

Supporting Information for

A Cavitand Microenvironment Supports the Meisenheimer Complex of S_NAr Reactions

Sara M. Butterfield and Julius Rebek, Jr.

The Skaggs Institute for Chemical Biology and the Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

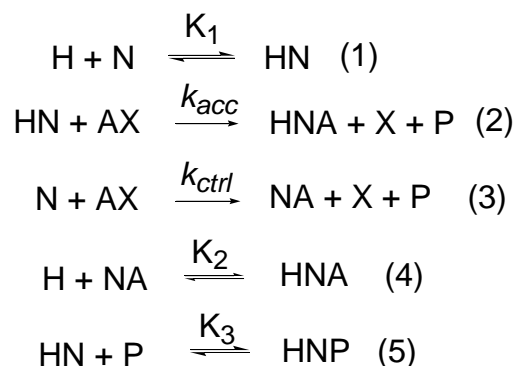
General Experimental

NMR spectra were recorded on a Bruker DRX-600 MHz spectrometer. Spectra were referenced to residual p-xylene peaks. Deuterated solvents were obtained from Cambridge Isotope Laboratories, Inc., Andover, MA. Amines, electrophilic aromatics, and “proton sponge” were obtained from Sigma-Aldrich, St. Louis, MO. Cavitand **1** was synthesized following established procedures.¹ The synthesis of wall mimic **2** has been described previously.²

Kinetic Measurements and Experimental Data

Samples were prepared for kinetic measurements by dissolving the amine of interest (~20 mM, 2 eq) with (or without) cavitand **1** (~10 mM, 1 eq) and “proton sponge” **9** (20 mM) in 500 μ l d_{10} -p-xylene in an NMR tube. The electrophilic aromatic substrate (~10 mM, 1 eq) was added from a concentrated stock solution to initiate the reactions.

The progress of reactions were monitored by integrating the peaks for bound and free S_NAr adduct as a function of time. Initial rates for the background and accelerated reactions were determined from the initial slopes of the [adduct] vs. time plots. The rate constants for reactions accelerated by **1** were obtained by fitting the experimental data with KinTekSim Software. The best fitting results were obtained with the model described below which accounts for product inhibition.



H = cavitand host; N = amine nucleophile; HN = host-nucleophile complex; AX = electrophilic aromatic; HNA = host-adduct complex; X = leaving group; P = proton; HNP = host-protonated amine complex.

The association constant for **1** binding to the amines was determined separately. The binding affinities of **1** for the S_NAr adduct were at least an order of magnitude greater than the amine starting materials. The association constants for the protonated amines was larger than what could be detected by NMR. The binding equilibria (1), (4), and (5) were treated as reversible reactions and were assumed to be fast relative to the reaction steps (2) and (3). k_{ctrl} was determined separately, so the data was fit by solving for k_{acc} . The kinetics simulation was simultaneously fit to the time-dependant concentrations of bound and free product. Tabulations of kinetic data and linear fits to determine initial rates are shown below.

I. **3 + 6**

[**3**] = 20.9 mM; [**6**] = 10.4 mM; [**1**] = 10.4 mM; [**9**] = 20.9 mM; 500 μ l *d*₁₀-p-xylene

Table S1: control reaction

Time/hrs	[adduct] mM
0.00	0.00
0.20	0.00
2.7	0.61
4.2	0.90
6.2	1.27
8.1	1.50
21.6	3.61
30.6	4.25

Table S2: accelerated reaction

Time/hrs	[adduct] _{free} , mM	[adduct] _{bound} , mM	[adduct] _{total} , mM
0.00	0.00	0.00	0.00
0.14	0.00	0.00	0.00
0.33	0.00	0.90	0.90
0.46	0.00	1.27	1.27
0.61	0.00	1.57	1.57
0.96	0.00	1.99	1.99
2.6	1.46	3.20	4.66
4.1	1.43	3.80	5.23
6.1	2.32	3.51	5.83
21.5	3.61	3.22	6.83
30.7	4.27	2.88	7.15

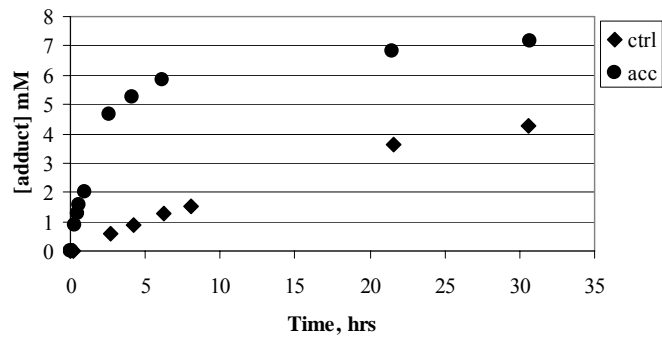


Figure S1. Acceleration of Reaction between **3** and **6** by **1**.

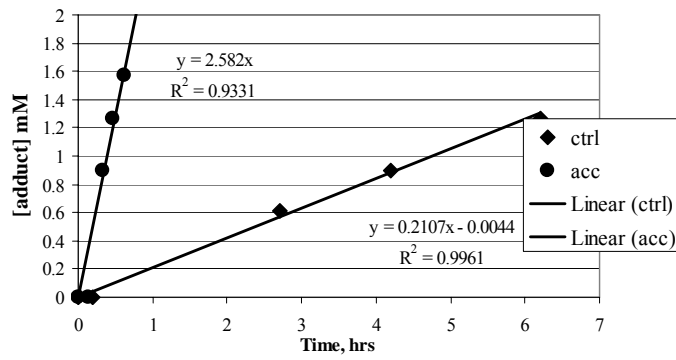


Figure S2. Linear Fits to Initial Rates (V_{ctrl} & V_{acc})

II. 3 + 7

[3] = 20.77 mM; [7] = 10.54 mM; [1] = 10.38 mM; [9] = 20.77 mM; 500 μ l d_{10} -p-xylene

Table S3: control reaction

Time, min	[adduct] mM
0.00	0.00
3.22	0.14
6.17	0.38
8.92	0.53
12.5	0.88
17.5	1.4
53.1	2.6

Table S4: accelerated reaction

Time, min	[adduct] _{total} mM
0.00	0.00
2.53	5.95
5.73	6.47
8.43	6.65
11.3	7.36

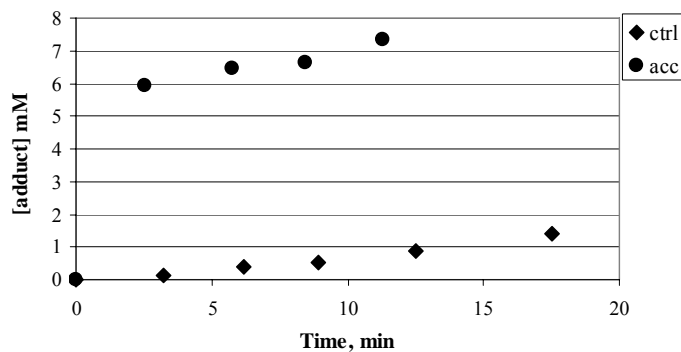


Figure S3. Acceleration of S_NAr Reaction between 3 & 7 with 1.

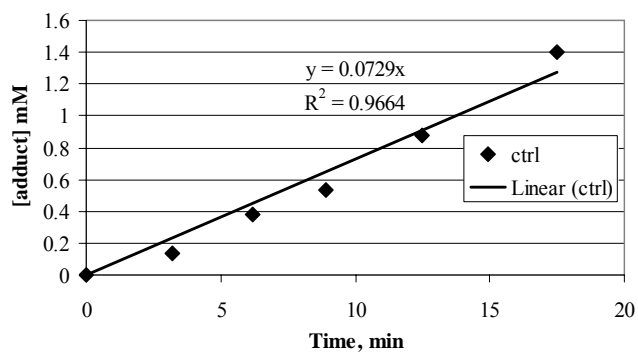


Figure S4. Linear fit of control reaction for 3 + 7

III. 3 + 8

[3] = 20.85 mM; [8] = 11.2 mM; [1] = 10.42 mM; [9] = 20.77 mM; 500 μ l *d*₁₀-p-xylene

no reaction in the absence of **1**

Table S5: accelerated reaction

Time, hrs	[adduct] _{total} , mM
0.00	0.00
0.69	0.00
3.64	1.94
6.83	1.99
8.89	2.35
23.2	3.79
29.2	4.00
47.3	4.69
51.8	4.95
97.9	5.60

IV. 4 + 6

[4] = 20.77 mM; [6] = 10.38 mM; [1] = 10.38 mM; [9] = 20.77 mM; 500 μ l *d*₁₀-p-xylene

Table S6: control reaction

Time, hrs	[adduct] mM
0.00	0.00
1.20	0.30
1.41	0.41
1.85	0.56
2.29	0.57
2.95	0.63
3.40	0.78
4.07	0.89
4.74	0.95
6.08	1.24
6.52	1.34

Table S7: accelerated reaction

Time, hrs	[adduct] _{free} , mM	[adduct] _{bound} , mM	[adduct] _{total} , mM
0.00	0.00	0.00	0.00
0.065	0.00	0.96	0.96
0.103	0.00	1.60	1.60
0.166	0.00	2.15	2.15
0.210	0.00	2.20	2.20
0.293	0.00	2.94	2.94
0.438	0.16	2.28	2.44
0.630	0.48	3.22	3.70
0.965	0.56	3.32	3.88
1.13	0.62	3.41	4.03
1.30	0.93	3.56	4.49
1.63	1.15	3.6	4.75

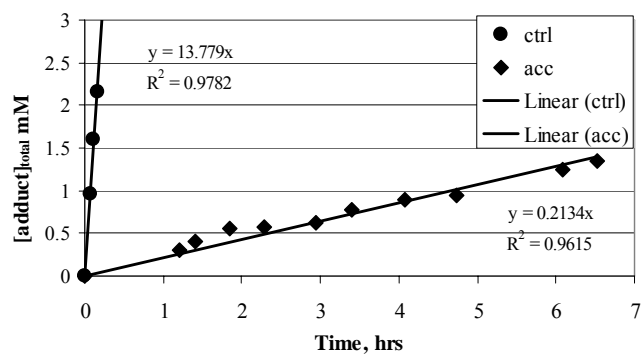


Figure S5. Linear fits to Initial Rates

V. 5 + 6

[5] = 21.07 mM; [6] = 10.38 mM; [1] = 10.38 mM; [9] = 20.7 mM; 500 μ l *d*₁₀-p-xylene

Table S8: control reaction

Time, hrs	[adduct] mM
0.00	0.00
0.32	0.00
1.33	0.42
1.58	0.47
2.57	0.62
2.82	0.63
3.07	0.66
3.57	0.79
4.07	0.84
4.57	1.01
5.07	1.11
5.57	1.26
6.07	1.28
7.32	1.47
8.56	1.67

Table S9: accelerated reaction

Time, hrs	[adduct] _{free} , mM	[adduct] _{bound} , mM	[adduct] _{total} , mM
0.00	0.00	0.00	0.00
0.05	0.00	0.465	0.465
0.10	0.00	0.860	0.860
0.17	0.00	1.18	1.18
0.22	0.34	1.22	1.56
0.24	0.39	1.40	1.79
0.37	0.64	1.72	2.36
0.52	0.74	2.12	2.86
0.67	1.13	2.05	3.18
0.82	1.08	2.15	3.23
0.97	1.22	2.35	3.57
1.27	1.65	2.04	3.69
1.72	1.75	1.97	3.72
2.02	1.96	1.96	3.92
2.63	2.83	1.56	4.38

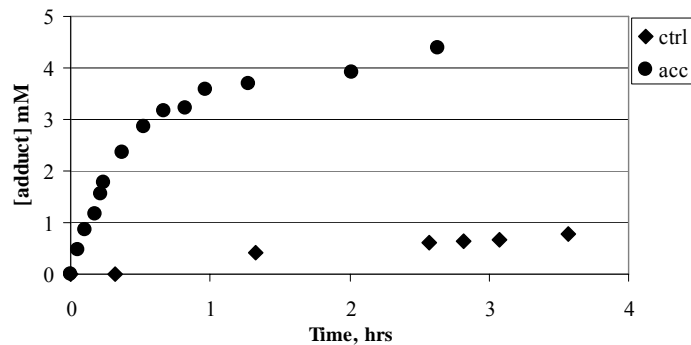


Figure S6. Acceleration of S_NAr Reaction between **5** and **6** with **1**.

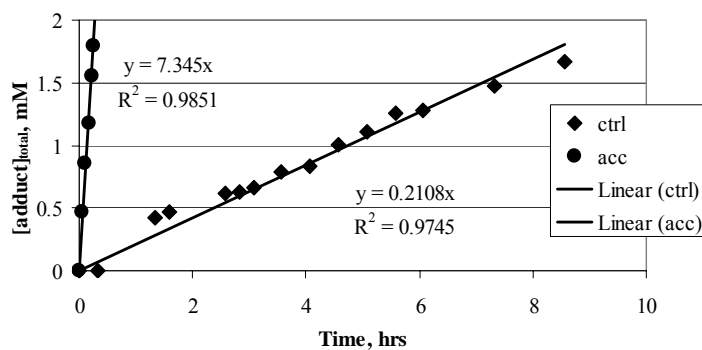


Figure S7. Linear Fits to Initial Rates

VI. **3** + **6** with wall mimic **2**

[**3**] = 17.5 mM; [**6**] = 8.7 mM; [**2**] = 37 mM; [**1**] = 8.7 mM; 600 μ l d_{10} -p-xylene.

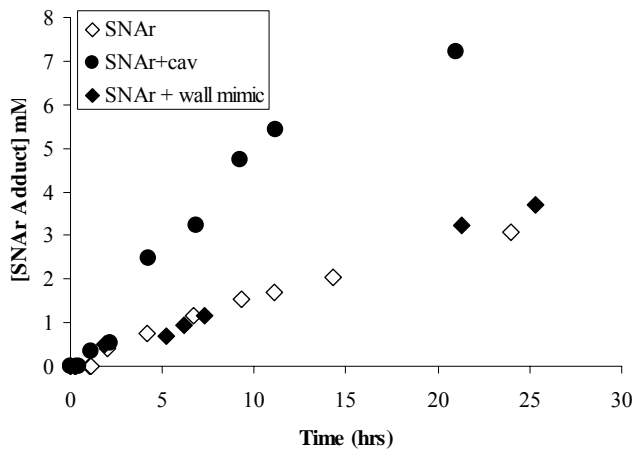


Figure S8. Overlay of S_NAr reaction between **3** & **6** alone (\diamond), in the presence of ~ 4 eq wall mimic **2** (\blacklozenge), and in the presence of cavitand **1** (\bullet).

¹ Renslo, A. R.; Tucci, F. C.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 4573-4582.

² Purse, B. W.; Gissot, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 11222-11223.