Acid Catalysis in Basic Solution: A Supramolecular Host Promotes Orthoformate Hydrolysis

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sublattice that is correlated with the stacking of adjacent Al layers (*16*). This slight deviation in oxygen positions can be schematically seen in the projected structure model of Fig. 1A. If these deviations were a spatially fixed part of the structure, the motion of a single partial would result in a stacking fault in the oxygen sublattice. In the present slip model, the O plane in between slip planes 1 and 2 is sheared by only one partial, and thus a stacking fault on the O sublattice would be produced if we assume rigid O layers. However, the deviations are related to the positions of the Al atoms, neighboring O, atoms and vacant sites sandwiched between the O layers. Because the perfect Al stacking is preserved after the dislocation motion, the O sublattice can also preserve a perfect stacking sequence by an appropriate small modification in the O atom positions. It is important to note that these two partial motions are not independent in our proposed model. Both partials move simultaneously on adjacent {0001} basal planes to complete the perfect dislocation slip. A total basal dislocation is thus considered to possess two atomic slip planes. This core structure is expected to dissociate after the dislocation stops moving and form two partials, consistent with our observations in Fig. 2.

We propose that basal slip in α-Al_2O_3 is controlled by the partial dislocations that dissociate from the perfect $\frac{1}{3}\langle 11\bar{2}0\rangle$ dislocation. The structure of these partials is based on our low-temperature observations, in which each partial core is terminated by Al and O columns, respectively, but the total dislocation preserves Al_2O_3 stoichiometry. Bilde-Sørensen *et al*. (*5*) also proposed a stoichiometric core model, but the slip plane (located at the midplane on the puckered Al layer) is not consistent with our images. Our images clearly show that the termination of both partials is located in between the Al and O layers at low temperature. Our results represent a definitive starting point for realistic atomic-level modeling of slip processes, dislocation generation, and their effects on the mechanical properties of α-Al_2O_3. Also, the present results will provide a crucial check for future theoretical calculations of dislocations in complex oxides.

We have provided experimental evidence that locally nonstoichiometric structures are allowed in crystals with strong ionic character. Simultaneous HAADF and bright-field STEM imaging with aberration correction is a powerful tool for observing such localized defect structures, even in very complex crystals. The possibility for atomic-scale characterization of dislocation core structures will assist our understanding of dislocation activity and its effects on the electrical, optical, and mechanical properties of complex, multicomponent materials.

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Acid Catalysis in Basic Solution: A Supramolecular Host Promotes Orthoformate Hydrolysis

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Although many enzymes can promote chemical reactions by tuning substrate properties purely through the electrostatic environment of a docking cavity, this strategy has proven challenging to mimic in synthetic host-guest systems. Here, we report a highly charged, water-soluble, metal-ligand assembly with a hydrophobic interior cavity that thermodynamically stabilizes protonated substrates and consequently catalyzes the normally acidic hydrolysis of orthoformates in basic solution, with rate accelerations of up to 890-fold. The catalysis reaction obeys Michaelis-Menten kinetics and exhibits competitive inhibition, and the substrate scope displays size selectivity, consistent with the constrained binding environment of the molecular host.

Synthetic chemists have long endeavored to design host molecules capable of selectively binding slow-reacting substrates and catalyzing their chemical reactions. Whereas synthetic catalysts are often site-specific and require certain properties of the substrate to insure catalysis, enzymes are often able to modify basic properties of the bound substrate such as pK_a (where K_a is the acid dissociation constant) in order to enhance reactivity. Two common motifs used by nature to activate otherwise unreactive compounds are the precise arrangement of hydrogen-bonding networks and electrostatic interactions between the substrate and adjacent residues of the protein (*1*). Precise arrangement of hydrogen bonding networks near the active sites of proteins can lead to well-tuned pK_a matching (*2*) and can result in pK_a shifts of up to eight units, as shown in bacteriorhodopsin (*3*). Similarly, purely electrostatic interactions can greatly favor charged states and have been responsible for pK_a shifts of up to five units for acetoacetate decarboxylase (*4*). Attempts have been made to isolate the contributions of electrostatic versus covalent interactions to such pK_a shifts; however, this remains a difficult challenge experimentally. This challenge emphasizes the importance of synthesizing host molecules that, like enzyme cavities, can enhance binding of small molecular guests and, in a few cases, catalyze chemical reactions (*5*–*9*).

Supramolecular assemblies with available functional groups have been used to generate solution-state pK_a shifts of up to two pK_a units (*10*–*13*) and to catalyze chemical reactions (*14*, *15*). Synthetic hosts often rely on hydrogen bonding or ion-dipole interactions for guest inclusion, and numerous studies have investigated the effects of charge on guest binding affinities in supramolecular host-guest systems (*16*, *17*). We report here a synthetic supramolecular host assembly that relies exclusively on electrostatic and hydrophobic interactions for thermodynamic stabilization of protonated

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substrates. As nature has exploited pK_a shifts to activate otherwise unreactive substrates toward catalysis, this stabilization is exploited to promote acid-catalyzed hydrolyses in strongly basic solution.

During the past decade, the Raymond group has reported the formation and guest-hosting properties of supramolecular assemblies of the stoichiometry M_4L_6 [M is Ga^{III} (**1**), Al^{III}, In^{III}, Fe^{III}, Ti^{IV}, or Ge^{IV}; L is *N,N′-bis*(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene] (*18*, *19*). These components self-assemble in solution to form tetrahedral clusters with chiral metal ions at the vertices and bridging ligands spanning each edge (Fig. 1). The strong mechanical coupling of the ligands transfers chirality from one metal vertex to the others, thereby leading exclusively to ΔΔΔΔ or ΛΛΛΛ configurations with respect to the vertices. These enantiomers are stable, noninterconverting, and resolvable (*20*). The metal-ligand assembly **1** is able to encapsulate a wide variety of small monocationic guests in a 300 to 500 $Å^3$ cavity protected from the bulk solution. The naphthalene walls render the interior hydrophobic, whereas the tetra-anionic ligands in combination with the trivalent metal centers confer a 12^- overall charge to the assembly. As a host, **1** stoichiometrically mediates (*21*, *22*) as well as catalyzes (*5*, *23*) several important organic and organometallic reactions. In addition, it stabilizes reactive guests, such as the tropylium cation (*24*), phosphine-acetone adducts (*25*), and iminium cations (*26*), all of which rapidly decompose in water and are only stable under anhydrous or extremely acidic conditions.

The binding strength of monocationic guests prompted our investigation into the ability of **1** to thermodynamically drive the monoprotonation of guest molecules within the cavity. Neutral guests could then be either stoichiometrically or transiently protonated to promote acid-catalyzed reaction on encapsulation. To test our hypothesis, we added a variety of amines and phosphines to solutions of **1** in D_2O. Upon addition of *N,N,N′,N′*-tetramethyl-1,4-diaminobutane (**2**) or *N,N,N′,N′*-tetraethyl-1,2-diaminoethane (**3**), upfield nuclear magnetic resonance (NMR) resonances characteristic of encapsulation were observed, corresponding to a 1:1 host-guest complex. Similarly, two-dimensional ^{1}H nuclear overhauser effect spectroscopy (NOESY) (fig. S1) shows strong through-space correlation between the naphthalene protons of the assembly and the encapsulated guest (*27*).

In order to confirm that these weakly basic compounds were being encapsulated in their conjugate acid forms, we added an isostructural phosphine, 1,2-*bis*(dimethylphosphino)methane (**4**) to **1** and probed by using ^{31}P NMR spectroscopy. As with both amines, new upfield resonances corresponding to $[\mathbf{4}\text{-}H^+\subset \mathbf{1}]^{11-}$ (⊂ denotes encapsulation) were observed in both the ^{1}H NMR and the ^{31}P NMR spectra. In D_2O, the proton-decoupled phosphorus ($^{31}P\{^1H\}$) NMR spectrum showed a 1:1:1 triplet with spin-spin H-P coupling constant ($^1J_{DP}$) = 75 Hz. In H_2O, the undecoupled ^{31}P NMR spectrum showed a doublet ($^1J_{HP}$ = 490 Hz) corresponding to a one-bond P-H coupling that definitively establishes binding of a proton to phosphorus. Because similarly substituted amines and phosphines exhibit analogous base strengths, by inference the encapsulated amines must be protonated as well, even at high pH.

For the amines encapsulated in **1**, the magnitude of the effective shift in basicity was investigated by monitoring 1:1 host guest complexes as a function of pH. In order to confirm that the encapsulated amines were exchanging with the amines in free solution and that **1** was

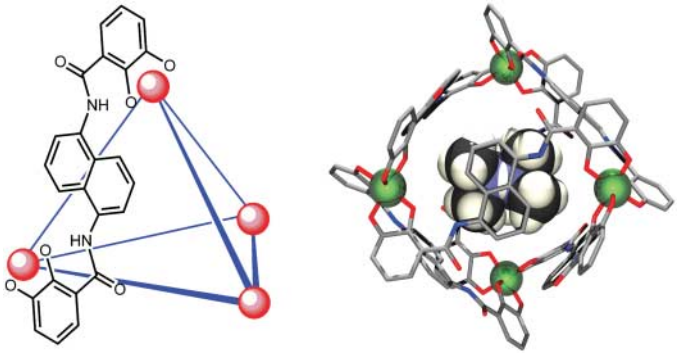

Fig. 1. (**Left**) A schematic representation of the host M_4L_6 assembly. Only one ligand is shown for clarity. (**Right**) A model of $[\mathbf{2}\text{-}H^+ \subset \mathbf{1}]^{11-}$; hydrogen atoms on the host assembly are omitted for clarity.

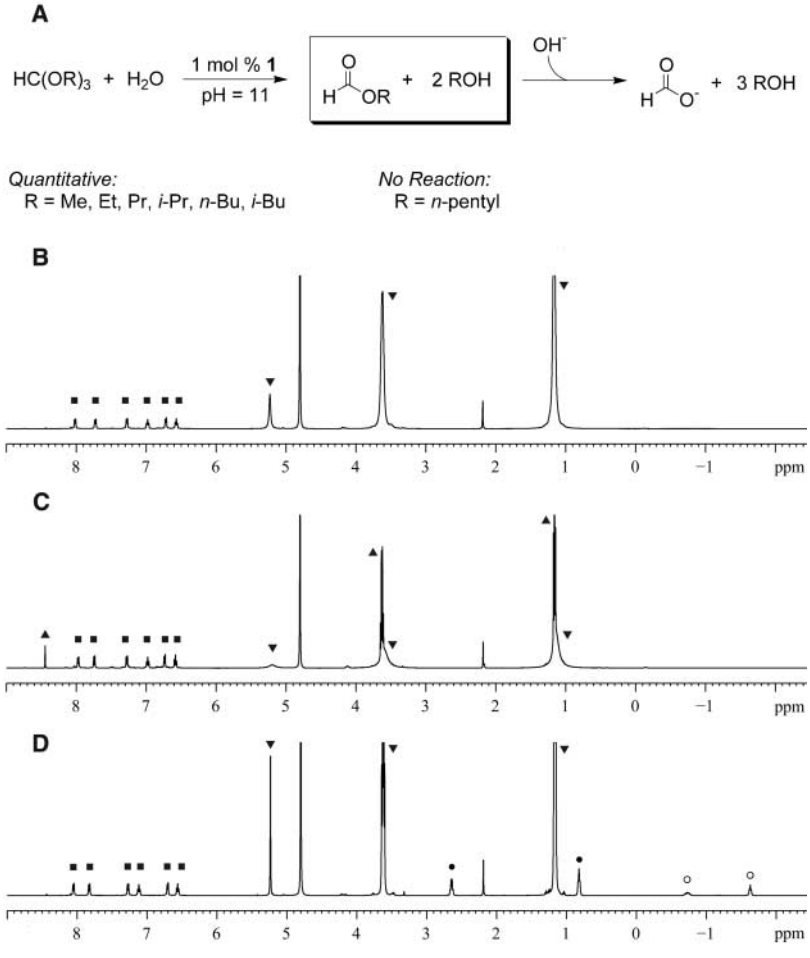

Fig. 2. (**A**) Reaction and substrate scope for orthoformate hydrolysis in the presence of catalytic **1**. Bu, butyl; Me, methyl; Pr, propyl. (**B** to **D**) All spectra taken with 50 equivalents (equiv.) of triethyl orthoformate with respect to **1** at pD = 11.0, 100 mM K_2CO_3, 22°C, in D_2O. (B) Initial spectrum. (C) Spectrum after 60 min. (D) Spectrum of **1** with 2 equiv. NEt_4^+ after 60 min. Molecule **1** represented by ■; $HC(OEt)_3$, ▼; NEt_4^+, ● for exterior and ○ for interior, and product HCO_2H, ▲.

not acting as a kinetic trap, we measured the guest self-exchange rates of the encapsulated amines (*28*) by using the selective inversion recovery (SIR) method (*29*) and found the amines to be exchanging on the NMR time scale [for **2**, k_{320K} = 0.24(3) s^{-1}; for **3**, k_{320K} = 0.13(2) s^{-1}] (*30*). We carried out the SIR experiments at five different temperatures from 300 K to 340 K to extract the activation parameters (fig. S3). The activation parameters for guest exchange for **2** were $\Delta G^{\ddagger}_{298}$ (standard Gibbs energy of activation) = 19(2) kcal mol^{-1}, $\Delta H^{\ddagger}$ (standard enthalpy of activation) = 10.8(9) kcal mol^{-1}, and $\Delta S^{\ddagger}$ (standard entropy of activation) = –28(4) entropy units (e.u.) and for **3** were $\Delta G^{\ddagger}_{298}$ = 19.9(8) kcal mol^{-1}, $\Delta H^{\ddagger}$ = 16.7(6) kcal mol^{-1}, and $\Delta S^{\ddagger}$ = –10.9(6) e.u. These values are consistent with those for the self-exchange activation parameters of tetraalkylammonium cations encapsulated in **1**, suggesting that the same exchange mechanism is present (*31*). Upon monitoring 1:1 host-guest solutions of $[\mathbf{2}\text{-}H^{+} \subset \mathbf{1}]^{11-}$ and $[\mathbf{3}\text{-}H^{+} \subset \mathbf{1}]^{11-}$ at different pHs, the free energies of binding ($-\Delta G°$) for the amines were found to be 5.2(5) kcal mol^{-1} and 4.8(4) kcal mol^{-1}, respectively. Heating the host-guest complexes to 75°C for 24 hours and returning the sample to room temperature did not change the ratio of encapsulated to free guest, confirming that the thermodynamic equilibrium had been reached. Although the pK_a of **3**-H^{+} is 10.8 in free solution, stabilization of the protonated form by **1**, which can be calculated as the product of the pK_a and the binding constant of the protonated amine, shifts the effective basicity to 14.3 (*32*). This dramatic shift highlights the substantial stabilization of the protonated species over the neutral species upon encapsulation in the highly charged cavity (*33*).

We next sought to apply this host-induced shift in effective basicity to promote reaction chemistry. We focused on the hydrolysis of orthoformates, $HC(OR)_3$ (where R is an alkyl or aryl group), a class of molecules responsible for much of the formulation of the Brønsted theory of acids almost a century ago (*34*). Although orthoformates are readily hydrolyzed in acidic solution, they are exceedingly stable in neutral or basic solution (*35*). However, we found that in the presence of a catalytic amount of **1** in basic solution, triethyl orthoformate is quickly hydrolyzed ($t_{1/2}$ ~ 12 min, pH = 11.0, 22°C) to the corresponding formate ester, HC(O)(OR), and finally to formate, HCO_2^- (*36*). We monitored the reaction by ^{1}H NMR spectroscopy and observed that the resonances of host **1** shifted upon substrate addition, suggesting that **1** is intimately involved in the reaction. The substrate C-H resonance broadens to $\nu_{1/2}$ = 14.3 Hz compared with the nonencapsulated $\nu_{1/2}$ = 3.2 Hz, which is suggestive of fast guest exchange. Increasing the concentration of **1** to 80 mM makes the encapsulated substrate observable (fig. S3). With a limited volume in the cavity of **1**, substantial size selectivity was observed in the orthoformate hydrolysis, with orthoformates smaller than tripentyl orthoformate being readily hydrolyzed with 1 mole percent of **1** (Fig. 2).

To further establish that the interior cavity of **1** was catalyzing the hydrolysis, we explored the propensity of a strongly binding guest, NEt_4^+ (where Et is ethyl) [$-\Delta G° = 6.20(8)$ kcal mol^{-1}], to inhibit substrate binding. As expected, addition of NEt_4^+ to the solution completely inhibited the hydrolysis of orthoformates. In the presence of NEt_4^+, the orthoformate methine resonances sharpened to $\nu_{1/2}$ = 3.4 Hz, confirming lack of encapsulation.

We probed the reaction mechanism by using triethyl orthoformate as the substrate at pH = 11.0 and 50°C. First-order substrate consumption was observed under stoichiometric conditions (fig. S4). Working under saturation conditions (see below), kinetic studies revealed that the reaction is also first-order in proton concentration and first-order in the concentration of **1** while being 0th-order in substrate (fig. S4). When combined, these mechanistic studies establish that the rate law for this catalytic hydrolysis of orthoformates by host **1** obeys the overall termolecular rate law: $rate = k[H^+][\text{Substrate}][\mathbf{1}]$ but under saturation conditions reduces to $rate = k'[H^+][\mathbf{1}]$.

We conclude that the neutral substrate enters **1** to form a host-guest complex, leading to the observed substrate saturation. We considered the possibility that saturation is due to complete protonation of substrate outside of the assembly; however, it would not be possible to attain saturation at pH = 11, because protonated orthoformates have estimated pK_a values of about –5 (*30*). Similarly, we considered that protonation of the interior of the assembly was the first step in the mechanism; however, this mechanism would require a binding constant of H^+ in the assembly to be greater than 10^{10}, which is not attainable. In the next step of the cycle, the encapsulated substrate is protonated, presumably by deprotonation of water, and undergoes two successive hydrolysis steps in the cavity, liberating two equivalents of the corresponding alcohol.

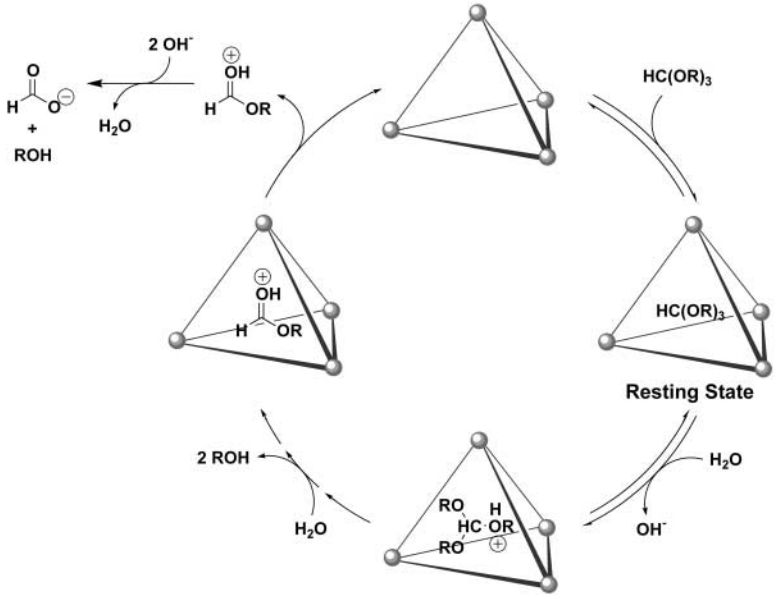

Fig. 3. Mechanism for catalytic orthoformate hydrolysis in the presence of catalytic **1**.

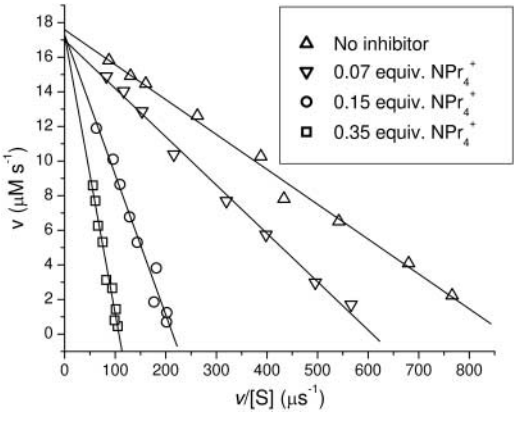

Fig. 4. Eadie-Hofstee plot showing competitive inhibition of the hydrolysis of $HC(OEt)_3$ by NPr_4^+ in H_2O, pH = 11.0, 50°C, and 4.0 mM **1**.

Lastly, the protonated formate ester is ejected from **1** and further hydrolyzed by base in solution (Fig. 3) (*37*).

The reaction mechanism in Fig. 3 shows direct parallels to enzymatic pathways that obey Michaelis-Menten kinetics because of an initial pre-equilibrium followed by a first-order rate-limiting step. Lineweaver-Burk analysis (fig. S5) using the substrate saturation curves affords the corresponding Michaelis-Menten kinetic parameters of the reaction. Representative Michaelis-Menten parameters for triethyl orthoformate ($V_{max} = 1.79 \times 10^{-5}$ M s^{-1}, $K_M = 21.5$ mM, and $k_{cat} = 8.06 \times 10^{-3}$ s^{-1}, where V_{max} is the maximum velocity of the reaction, K_M is the Michaelis constant, and k_{cat} is the turnover rate of the bound substrate) and triisopropyl orthoformate ($V_{max} = 9.22 \times 10^{-6}$ M s^{-1}, $K_M = 7.69$ mM, and $k_{cat} = 3.86 \times 10^{-3}$ s^{-1}) show substantial rate acceleration over the background reaction. When compared to the background hydrolysis reactions under the same reaction conditions (triethyl orthoformate $k_{uncat} = 1.44 \times 10^{-5}$ s^{-1} and triisopropyl orthoformate $k_{uncat} = 4.34 \times 10^{-6}$ s^{-1}), the rate accelerations (k_{cat}/k_{uncat}) for triethyl orthoformate and triisopropyl orthoformate are 560 and 890, respectively. Further analysis of the Michaelis-Menten kinetic parameters yielded additional information about the catalytic reaction. Assuming a fast pre-equilibrium with respect to k_{cat}, K_M is essentially the dissociation constant of the encapsulated neutral substrate. In order to compare how efficiently **1** catalyzes the hydrolysis of different substrates, the specificity factor (k_{cat}/K_M) can be examined. This parameter corresponds to the second-order proportionality constant for the rate of conversion of preformed enzyme-substrate complex, in this case [orthoformate ⊂ **1**]$^{12-}$, to product, thus providing a measure of the effectiveness with which two substrates can compete for the same site. Triethyl orthoformate and triisopropyl orthoformate have specificity constants of 0.37 M^{-1} s^{-1} and 0.50 M^{-1} s^{-1}, respectively, showing that triisopropyl orthoformate is more efficiently hydrolyzed by **1**.

Also characteristic of enzymes that obey Michaelis-Menten kinetics is that suitable inhibitors can compete with the substrate for the enzyme active site, thus leading to inhibition. The binding of an inhibitor to the enzyme active site prevents the substrate from entering and impedes the reaction. If the inhibitor binds reversibly to the enzyme active site, then the substrate can compete for the substrate and at suitably high concentrations will completely displace the inhibitor, leading to competitive inhibition. In order to test for competitive inhibition for the hydrolysis of orthoformates with **1**, we measured the rates of hydrolysis of triethyl orthoformate in the presence of a varying amount of the strongly binding inhibitor NPr_4^+ [$-\Delta G° = 2.7(2)$ kcal mol^{-1}]. The lower binding constant of NPr_4^+ with respect to NEt_4^+ facilitates the competitive binding experiments by allowing for the weakly binding substrate, $HC(OEt)_3$, to more readily compete for the binding cavity of **1**. By varying the concentration of substrate for each amount of inhibitor, we compared the saturation curves with use of an Eadie-Hofstee plot (Fig. 4) (*38*, *39*). The saturation curves intersect on the *y* axis, signifying that at infinite substrate concentration the maximum reaction velocity is independent of the amount of inhibitor, confirming competitive inhibition. If NPr_4^+ were competing for a different site than the active site of **1** responsible for the catalytic hydrolysis, such as an exterior ion-pairing site, then the saturation curves in the Eadie-Hofstee plot would be parallel. Back calculation of the binding constant of the NPr_4^+ inhibitor affords $-\Delta G° = 2.8(1)$ kcal mol^{-1}, which is consistent with the known affinity of this guest.

Using synthetic hosts to modify the chemical properties of encapsulated substrates was used to greatly enhance the reactivity of orthoformates and promote the acid catalyzed hydrolysis in basic solution. Similar strategies could be used to hydrolyze other acid-sensitive molecules in which the charged transition state of the reaction can be stabilized by a molecular host. The size selectivity in synthetic molecular hosts is a property often used by nature but rarely incorporated into standard homogeneous or heterogeneous catalysis. This type of selectivity could be used to differentiate reactive sites of a substrate which would otherwise exhibit equivalent reactivity toward standard organic, organometallic, or inorganic catalysts. Such strategies would be synthetically useful for common organic protecting groups such as acetals or ketals and could also be applied to more biologically relevant substrates such as amides or phosphate esters, furthering the analogy to enzymatic systems.

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32. Formally, this is a shift in the pK_a of the amine, but because we are unable to observe the neutral amine guest inside of **1**, this is more accurately referred to as an effective shift in basicity.
33. Examination of crystal structures of **1** with various guests shows that the catechol oxygens are not accessible to a bound guest, thus removing the possibility that hydrogen bonding between **1** and the guest is taking place. Furthermore, examination of NOEs between **1** and the guest reveals strong through-space interactions between the guest and naphthyl protons but not between the guest and catechol protons (fig. S1).
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37. After the initial catalyzed step inside of **1**, any of the intermediates can be hydrolyzed by either acid or base; however, we have not observed any intermediates free in solution.
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