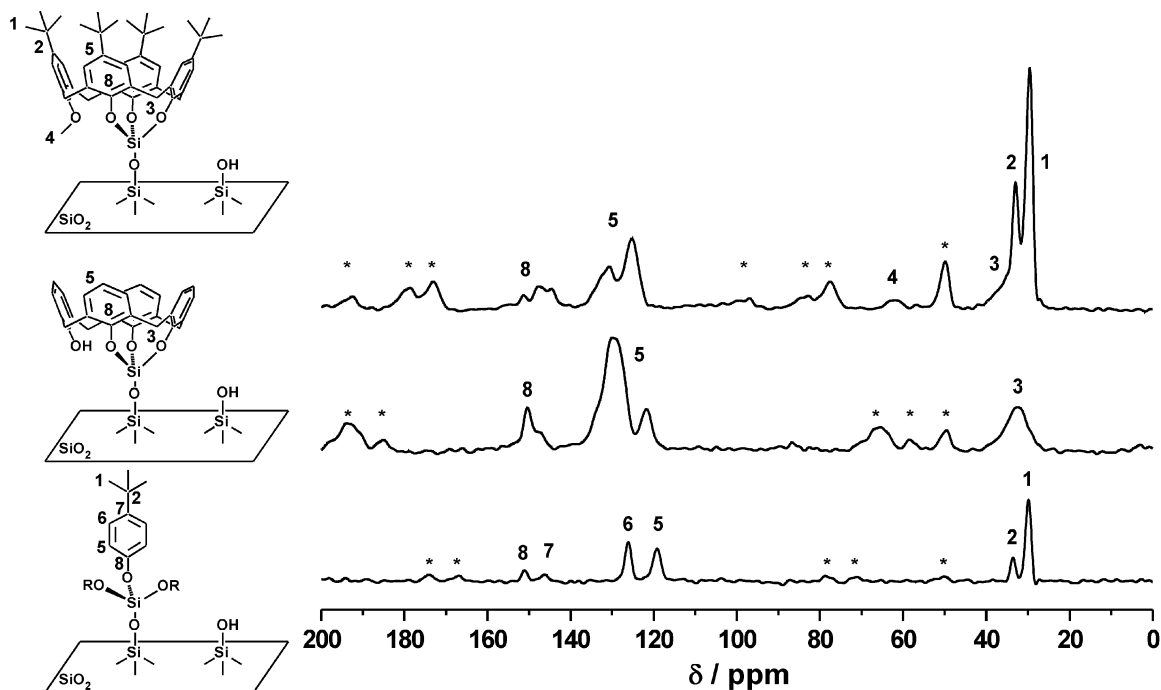


Figure 2. Solid-state ^{13}C CP/MAS NMR of **4**(17), top; **2**(25), middle; and **3**(58), bottom. Resonances labeled in adjacent structures. (*) Spinning sideband or resonance from surface methoxide created during the methanol wash. Resonances closely match solution spectra of the precursor calixarene given in the Supporting Information. The breadth of calixarene resonances **3** and **5** suggests that conformational flexibility is lower than in grafted phenol.

Table 1. Summary of Physical Characterization for Materials Synthesized^a

material	calixarene content		
	mmol g ⁻¹ ^b	wt % ^b	nm ⁻² ^c
1 (02)	0.013	0.8	0.02
1 (15)	0.118	7.6	0.15
1 (23)	0.167	10.8	0.23
1 (18-M) ^d	0.272	17.6	0.18
2 (25)	0.191	8.1	0.25
4 (15)-C ₁₂ OH	0.112	7.3	0.15
4 (06)-TMSCl	0.050	3.2	0.06
4 (15)-R _f SiCl	0.112	7.3	0.15
1 (15)-MgSO ₄	0.112	7.3	0.15
1 (15)-CaCl ₂	0.112	7.3	0.15
1 (15)-CsCl	0.112	7.3	0.15
1 (23)-CsCl	0.167	10.8	0.23
2 (23)-CsCl	0.178	7.6	0.23
3 (58)-CsCl	0.452	6.8	0.58

^a Except where noted, the support is mesoporous silica gel. ^b Per gram of total mass, before modifier addition. ^c Per N₂ physisorption surface area of unmodified support. ^d MCM41-type silica support.

from molecular models, single crystals,^{22,48–50} and compressed monolayers.¹⁹ Barrett–Joyner–Halenda (BJH) methods⁵⁴ indicate that pore radii decrease by ~1 nm after grafting at high surface densities [e.g., **1**(23)], also consistent with the dimensions of a grafted calixarene (Scheme 1). As previously noted, such samples show some N₂ physisorption in the microporous regime as a result of small voids between and within grafted calixarenes.³⁶ When H₂O physisorption at 303 K on **1**(23) is described by a standard BET isotherm, H₂O monolayer capacities, which reflect accessible silica surfaces, are ~10% lower than those on unmodified silica, even though calixarene *tert*-butyl groups occupy >40% of the available surface area based on measured calixarene surface densities. Only calixarene cone conformations allow the H₂O-accessible silica surface area to be larger than the

area occupied by the calixarenes, as illustrated by the solvent shell in Figure 1. Both N₂ and H₂O physisorption experiments show that all grafted calixarenes and the residual silica surface are accessible to small molecules.

The calixarenes are expected to be grafted covalently to silica via three attachment points, as in reactions of calixarene **1** with CH₃SiCl₃^{50,55} or SiCl₄^{48,56} in solution, which form tripodal Si-bridged structures. Such structures are rigid, both in their attachment to the surface and in their lack of internal conformational mobility, an assumption supported by the pronounced line broadening⁵⁷ observed in solid-state ^{13}C CP/MAS NMR spectra of grafted calixarenes (Figure 2). Aromatic and bridging methylene resonances **5** and **3**, respectively, are much broader than *tert*-butyl methyl lines, consistent with increasing rigidity as the structure approaches its anchor point to the silica surface. Also, resonance **5** is much broader for grafted calixarenes than for grafted *tert*-butyl phenol **3**, also consistent with less mobile phenolic units in grafted calixarenes. The rigid covalent attachment to silica dictates the calixarene conformation, independent of the solvent, which in principle enables adsorption to occur on identical sites, regardless of the prevalent solvent or vapor environment, and is expected to lead to stronger guest binding relative to a flexible cavity.¹⁷

Adsorption of Aromatics from Aqueous Solution. Parts A and B of Figure 3 show nitrobenzene adsorption uptakes (per nm² and per calixarene, respectively) from dilute aqueous solutions at 298 K on grafted calixarene **1** with surface densities of 0.02–0.23 nm⁻². These studies specifically probe whether adsorption uptakes of small aromatics reflect interactions with an isolated calixarene cavity, as in host/guest complexes of soluble calixarenes,^{13,58} or the binding properties of multiple calixarenes

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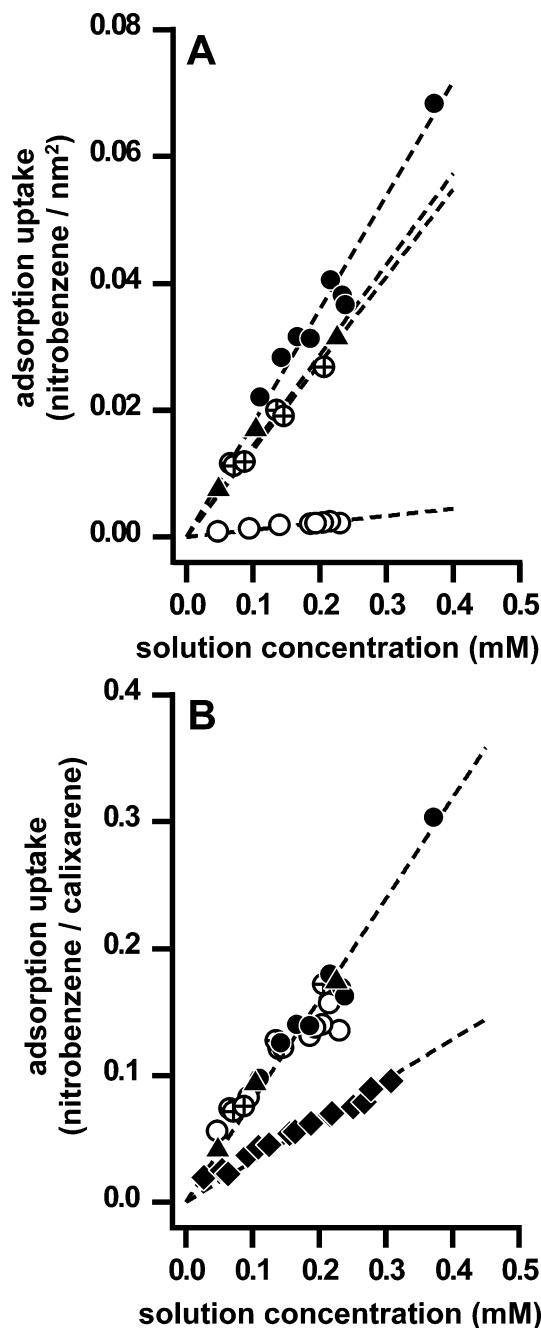


Figure 3. Aqueous adsorption uptakes on 1-SiO₂ materials and 2(25) given in (A) nitrobenzene per nm² silica and (B) nitrobenzene per calixarene. Linear regressions merge on a calixarene basis, consistent with a common host/guest stoichiometry for all surface densities of each calixarene. Calixarene 2 has fewer van der Waals contacts with nitrobenzene than calixarene 1, and the adsorption uptake of nitrobenzene is correspondingly decreased. (▲) 1(18-M), (●) 1(23), (⊕) 1(15), (○) 1(02), and (◆) 2(25).

in proximity, as in calixarene crystals^{59–61} or dense monolayers.¹⁵ Nitrobenzene adsorption uptakes in Figure 3A collapse to the

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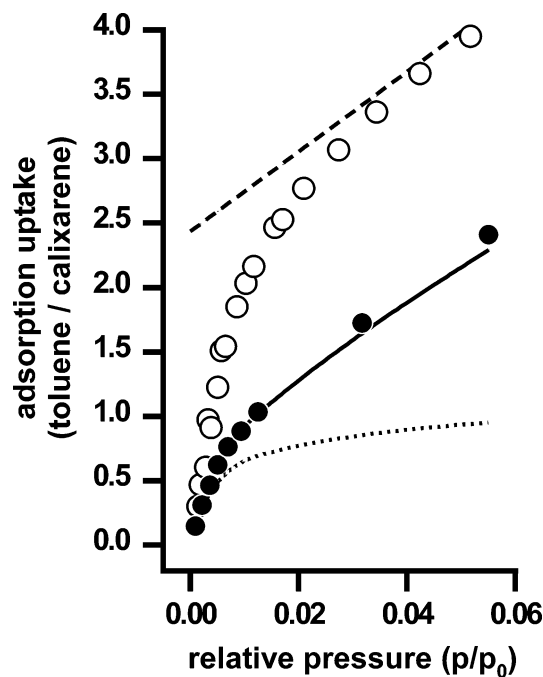


Figure 4. Vapor-phase toluene adsorption uptakes at 303 K on 1(23) (○) with linear extrapolation to 0 pressure (---) and uptakes on 1(23)-CsCl (●) with nonlinear regression to eq 5 (—) and with calixarene-only component of regression to eq 5 (⋯).

same isotherm for all materials when uptakes are normalized by the number of calixarenes (Figure 3B). This result indicates that the host/guest interactions are specific to the interior of calixarene cavities and that accessibility, host/guest stoichiometry, and interaction energies are independent of calixarene surface density. These data confirm that lateral interactions between adsorbed species do not influence adsorption properties, because the number of adsorption sites exo to the calixarene cavity increases as higher densities bring grafted calixarenes closer to each other on silica surfaces. The use of silica gel or MCM-41-type silica as a support did not influence adsorption uptakes, even though their pore structures differ, indicating that adsorption is intrinsic to calixarenes and insensitive to the nature of the silica surface or its interconnecting voids.

Adsorption on grafted calixarenes with *tert*-butyl (calixarene 1) or H (calixarene 2) upper rims confirms the specificity of adsorption on calixarene cavities. Figure 3B shows that the linear portion of the nitrobenzene adsorption isotherm on grafted calixarene 2(25) (H upper rim) is ~60% lower than on grafted calixarene materials 1-SiO₂ (*tert*-butyl upper rim). The stronger binding on grafted calixarene materials 1-SiO₂ is consistent with the reported complexation of toluene in chloroform solutions of calixarene 1¹³ and with the formation of solid-state inclusion complexes with calixarene 1,²² neither of which have been observed with calixarene 2.

Adsorption Uptakes of Aromatics from Vapor. Figure 4 shows that adsorption uptakes from toluene vapor on 1(23) exceed one toluene per calixarene at relatively low pressures ($p/p_0 < 0.005$). Simple linear extrapolation of higher pressure data ($0.05 < p/p_0 < 0.10$) back to the strongest adsorption sites yields a toluene/calixarene stoichiometry of >2 . This suggests that absorption into voids between grafted calixarenes is significant. Similar strong binding at interstitial sites was previously reported on resorcinarene-alkylsulfide SAMs supported on gold surfaces.¹⁵ Adsorption from the vapor phase directly measures ΔG_g in the Born-Haber thermodynamic cycle in Figure 1A, which allows for comparisons with aqueous adsorption uptakes, but

only for those cases in which both media lead to specific binding on calixarene cavities. Thus, the materials used for the vapor adsorption studies require post-synthetic modification for directing guests preferentially to the calixarene cavities, without additional contributions from silica surfaces or intercalixarene voids, to enable a rigorous analysis based on the thermodynamic cycle in Figure 1A.

New materials were developed to minimize the effect of interstitial adsorption sites by titrating surface silanols⁶² without introducing adsorption site heterogeneity.^{63–65} In this context, water is quite effective, because it interacts strongly with silanols via hydrogen bonding and renders them inert toward hydrocarbon adsorption from aqueous media. The reaction of 4-SiO₂ materials with surface-capping agents TMSCl,^{62,66} R_fSiCl,⁶⁷ or C₁₂OH³⁵ does not decrease adsorption uptakes at low pressures, apparently because of residual adsorption at defects in the surface layers (for C₁₂OH or R_fSiCl) or adsorption on a hydrophobic surface (for TMSCl). Incipient wetness impregnation with aqueous CsCl (6 equiv nm⁻²)⁶⁸ strongly decreases toluene adsorption uptakes on 1-SiO₂ materials (Figure 4), while retaining strong adsorption sites, as shown by a weak inflection point in the toluene adsorption curve at p/p_0 values of ~ 0.1 (see the Supporting Information). CaCl₂ is also effective at decreasing the adsorption uptakes, but MgSO₄ is not. After CsCl addition, N₂ physisorption pore volumes did not decrease more than expected from the volume of the CsCl present, indicating that inhibited adsorption reflects surface passivation rather than pore blocking. Salt impregnation is unlikely to influence hydrophobic grafted calixarene binding sites because of the unfavorable ion pair separation required to place a cation within a calixarene cavity.⁶⁹

The strong binding sites evident from the isotherm of Figure 4 must reflect grafted calixarene cavities as in the case of adsorption from the aqueous phase, as discussed below. First, CsCl added at surface densities of 3, 5, and 6 Cs/nm² to 1(15) all decrease toluene adsorption uptakes; these effects become slightly stronger as CsCl surface density increases, indicating that the salt inhibits adsorption and does not act itself as an adsorption site. Second, low-pressure toluene adsorption uptakes on 1(15)-CsCl (6 Cs/nm²) and 1(15)-CaCl₂ (6 Ca/nm²) are

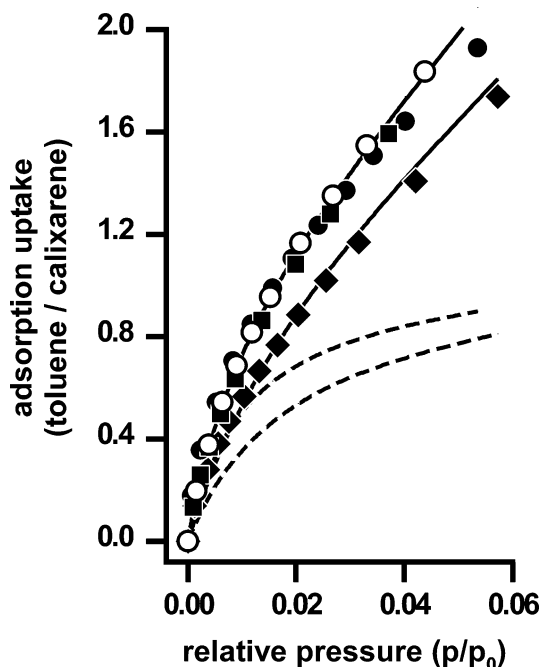


Figure 5. Toluene adsorption uptakes at 333 K on 1(15)-CsCl (○), 1(23)-CsCl (●), 2(23)-CsCl (◆), 3(58)-CsCl (■). Regression of experimental uptakes to eq 5 (—) and calixarene-only component of regression to eq 5 (---). For 3(58)-CsCl, 2,5 phenols are defined to be equivalent to a single grafted calixarene site.

identical. This confirms that CsCl does not form specific adsorption sites, because otherwise the interaction between the softer Cs⁺ cation and the soft π system of toluene would lead to different uptakes than the interaction with harder Ca²⁺ cations.⁷⁰ Calixarene binding sites are not blocked by CsCl, because adsorption uptakes remain constant (per calixarene) on salt-modified samples (Figure 5). Finally, the free energy describing toluene adsorption uptakes at 333 K on 2(23)-CsCl is $\sim 50\%$ lower than on 1(23)-CsCl (Figure 5). This result indicates that calixarene upper rims remain as accessible as during adsorption from aqueous solution.

Adsorption Enthalpies and Entropies of Aromatics from Aqueous Solution. Nitrobenzene adsorption uptakes on 1(15) and 2(25) were measured at 298, 318, and 338 K to determine enthalpies of adsorption from aqueous solution. Nitrobenzene isotherms on 1(15) are shown in Figure 6A. Temperature cycling shows that these adsorption processes are reversible and equilibrated and that uptake measurements do not reflect the dynamics of highly cooperative processes, such as those prevalent in calixarene clathrate decomposition^{59,71} or adsorption into close-packed calixarene crystals,^{61,72} whose temperature dependences reflect activation energies instead of adsorption enthalpies.⁷³ Non-equilibrium adsorption uptakes can also reflect the dynamics of hydrogen-bonding interactions, as can occur for resorcinarene hosts.⁷⁴

Adsorption enthalpies ($\Delta H_{ad,aq}$) and entropies ($\Delta S_{ad,aq}$) calculated from van't Hoff plots are shown in Table 2 for 1(15) and 2(25). Table 2 also includes selected literature values for

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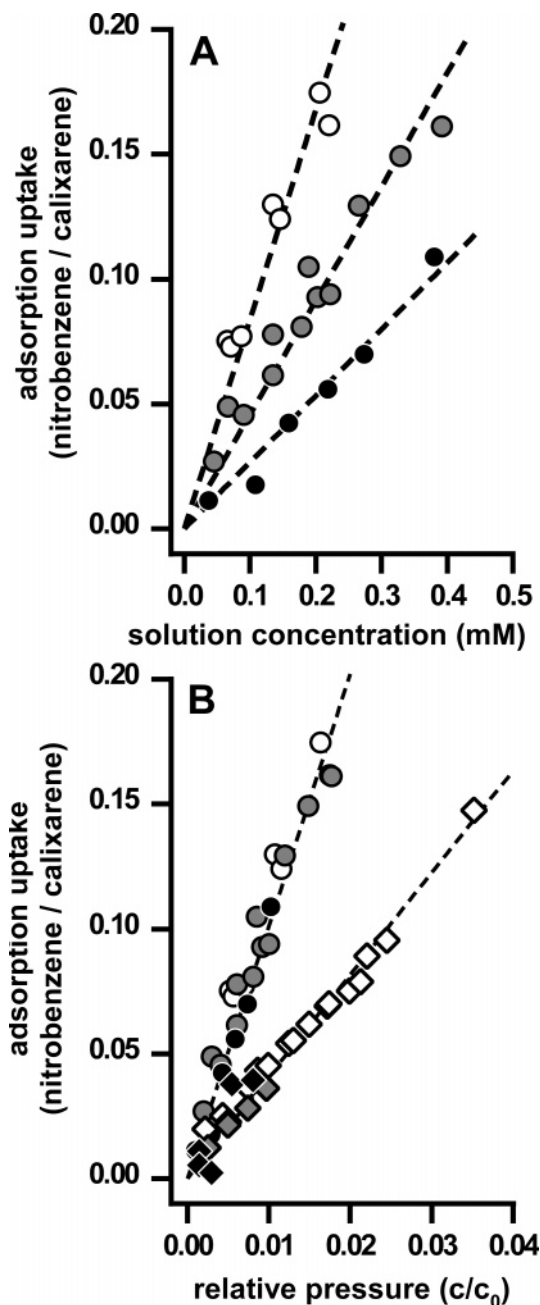


Figure 6. (A) Aqueous nitrobenzene adsorption uptakes on **1**(15) decrease with increasing temperature at 298 K (white), 313 K (gray), and 333 K (black). Van't Hoff plots of these data determine ΔH_{aq} and ΔS_{aq} in Table 2. (B) Nitrobenzene adsorption uptakes on **1**(15) (O) and **2**(25) (◇) at 298 K (white), 313 K (gray), and 333 K (black) at low relative concentrations (c/c_0 , see the text) are insensitive to temperature, indicating that $\Delta H_{\text{ex}} \sim \Delta H_{\text{cond,g}}$ ($\Delta\Delta H_{\text{ex}} \sim 0$).

complexation of small aromatics with water-soluble small molecules and engineered protein hosts. These adsorption energies describe the entire process of guest adsorption, including the effects of solvent rearrangement upon binding. The free energies of complexation of aqueous guests are slightly larger on grafted calixarenes than for dissolved small molecule hosts but smaller than for adsorption into the nonpolar cores of mutant T4 lysozyme proteins. This suggests that calixarene cavities provide a larger number of van der Waals contacts than these small molecule hosts but are unable to fully encapsulate a guest within a hydrophobic interior, as in the case of protein hosts. Also, complexation with β cyclodextrin has a favorable entropy change,^{75,76} but is unfavorable in these grafted calixarenes and

Table 2. Energies of Adsorption on Synthetic Materials and Representative Comparisons

material	adsorbate	C_{vap}^a	$\Delta\Delta H^a$ (kJ/mol)	$\Delta\Delta S^a$ (J/mol ⁻¹ /K)
1-CsCl	C ₆ H ₆	240	-19.9	-21.4
1-CsCl	C ₇ H ₈	236	-19.9	-21.5
3-CsCl ^b	C ₇ H ₈	236	-19.9	-21.5
1-CsCl	<i>p</i> -C ₈ H ₁₀	266	-19.9	-20.5
1-CsCl	<i>m</i> -C ₈ H ₁₀	267	-19.9	-20.5
2-CsCl	C ₆ H ₆	90	-17.9	-22.6
2-CsCl	C ₇ H ₈	115	-17.9	-20.6
2-CsCl	<i>p</i> -C ₈ H ₁₀	107	-17.9	-21.1
all	all	1.3 ^c	-0.7	0

material	adsorbate	C_{ex}^d	$\Delta\Delta H_{\text{ex}}^d$	$\Delta\Delta S_{\text{ex}}^d$
1	C ₆ H ₆	10	~0 ^e	
1	C ₇ H ₈	5	~0 ^e	
1	C ₆ H ₅ NO ₂	11	~0	+20
2	C ₆ H ₅ NO ₂	4	~0	+12

material	adsorbate	K_{aq}^f	ΔH_{aq}^f	ΔS_{aq}^f
1	C ₆ H ₆	310		
1	C ₇ H ₈	540		
1	C ₆ H ₅ NO ₂	820	-24.0	-24.5
2	C ₆ H ₅ NO ₂	410	-24.2	-33.3
SO ₃ -calix ⁹¹	C ₆ H ₆	21		
resorcin ²⁹	C ₆ H ₆	229		
terpy-Pd ⁹²	C ₁₄ H ₁₀	650		
β -CD ⁷⁵	C ₆ H ₆	170	-1.9	+36.3
lysozyme ⁸	C ₆ H ₆	5700	-26.5	-17.0

^a BET C_{vap} value given at 298 K, from regression of direct vapor adsorption uptakes to eq 5. ^b When considered to be 0.23 sites/nm² or 2.5 phenols/site. ^c BET B value from eq 5 at 298 K, common to all materials. ^d BET C_{ex} value given at 298 K, from regression of aqueous adsorption uptakes to eq 4. ^e There is no significant temperature dependence of K_{aq} within the limits of error, indicating $\Delta\Delta H_{\text{ex}} \sim 0$. Large standard deviations for these adsorbates above 298 K do not permit more quantitative statements. ^f Linear regression to adsorption uptakes from dilute aqueous solution ($c/c_0 < 0.2$), K (mole of uptake per mole of calixarene per molar solution), given at 298 K.

within T4 lysozyme cores,⁸ which requires losses in guest translational entropy to not be fully compensated by gains in the entropy of the solvent molecules detached upon guest binding. These results suggest that grafted calixarenes provide a more representative model binding site to mimic the thermodynamics of apolar cores in proteins or other isolated nonpolar binding sites than water-soluble small molecule hosts, such as cyclodextrins.

Specific and Nonspecific Binding Sites from Analysis of BET Isotherms. The adsorption uptakes of benzene, toluene, and nitrobenzene from aqueous solutions and of benzene, toluene, *m*-xylene, and *p*-xylene from vapor are described using a two-layer BET model (see the Experimental Procedures). Because adsorption isotherms do not and are not expected to exhibit plateau regimes that clearly indicate saturation behavior, nonlinear regression of isotherm data to the BET model was used to determine a self-consistent value of the host/guest stoichiometry and adsorption free energy of the calixarene sites for materials with a range of calixarene surface coverages. Equation 4 accurately describes adsorption uptakes from aqueous solutions for all guests at concentrations (c/c_0) between 0.001 and 0.6. Adsorption uptakes from the vapor are described by eq 5. For adsorption from both aqueous and vapor phases, optimal fits are obtained when saturation adsorption uptakes correspond to the number of calixarenes in each sample [for example, see Figures

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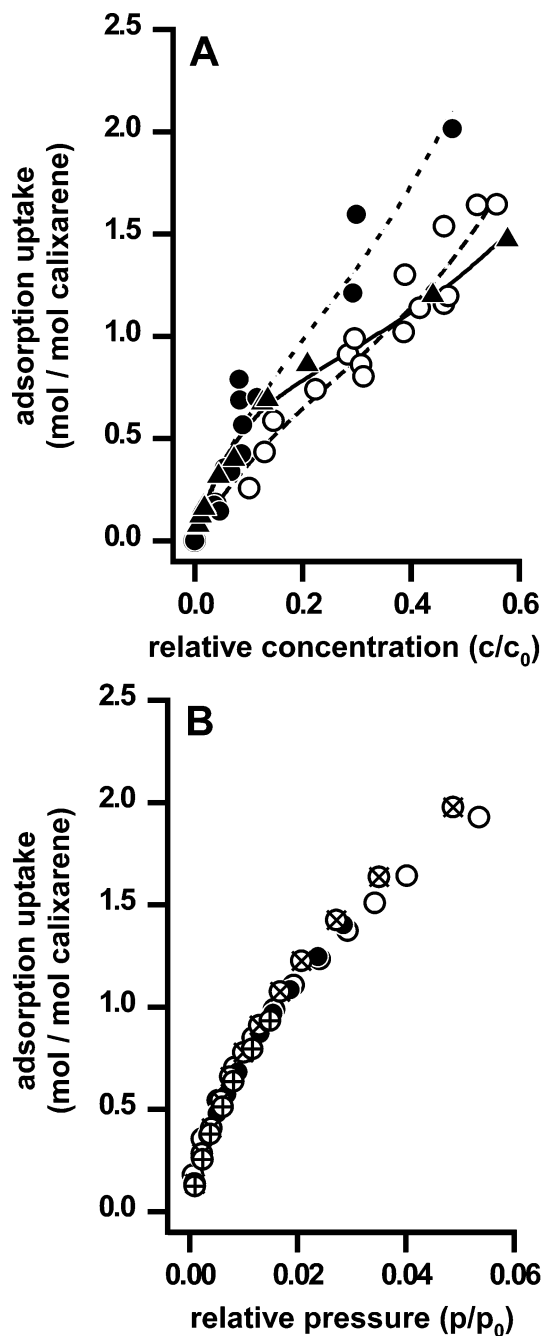


Figure 7. Adsorption uptakes of benzene (●), toluene (○), nitrobenzene (▲), *p*-xylene (⊗), and *m*-xylene (⊕) from (A) an aqueous solution at 298 K on 1-SiO₂ materials and (B) vapor at 333 K on 1(23)-CsCl. Points represent individual experiments, and solid lines are regressions to eq 4. The regressed values of *C* are in Table 2. In all cases, the monolayer capacity is defined *a priori* by the synthesized calixarene surface density.

4 and 5 (vapor) and Figure 7A (aqueous)]. Table 2 shows enthalpies ($\Delta\Delta H_{\text{ex}}$ and $\Delta\Delta H_{\text{vap}}$), entropies ($\Delta\Delta S_{\text{ex}}$ and $\Delta\Delta S_{\text{vap}}$), and free energies for adsorption (BET constants C_{ex} and C_{vap}) relative to those for liquid-like multilayer formation. Uptakes from aqueous solution and vapor are denoted by the subscripts ex and vap, respectively. Note that in all cases, adsorption free energies are calculated from a vapor reference state, which allows for adsorption isotherms to be compared directly for different guests and from either medium, independent of the effect of solvation on the guest. For adsorption from solution and vapor, the ability to describe all adsorbates and calixarene surface concentrations by a BET model with the number of adsorption

sites defined *a priori* by the composition of the materials confirms the assertion that adsorption on grafted calixarene materials occurs specifically and with 1:1 stoichiometry on calixarene sites with uniform binding properties. This is in distinct contrast with other host cavities immobilized on supports, which can lead to adsorption uptakes that are orders of magnitude larger than the number of hosts (e.g., adsorption of aqueous pyrene alkyl amides on polystyrene-immobilized deep cavity resorcinarenes⁷⁷) or to an increasing adsorption stoichiometry as the number of solvent-cast calixarene⁷⁸ or resorcinarene layers increases,⁷⁹ leading ultimately to swelling of films and guest uptakes similar to bulk condensation phenomena in cast polymers.^{27,80} Thus, adsorption on grafted calixarenes measures interactions for individual host/guest complexes, instead of ensemble-averaged values on nonuniform assemblies of binding sites. This allows, in turn, rigorous characterization and a comparison of grafted calixarene binding sites with other isolated host/guest sites, particularly those in solution.

The Effect of Guest Structure on the Adsorption Uptake of Aromatics. Benzene, toluene, and nitrobenzene adsorb from aqueous solutions at 298 K on 1-SiO₂ with binding constants (K_{aq}) of 310, 540, and 820 M⁻¹, respectively, up to c/c_0 values of 0.2. Intrinsic interactions between host and guest were investigated by removing guest solvation and condensation effects through comparisons of free energies ΔG_{ex} and ΔG_{vap} based on actual and virtual pressures for adsorption from vapor and solution, respectively (see the Experimental Procedures). Figure 6B shows nitrobenzene adsorption uptakes on 1(15) and 2(25) at 298, 318, and 338 K as a function of c/c_0 , instead of as a function of the absolute concentration (Figure 6A). In this form, the adsorption of nitrobenzene on 1(15) and 2(23) is independent of temperature, a finding that requires that the net exchange of solvent water for vapor nitrobenzene at calixarene cavities be equal to the heat of condensation of nitrobenzene.⁸¹ The entropy of complexation with grafted calixarene is favorable (positive) compared to condensation, because of the removal of bound water from calixarene cavities upon binding of guests from aqueous solutions. Throughout the concentration range examined, regressions to eq 4 for benzene, toluene, and nitrobenzene aqueous adsorption uptakes lead to BET *C* constants of 11 ± 4 , 5 ± 2 , and 10 ± 2 (dimensionless), respectively. This method of comparing the adsorption of various molecules removes guest desolvation effects but introduces a systematic uncertainty in the *C* values (up to 50%) because of large variability in tabulated solubility data as a function of temperature.⁴⁰ These *C* values correspond to exchange free energies that differ by no more than 2 kJ/mol from each other and are <6 kJ/mol (~20%) larger than free energies of condensation for each respective adsorbate. The relatively close correspondence and small absolute value of the *C* values suggest that the adsorption energetics of these three molecules from aqueous media on calixarene materials cannot be meaningfully distinguished from each other by any parameter other than their respective vapor pressures.

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(81) The relative free energy of adsorption onto 1-SiO₂ versus 2-SiO₂, ($\Delta\Delta G_{\text{ex},1} - \Delta\Delta G_{\text{ex},2}$) - ($\Delta G_{\text{ad},\text{aq},1} - \Delta G_{\text{ad},\text{aq},2}$), is thermodynamically required to be 0 for any given guest because eq 1 states that for any given calixarene, ($\Delta\Delta G_{\text{ex},1} - \Delta\Delta G_{\text{ex},2}$) - ($\Delta G_{\text{ad},\text{aq},1} - \Delta G_{\text{ad},\text{aq},2}$) = ($\Delta G_{\text{ad},\text{aq},1} - \Delta G_{\text{desolv},g} + \Delta G_{\text{vap},g} - \Delta G_{\text{ad},\text{aq},2} + \Delta G_{\text{desolv},g} - \Delta G_{\text{vap},g}$) - ($\Delta G_{\text{ad},\text{aq},1} - \Delta G_{\text{ad},\text{aq},2}$) = 0. The experimentally observed value of 0.6 kJ/mol determines the precision of the isotherm fitting.

Adsorption uptakes from the vapor phase can be measured with greater accuracy than from the aqueous phase and are unaffected by uncertainties in Henry's law constants because contacting pressures are measured directly. These isotherms confirm that grafted calixarenes discriminate among small aromatic molecules based only on their tendency to form van der Waals contacts, which also account for their differences in saturation vapor pressure. The adsorption uptakes of benzene, toluene, *p*-xylene, and *m*-xylene at 303 K on **1**(23)-CsCl are identical when expressed in terms of their respective p/p_0 values (Figure 7B). Similar trends in adsorption isotherms were measured at other temperatures and on **2**(23)-CsCl. $\Delta\Delta H_{\text{vap}}$ values were found to depend upon the calixarene upper rim substituents but not on the guest identity or the calixarene surface density. Measured values of $\Delta\Delta S_{\text{vap}}$ were unaffected by the calixarene upper rim, surface density, or guest identity.

Within the family of substituted aromatics investigated, adsorption uptake selectivity is primarily determined by the saturation vapor pressure of the guest. This family includes electron-donating (CH_3) and electron-withdrawing (NO_2) substituents and several positional isomers of methyl benzenes. This study does not show any evidence for π stacking⁸² or $\text{CH}-\pi$ interactions⁸³ beyond those that may be present in the pure condensed phase of each guest; these results therefore require that adsorption on grafted calixarenes be controlled by general dispersive interactions. These interactions become stronger as the number of van der Waals contacts surrounding the cavity increases, as evident from the effects of changes in the upper rim structure from **H** (calixarene **2**) to *tert*-butyl (calixarene **1**). These results are also in contrast to those in several studies that have observed xylenes positional isomer selectivity,⁶⁵ which indicates that this selectivity must originate in interactions other than those with an isolated calixarene cavity. In general, the adsorption measurements presented here do not rule out the existence of specific contacts between host and guest, as seen in solution by NMR spectroscopy or in solid crystals,^{22,24,49} but the data require that these interactions be much weaker than nonspecific interactions present during guest condensation.⁸³ These data also indicate that directional preferences for host/guest structures must arise predominately from concerted effects of multiple van der Waals contacts, as suggested recently.²⁴

Significance of Functional Group Preorganization in Grafted Calixarene Cavities. The adsorption of guests on grafted calixarenes is compared to guest condensation processes and to adsorption on an unorganized monomeric grafted phenol surface to assess the role of calixarene functional group organization on adsorption. The absolute enthalpy of adsorption from vapor on grafted calixarene materials is larger (more negative) than the condensation enthalpy (Table 2). This increase in magnitude arises because of the simultaneous, cooperative⁸⁴ interactions of all four calixarene subunits and guest. Figure 5 compares toluene adsorption uptakes on **3**(58)-CsCl with those on **1**(15)-CsCl and **1**(23)-CsCl to address the degree of cooperativity in calixarene binding sites more directly. To compare uptakes on all materials on a per site basis, each site on high surface density grafted phenol material **3**(58)-CsCl must be equivalent to 2.5 phenols. The number of phenols per site is likely to be a strong function of the phenol surface density, as expected for materials without pre-organized binding sites. The value of 2.5 phenols/site indicates that adsorption interactions between calixarenes and guests can be described by concerted van der Waals interactions with several

surface species contained within a calixarene subunit. Both condensation and adsorption reflect van der Waals interactions among aromatic molecules, but adsorption processes benefit from the calixarene cavity, which acts as a pre-formed condensation nucleus within which many van der Waals interactions can occur simultaneously.

Adsorption of Aromatics from the Vapor Phase: Comparison to Aqueous. Understanding the specific interactions of water with grafted calixarene cavities requires that solvent and complexation effects on host/guest interactions are investigated separately. This is essential to understand host/guest interactions at surfaces that are also accessible to the solvent and to verify models describing interactions of water with hydrophobic patches on a protein surface,⁸⁵ on solvent-accessible hydrophobic pockets,⁸⁶ and at interfaces between hydrophobic surfaces.⁸⁷ In general, these processes are complex because of the possibility of solvent- and guest-induced host reorganization in both synthetic and protein-based systems and because of strong effects of guest solvation on the total free energy of complexation.⁴⁴ These complications are overcome here by the fact that the grafted calixarene binding site is rigid and identical in aqueous solution and vapor phase. This property enables direct comparisons of adsorption isotherms from aqueous solution and vapor phase based on rigorous activity and chemical potential concepts. The differences between the free energies for adsorption from aqueous solution and vapor reflect the energetics of the interactions between water and calixarenes ($\Delta G_{\text{ex}} - \Delta G_{\text{ad,vap}} = \Delta G_{\text{w}} + \Delta G_{\text{cond,w}}$, eq 1). From the adsorption data for each host/guest pair (Table 2), ΔG_{w} is larger (more positive) than the vaporization of bulk water by 8–10 kJ/mol calixarene ($\Delta\Delta G_{\text{w}} = 8\text{--}10$ kJ/mol) at 298 K. Relative to condensation, all guests adsorb with similar entropies and enthalpies on a given calixarene material; therefore, guest-averaged values are used in the discussion that follows. The subtraction of aqueous exchange and vapor adsorption enthalpies and entropies shows that $\Delta\Delta H_{\text{w}} = \sim 20$ kJ/mol and $\Delta\Delta S_{\text{w}} = \sim 40$ J mol⁻¹ K⁻¹ for calixarene **1** and $\Delta\Delta H_{\text{w}} = \sim 18$ kJ/mol and $\Delta\Delta S_{\text{w}} = \sim 30$ J mol⁻¹ K⁻¹ for calixarene **2**. A strong enthalpy–entropy compensation for the calixarene–water interaction is evident from these data and significantly alters the apparent interactions of a calixarene with aqueous guest. For example, while the difference in the free energy for guest adsorption on the two calixarenes, $\Delta\Delta G_{\text{calix}} = \Delta G_1 - \Delta G_2 = -2.2 \pm 0.3$ kJ/mol for aqueous exchange and for vapor adsorption at 298 K, $\Delta\Delta G_{\text{calix,ad,vap}}$ is dominated by enthalpy, whereas $\Delta\Delta G_{\text{calix,ex}}$ is dominated by entropy due to the contribution from solvent water. Also, the close similarity between adsorption from the two phases requires that ΔG_{w} be similar on calixarenes **1** and **2** and confirms the thermodynamic consistency among these data.⁸⁸ We note that $\Delta\Delta H_{\text{w}}$ values above resemble those previously measured for the desolvation of small alkane molecules (19–25 kJ/mol).⁸⁹ This coincidence supports the premise that only the interior of the calixarene is desolvated throughout the net exchange process, instead of the exterior calixarene surface, which is also exposed to the solvent.

This analysis shows that interactions of water with calixarene cavities via van der Waals interactions are favorable and similar in energy to interactions of aromatic guests with such cavities. The enthalpy associated with the removal of water required to

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bind small guest molecules leads to weaker binding from solution relative to the vapor phase by energies amounting to nearly 50% more than the vaporization enthalpy of water. It is likely that similar effects of competitive water adsorption are responsible for previous claims of enthalpy differences for adsorption from aqueous solution and vapor phase data on energetically heterogeneous binding sites;⁴³ these effects are also likely to prevail in other systems and specifically on protein surfaces.² The enthalpy of water desorption during binding of guests from aqueous solution is balanced in part by the entropy of water desorption, which is also about 50% greater than the entropy gain from water vaporization. These positive entropies and enthalpies of water desorption provide clear physical evidence that the interface between liquid water and the calixarene cavity possesses significant attractive interactions relative to the water–vapor interface.

Conclusions

We report synthetic protocols that lead to grafted calixarenes with diverse upper rims containing uniform cavities accessible to aromatic guest molecules adsorbing from aqueous and vapor phases. The uniform and rigid nature of these structures allows a rigorous assessment of solvent effects on reversible host/guest complexation and direct comparisons with single-site systems, such as synthetic hosts or protein cavities in solution. Aromatics adsorb from aqueous solutions onto grafted calixarenes more strongly than they form complexes with water-soluble hosts, because of a larger hydrophobic surface area accessible to make van der Waals contacts with guest molecules and the absence of solubilizing groups near the hydrophobic calixarene cavity, which would strengthen the interactions with water that need to be broken before adsorption can occur. The interactions of small aromatics with a given cavity scales with the condensation enthalpy of the guest, suggesting that binding is mediated by van der Waals interactions instead of CH– π or other types of specific interactions, some of which have been previously inferred from crystallography. Host/guest complexation is favored relative to condensation because of the pre-organization of phenolic subunits in calixarene cavities.

We have the first quantitative evidence that adsorption on calixarenes localized at interfaces can occur with 1:1 stoichiometry as in extended crystals or in solution, but only if the surrounding surface is passivated by the solvent or another agent. We have discovered a synthesis method that allows for sequential deposition of alcohols, silanes, and salts to alter the bulk surface properties but leaves the calixarene cavities intact and accessible. We have also shown that the guest adsorption capacity is defined *a priori* by the materials synthesis and becomes stronger as the groups surrounding the calixarene cavity increase in size. These

results suggest that calixarene-based adsorbents will be most useful as a scaffold for arranging functional groups around a well-defined number of adsorption sites.^{64,90}

The direct comparison of adsorption of aromatics from aqueous solution and from the vapor phase allows an assessment of the effect of bulk water on host/guest complexation at hydrophobic sites. The difference between the free energy of adsorption from the aqueous (as virtual vapor) and the vapor phase shows that bulk water is removed from *tert*-butyl calixarene **1** cavities with an additional enthalpy and entropy somewhat less than half of that required for vaporization of water. The significant enthalpy of the interaction of hydrophobic pockets with water observed here has implications for the understanding of biological phenomena driven by van der Waals interactions at solvent-accessible hydrophobic surfaces and cautions that the competitive adsorption of water may be common in other open hydrophobic cavities of broad interest.

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Supporting Information Available: Full details for all materials syntheses; a direct comparison of ¹³C NMR of immobilized **4**(17) and soluble **4** (Figure S1); a comparison of solid-state ¹H MAS NMR of **4**(17), **2**(25), and **3**(58) (Figure S2); a comparison of solid-state ¹³C MAS NMR of ¹³C-labeled **4**(06) and **4**(06)-TMSCl (Figure S3); vapor phase H₂O physisorption isotherms on **1**(23) and SiO₂ (Figure S4); representative 77 K N₂ physisorption isotherms on **1**(15), **1**(15)-CsCl, and the starting mesoporous silica gel (Figure S5); a correlation between occluded N₂ physisorption pore volume and calixarene loading (Figure S6); a correlation between N₂ physisorption pore volume and CsCl surface density (Figure S7); a comparison of vapor toluene adsorption at 303 K on **1**(15) modified with CsCl at surface densities of 0, 3, 5, and 6 eq nm⁻² (Figure S8); and a comparison of vapor toluene adsorption at 303 K on **1**(23), **4**(15)-R₃SiCl, **4**(15)-C₁₂OH, **4**(06)-TMSCl, **1**(15)-MgSO₄ (6 eq nm⁻²), **1**(15)-CsCl (6 eq nm⁻²), and **1**(15)-CaCl₂ (6 eq nm⁻²) (Figure S9). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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