Supporting Online Material for

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

Michael D. Pluth, Robert G. Bergman,* Kenneth N. Raymond*

*To whom correspondence should be addressed. E-mail: rbergman@berkeley.edu (R.G.B.); raymond@socrates.berkeley.edu (K.N.R.)

DOI: 10.1126/science.1138748

This PDF file includes:

Materials and Methods
Figs. S1 to S5
References
Supporting Online Material for

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

Michael D. Pluth, Robert G. Bergman,* Kenneth N. Raymond*

*To whom correspondence should be addressed.
E-mail: bergman@cchem.berkeley.edu (R.G.B.)
raymond@socrates.berkeley.edu (K.N.R.)

Experimental

General Procedures. All NMR spectra were obtained using Bruker DRX-500 or AV-500 MHz spectrometers at the indicated frequencies. Chemical shifts are reported as parts per million (δ) and referenced to residual protic solvent peaks. Suitable 13C{1H} spectra for the host-guest complexes could not be obtained after 8000 scans with a pre-scan delay of 2 seconds and all 13C{1H} spectra were recorded using a 2D DEPT-HSQC experiment. 31P{1H} NMR spectra were recorded at 202 MHz and were referenced to trimethylphosphate (1.67ppm). The following abbreviations are used in describing NMR couplings: (s) singlet, (d) doublet, (t) triplet, (q) quartet, b (broad), m (multiplet). The temperature of all variable temperature NMR experiments was calibrated with methanol or ethylene glycol standards. The binding constants for each amine were measured in H2O using the Watergate solvent suppression sequence at 25 °C at three different pH’s (10.5, 11.0, 11.5). Selective Inversion Recovery (SIR) experiments were performed at constant temperature using a 10 second delay time between experiments. (I-2) Data points for each Selective Inversion Recovery experiment were measured from 0.0005 seconds to 18 seconds in 42 increments. In all cases, the efficiency of the inversion pulse
was greater than 70%. The raw data were fit using CIFIT and all uncertainties in rate constants were reported as 3x the uncertainty generated by CIFIT. (3) Determination of the activation parameters for guest self-exchange were determined from Eyring analysis using the rate data obtained from the SIR experiments over a temperature range of 40 °C.

**Materials.** Orthoformates were either purchased from a commercial supplier or prepared by thermal alcoholysis of triethyl orthoformate and fractionally distilled through a 12-inch Vigreux column followed by distillation over powdered 3Å molecular sieves. (4) All orthoformates were stored under N₂ until use. The host assemblies K₁₂[Ga₄L₆] and Na₁₂[Ga₄L₆] were prepared as described in the literature and precipitated with either acetone or ether. (5)

**General Procedure for Amine/Phosphine Encapsulation** In an N₂ glovebox, 15mg of K₁₂Ga₄L₆ were added to an NMR tube at which point 0.5mL of D₂O was added. The amine (1.5-2 equiv.) was added by syringe and the NMR tube was shaken for 30 seconds.

**Binding Constant Determination**

A 1:1 solution of 1 and the desired amine was prepared in an N₂ glovebox using 20mg of the K₁₂Ga₄L₆ assembly in 0.5mL of H₂O. Samples were prepared in 100mM K₂CO₃ buffer at three different pH’s (10.5, 11.0, 11.5). The interior and exterior guest peaks were integrated to determine the binding constants of the protonated amines using the following formula. Each measurement was repeated three times at 25.0 °C.
\[ K_a = \frac{[SH^+ \subset 1]10^{-pK_a}}{[S][1]10^{-\mu pH}} \]

[bis(dimethylphosphino)methane-H\(^+\) \(\subset\) Ga\(_4\)L\(_6\)]\(^{11-}\)

\(^1\)HHhhddsfH NMR (500 MHz, D\(_2\)O): \(\delta\) 7.96 (bs, 12H, aryl), 7.86 (bs, 12H, aryl), 7.25 (bd, 12H, aryl), 7.02 (bd, 12H, aryl), 6.84 (bs, 12H, aryl), 6.59 (bs, 12H, aryl). Guest: -0.89 (dd, \(^2J_{PH} = 31.5\) Hz, \(^3J_{HH} = 15.0\) Hz, 2H, CH\(_2\)), -1.62 (d, \(^2J_{PH} = 31.5\) Hz, 12H).

\(^3\)P\(_{\{^1\}H}\) (D\(_2\)O, 202 MHz): \(\delta\) 32.1 (t, \(^1J_{PD} = 74.9\) Hz). \(^3\)P (D\(_2\)O, 202 MHz): \(\delta\) 32.1 (tm, \(^1J_{PD} = 74.8\) Hz, \(^2J_{PH} = 14.2\) Hz). \(^3\)P\(_{\{^1\}H}\) (H\(_2\)O, 202 MHz): \(\delta\) 34.0 (s). \(^3\)P (H\(_2\)O, 202 MHz): \(\delta\) 34.0 (dm, \(^1J_{PH} = 489\) Hz, \(^2J_{PH} = 14.4\) Hz).

\([N,N,N',N'-tetramethyl-1,4-butanediamine-H\(^+\) \(\subset\) Ga\(_4\)L\(_6\)]^{11-}\)

\(^1\)HHhhddsfH NMR (500 MHz, D\(_2\)O): \(\delta\) 7.93 (d, \(J = 8.0\) Hz, 12H, aryl), 7.86 (d, \(J = 8.5\) Hz, 12H, aryl), 7.34 (d, \(J = 7.5\) Hz, 12H, aryl), 7.06 (t, \(J = 8.5\) Hz, 12H, aryl), 6.80 (d, \(J = 7.5\) Hz, 12H, aryl), 6.64 (bs, 12H, aryl). Guest: -0.42 (s, 6H, N(CH\(_3\))\(_2\)), -0.86 (s, 6H, N(CH\(_3\))\(_2\)), -1.18 (s, 4H, CH\(_2\)), -1.44 (bd, \(J = 20\)Hz, 4H, CH\(_2\)). \(^{13}\)C\(_{\{^1\}H}\) NMR (125 MHz, D\(_2\)O): \(\delta\) 54.2 (CH\(_2\)), 39.8 (CH\(_3\)), 22.2 (CH\(_2\)).

\([N,N,N',N'-tetraethylethylenediamine-H\(^+\) \(\subset\) Ga\(_4\)L\(_6\)]^{11-}\)

\(^1\)HHhhddsfH NMR (500 MHz, D\(_2\)O): \(\delta\) 8.01 (bs, 12H, aryl), 7.74 (bs, 12H, aryl), 7.34 (bs, 12H, aryl), 7.00 (bs, 12H, aryl), 6.75 (d, \(J = 7.5\) Hz, 12H, aryl), 6.61 (bs, 12H, aryl). Guest: -0.57 - -0.64 (bm, 12H, N-CH\(_2\)), -1.12 (s, 12H, CH\(_3\)). \(^{13}\)C\(_{\{^1\}H}\) NMR (125 MHz, D\(_2\)O): \(\delta\) 46.7 (CH\(_2\)), 42.9 (CH\(_2\)), 9.4 (CH\(_3\)).

**Analysis of the Rate Law**

*Kinetic analysis for catalyzed hydrolysis reaction with M\(_4\)L\(_6\)\(^{12-}\) assembly*
\( \subset \) denotes encapsulation

\[
S + I + H^+ \xrightleftharpoons[k_i]{k_{-i}} [S \subset I] + H^+ \xrightleftharpoons[k_{-t}]{k_t} [SH^+ \subset I] \xrightarrow{k_i} P + I + H^+
\]

Applying the steady state analysis on \([S \subset I]\)

\[
\frac{+d[S \subset I]}{dt} = k_i[S][I] + k_{-t}[SH^+ \subset I] \quad \quad \frac{-d[S \subset I]}{dt} = k_{-i}[S \subset I] + k_t[S \subset I][H^+]
\]

\([I]_{tot} = [I] + [S \subset I] + [SH^+ \subset I]

\[
k_i[S][I]_{tot} - [S \subset I] - [SH^+ \subset I] + k_{-t}[SH^+ \subset I] = k_{-i}[S \subset I] + k_t[S \subset I][H^+]
\]

Solving for the concentration of \([S \subset I]\)

\[
[S \subset I] = \frac{k_i[S][I]_{tot} - [SH^+ \subset I]}{k_{-i} + k_t[H^+] + k_{-i}[S]}
\]

Taking \([SH^+ \subset I]\) to be small with respect to \([S \subset I]\) we get

\[
[S \subset I] = \frac{k_i[S][I]_{tot}}{k_{-i} + k_t[H^+] + k_{-i}[S]}
\]

The overall rate law for product formation of the original equilibria is

rate = \(k_3[SH^+ \subset I]\)

\([SH^+ \subset I] = k_3[S \subset I][H^+] - k_{-2}[SH^+ \subset I] - k_3[SH^+ \subset I]

\([SH^+ \subset I] = \frac{k_3[S \subset I][H^+]}{1 + k_{-2} + k_3}

Substituting the expression for \([S \subset I]\) from above, we are left with

\[
rate = \frac{k_i k_2 k_3[S]_{tot}[H^+]}{(1 + k_{-2} + k_3)[k_{-i} + k_t[H^+] + k_{-i}[S]]}
\]

However, saturation in \([H^+]\) is not observed, which implies that \(k_2 \ll k_1\) and requires a fast pre-equilibrium, which is consistent with Michaelis-Menten kinetics and competitive inhibition.
References


Figure S1 $^1$H 2D NOESY of $[2-\text{H}^+ \subset 1]^{11-}$ in D$_2$O, 22 °C, with 100 ms mixing time. The strong cross peaks between the naphthalene protons of 1 and the guest protons of 2-H$^+$ show strong through-space correlation indicative of encapsulation.
Figure S2 Eyring plot for the determination of activation parameters for $[\text{2-H}^+ \subset \text{1}]^{11-}$ (A) and $[\text{3-H}^+ \subset \text{1}]^{11-}$ (B).
Figure S3  (A) $^1$H NMR (500 MHz, H$_2$O) showing HC(OEt)$_3$ free in solution.  (B) $^1$H NMR (500 MHz, H$_2$O) showing the encapsulation of HC(OEt)$_3$ in an 80mM solution 1, pH = 11, 22 °C. The encapsulated guest resonances were confirmed by 1D NOE experiments as well as exchange cross peaks with free HC(OEt)$_3$ in solution.
Figure S4 (A) pD rate dependence of the hydrolysis of HC(OEt)₃ in D₂O, pD = 11.0, 100 mM K₂CO₃, 50 °C with 100 equivalents of HC(OEt)₃. (B) [Ga₄L₆]^{12−} rate dependence of the hydrolysis of HC(OEt)₃ in H₂O, pH = 11.0, 100 mM K₂CO₃, 50 °C. (C) Rate dependence on [HC(OEt)₃] in H₂O, pH = 11.0, 100 mM K₂CO₃, 50 °C. (D) Substrate consumption and product formation at saturation (200 equivalents of HC(OEt)₃) with 1 mol. % 1, pH = 11.0, 100 mM K₂CO₃, 50 °C showing 0th-order substrate consumption and product formation.
Figure S5 Lineweaver-Burk plot for the hydrolysis of HC(OEt)₃ with 1 in H₂O, pH = 11.0, 50 °C.