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Supporting Online Material for

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

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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 $^{13}C\{^1H\}$ spectra for the host-guest complexes could not be obtained after 8000 scans with a pre-scan delay of 2 seconds and all $^{13}C\{^1H\}$ spectra were recorded using a 2D DEPT-HSQC experiment. $^{31}P\{^1H\}$ 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 H_2O using the Watergate solvent suppression sequence at 25 ^oC 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. (*1-2*) 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 N_2 until use. The host assemblies $K_{12}[Ga_4L_6]$ and $Na_{12}[Ga_4L_6]$ were prepared as described in the literature and precipitated with either acetone or ether. (*5*)

General Procedure for Amine/Phosphine Encapsulation In an N_2 glovebox, 15mg of $K_{12}Ga_4L_6$ were added to an NMR tube at which point 0.5mL of D_2O 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 N_2 glovebox using 20mg of the $K_{12}Ga_4L_6$ assembly in 0.5mL of H_2O. Samples were prepared in 100mM K_2CO_3 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.

$$K_a = \frac{[SH^+ \subset \mathbf{1}]10^{-pKa}}{[S][\mathbf{1}]10^{-pH}}$$

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

^{1}HHhhddsfH NMR (500 MHz, D_2O): δ 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). $^{31}P\{^1H\}$ (D_2O, 202 MHz): δ 32.1 (t, $^1J_{PD}$ = 74.9 Hz,). ^{31}P (D_2O, 202 MHz): δ 32.1 (tm, $^1J_{PD}$ = 74.8 Hz, $^2J_{PH}$ = 14.2 Hz). $^{31}P\{^1H\}$ (H_2O, 202 MHz): δ 34.0 (s). ^{31}P (H_2O, 202 MHz): δ 34.0 (dm, $^1J_{PH}$ = 489 Hz, $^2J_{PH}$ = 14.4 Hz).

[*N*,*N*,*N*′,*N*′-tetramethyl-1,4-butanediamine-H$^+$ ⊂ Ga$_4$L$_6$]$^{11-}$

^{1}HHhhddsfH NMR (500 MHz, D_2O): δ 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* = 20Hz, 4H, CH_2). $^{13}C\{^1H\}$ NMR (125 MHz, D_2O): δ 54.2 (CH_2), 39.8 (CH_3), 22.2 (CH_2).

[*N*,*N*,*N*′,*N*′-tetraethylethylenediamine-H$^+$ ⊂ Ga$_4$L$_6$]$^{11-}$

^{1}HHhhddsfH NMR (500 MHz, D_2O): δ 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). $^{13}C\{^1H\}$ NMR (125 MHz, D_2O): δ 46.7 (CH_2), 42.9 (CH_2), 9.4 (CH_3).

Analysis of the Rate Law

Kinetic analysis for catalyzed hydrolysis reaction with $M_4L_6^{12-}$ assembly

(⊂ denotes encapsulation)

$$S + \mathbf{1} + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} [S \subset \mathbf{1}] + H^+ \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} [SH^+ \subset \mathbf{1}] \xrightarrow{k_3} P + \mathbf{1} + H^+$$

Applying the steady state analysis on $[S \subset \mathbf{1}]$

$$\frac{+d[S \subset \mathbf{1}]}{dt} = k_1[S][\mathbf{1}] + k_{-2}[SH^+ \subset \mathbf{1}] \qquad \frac{-d[S \subset \mathbf{1}]}{dt} = k_{-1}[S \subset \mathbf{1}] + k_2[S \subset \mathbf{1}][H^+]$$

$$[\mathbf{1}]_{tot} = [\mathbf{1}] + [S \subset \mathbf{1}] + [SH^+ \subset \mathbf{1}]$$

$$k_1[S]\left([\mathbf{1}]_{tot} - [S \subset \mathbf{1}] - [SH^+ \subset \mathbf{1}]\right) + k_{-2}[SH^+ \subset \mathbf{1}] = k_{-1}[S \subset \mathbf{1}] + k_2[S \subset \mathbf{1}][H^+]$$

Solving for the concentration of $[S \subset \mathbf{1}]$

$$[S \subset \mathbf{1}] = \frac{k_1[S]\left([\mathbf{1}]_{tot} - [SH^+ \subset \mathbf{1}]\right) + k_{-2}[SH^+ \subset \mathbf{1}]}{k_{-1} + k_2[H^+] + k_1[S]}$$

Taking $[SH^+ \subset \mathbf{1}]$ *to be small with respect to* $[S \subset \mathbf{1}]$ *we get*

$$[S \subset \mathbf{1}] = \frac{k_1[S]\left([\mathbf{1}]_{tot}\right)}{k_{-1} + k_2[H^+] + k_1[S]}$$

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

$$rate = k_3[SH^+ \subset \mathbf{1}]$$

$$[SH^+ \subset \mathbf{1}] = k_2[S \subset \mathbf{1}][H^+] - k_{-2}[SH^+ \subset \mathbf{1}] - k_3[SH^+ \subset \mathbf{1}]$$

$$[SH^+ \subset \mathbf{1}] = \frac{k_2[S \subset \mathbf{1}][H^+]}{1 + k_{-2} + k_3}$$

Substituting the expression for $[S \subset \mathbf{1}]$ *from above, we are left with*

$$rate = \frac{k_1 k_2 k_3[S][\mathbf{1}]_{tot}[H^+]}{\left(1 + k_{-2} + k_3\right)\left(k_{-1} + k_2[H^+] + k_1[S]\right)}$$

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

References

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Supplemental Figures

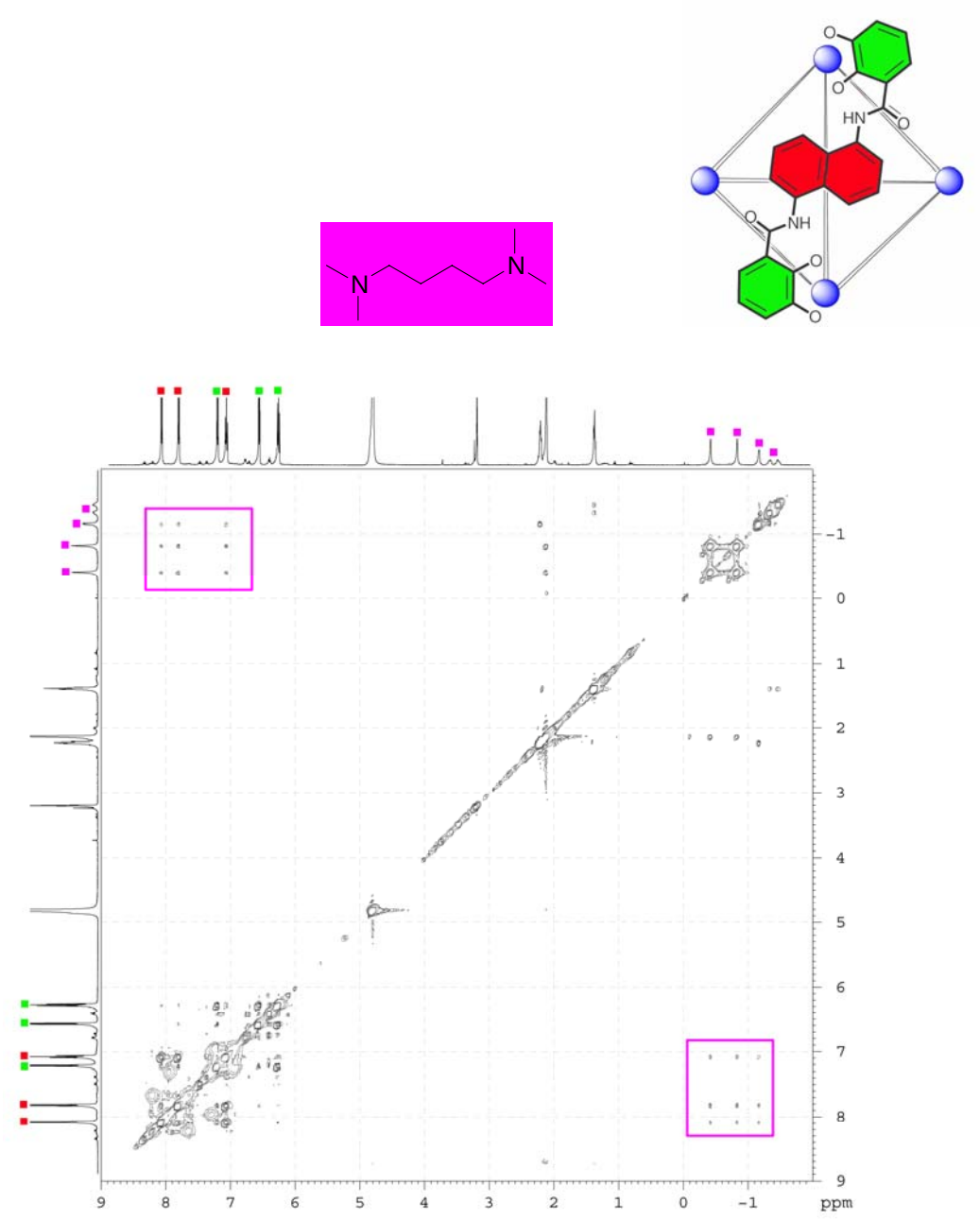

Figure S1 ^{1}H 2D NOESY of [**2**-H^{+} ⊂ **1**]$^{11-}$ in D_2O, 22 °C, with 100 ms mixing time. The strong cross peaks between the naphthalene protons of **1** and the guest protons of **2**-H^{+} show strong through-space correlation indicative of encapsulation.

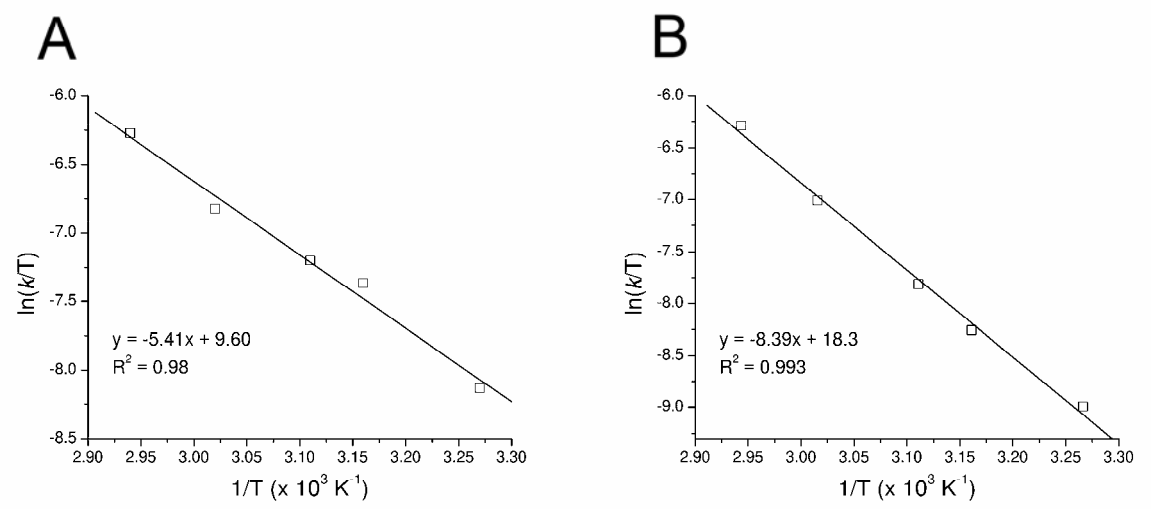

Figure S2 Eyring plot for the determination of activation parameters for [**2**-H^+ ⊂ **1**]$^{11-}$ (A) and [**3**-H^+ ⊂ **1**]$^{11-}$ (B).

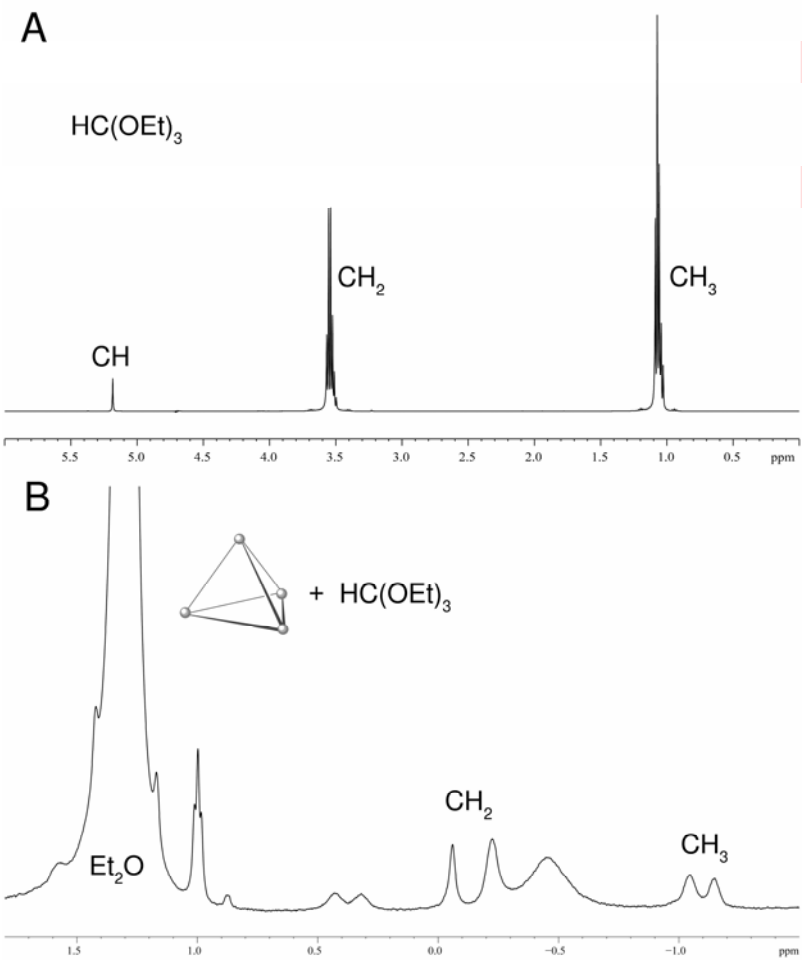

Figure S3 (A) ^{1}H NMR (500 MHz, H_2O) showing $HC(OEt)_3$ free in solution. (B) ^{1}H NMR (500 MHz, H_2O) showing the encapsulation of $HC(OEt)_3$ in an 80mM solution **1**, pH = 11, 22 °C. The encapsulated guest resonances were confirmed by 1D NOE experiments as well as exchange cross peaks with free $HC(OEt)_3$ in solution.

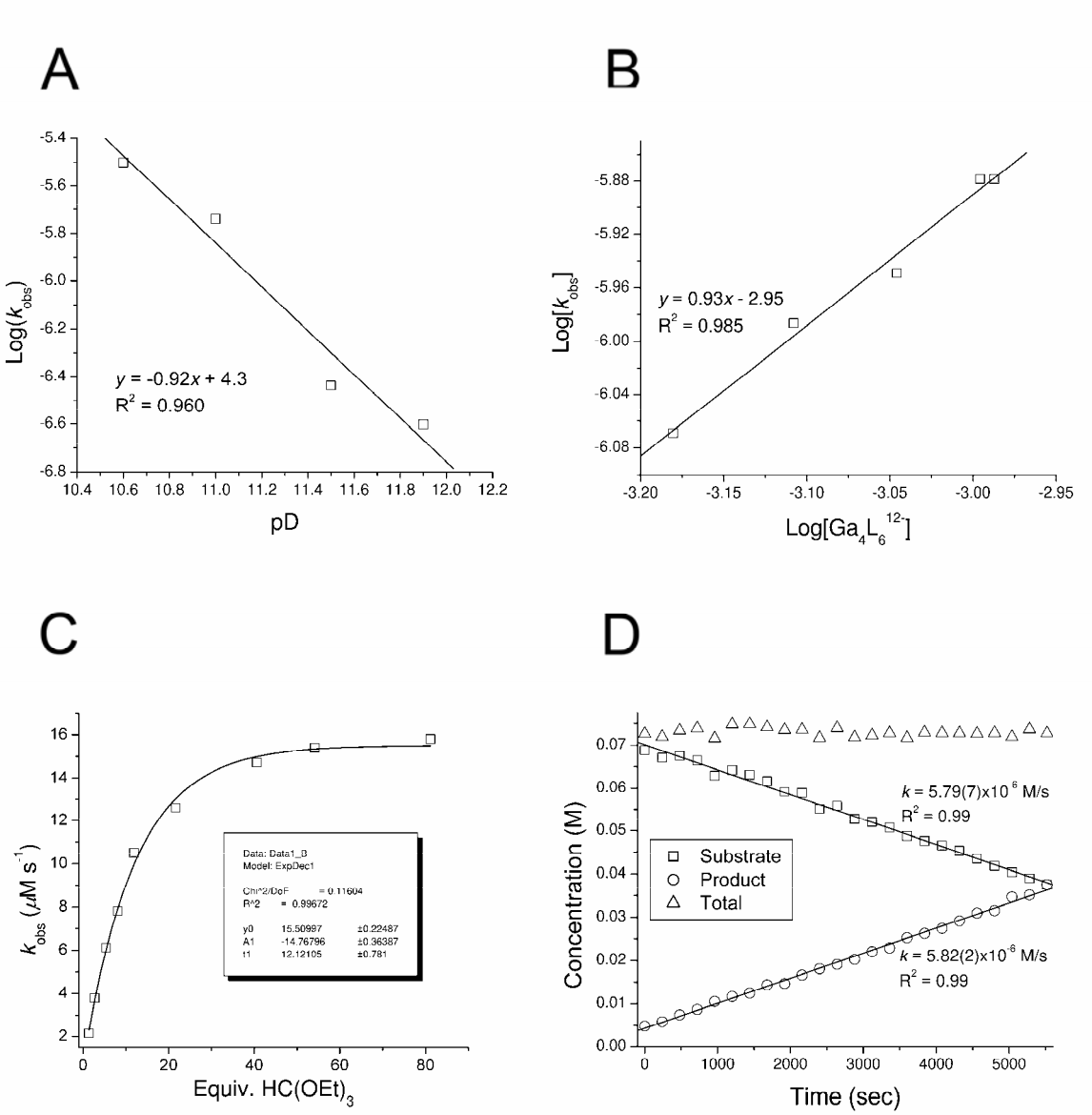

Figure S4 (A) pD rate dependence of the hydrolysis of $HC(OEt)_3$ in D_2O, pD = 11.0, 100 mM K_2CO_3, 50 °C with 100 equivalents of $HC(OEt)_3$. (B) $[Ga_4L_6]^{12-}$ rate dependence of the hydrolysis of $HC(OEt)_3$ in H_2O, pH = 11.0, 100 mM K_2CO_3, 50 °C. (C) Rate dependence on $[HC(OEt)_3]$ in H_2O, pH = 11.0, 100 mM K_2CO_3, 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 K_2CO_3, 50 °C showing 0^{th}-order substrate consumption and product formation.

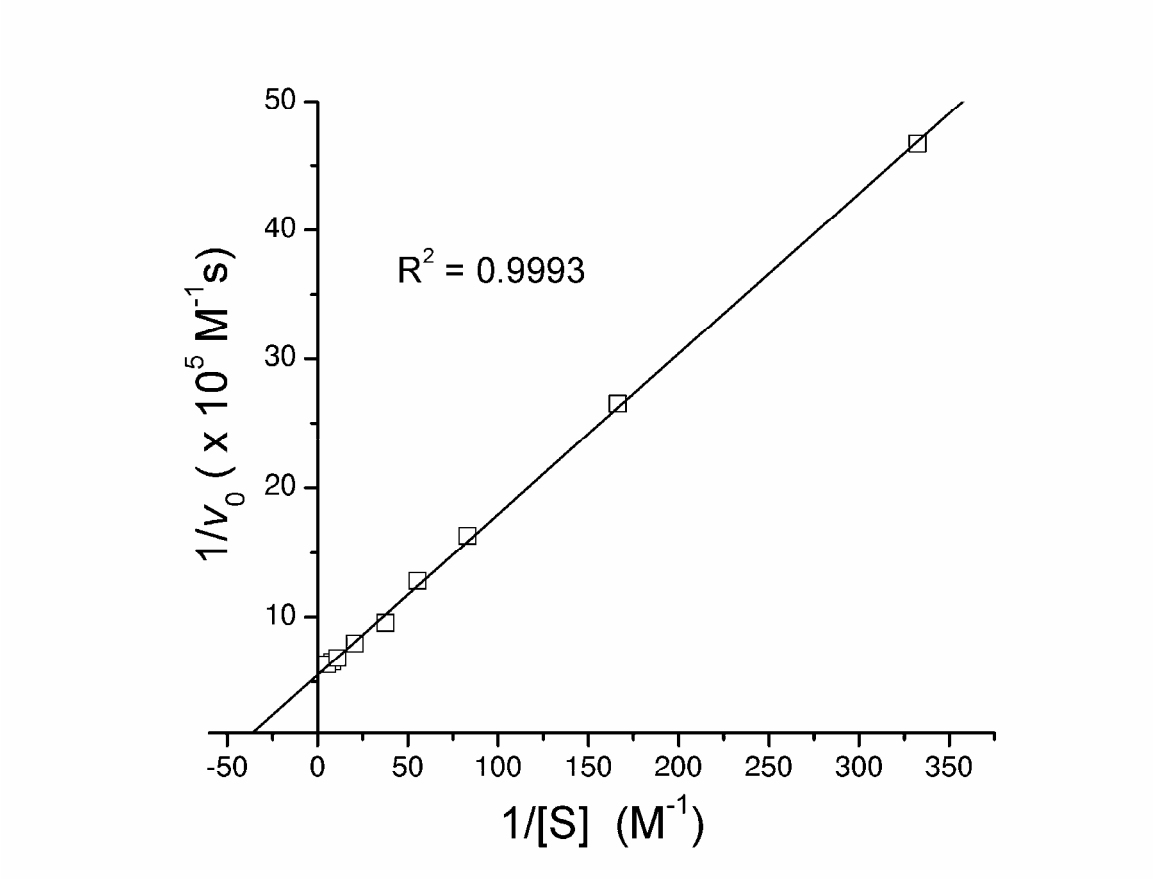

Figure S5 Lineweaver-Burk plot for the hydrolysis of $HC(OEt)_3$ with **1** in H_2O, pH = 11.0, 50 °C.