Supplementary Material

The Reaction of Hydroxylamine with Aspirin

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1. Kinetic data

Table S1. Rate constants as a function of hydroxylamine concentration in reactions with substituted aspirins at 25°C, pH=6.0 and μ =1.0 M

$[NH_2OH]_{neutral}$ mol/L	$10^3 k_{obs}$, s^{-1} 5-MeO	$10^3 k_{obs}$, s^{-1} H	$10^3 k_{obs}$, s^{-1} 5-F	$10^3 k_{obs}$, s^{-1} 5-Cl	$10^3 k_{obs}$, s^{-1} 5-NO_2
0.0125	-	0.243	0.236	0.487	9.25
0.025	-	0.525	0.519	1.05	19.8
0.0375	-	-	-	-	28.9
0.05	0.699	1	1.06	1.8	38.3
0.075	1.09	1.68	1.68	3.44	60.5
0.1	1.63	2.15	2.28	4.72	71.3
0.125	-	2.94	2.74	5.93	109
0.15	2.54	3.55	3.49	7.3	-

Table S2. Rate constants for reactions of substituted aspirins with hydroxylamine as a function of pH at 25.0°C, ($[NH_2OH] + [NH_3^+OH]$) = 0.3 M and μ = 1.0 M (KCl)

pH	$10^4 k_{obs}$, s^{-1} H	$10^4 k_{obs}$, s^{-1} 5-F	$10^4 k_{obs}$, s^{-1} 5-Cl	$10^4 k_{obs}$, s^{-1} 5-NO_2
2.00	0.223	0.147	0.271	3.33
2.50	0.279	-	-	-
3.00	0.588	0.410	0.786	8.27
3.50	1.16	-	-	-
4.00	1.92	1.48	2.62	29.8
4.50	3.28	-	-	-
5.00	6.74	7.23	14.2	175
5.50	15.4	-	-	-
6.00	31.2	33.9	71.5	1220
6.50	48.2	--	-	-
7.00	58.5	86.1	162	2150
7.50	62.8	-	-	-
8.09	64.3	98.7	199	2530
8.50	64.8	-	-	-
9.00	65.0	110.4	210	2300

Buffers: $ClCH_2COOH$ (pH 2.00-3.00), CH_3COOH (pH 4.00-5.00), NH_2OH (pH 6.00-7.00) and TRIS (pH 8.00-9.00).

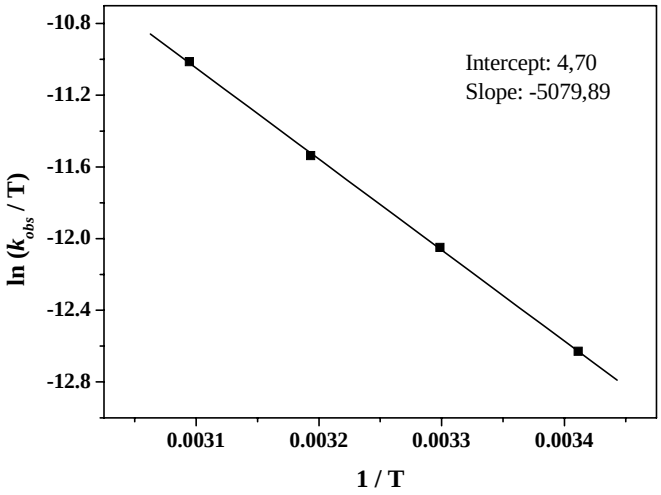

Figure S3. Eyring plot for reaction of aspirin with hydroxylamine (0.05 M), pH=8.50(Tris), and μ= 1.0 M (KCl).

Table S4. Rate constants for reaction of aspirin with hydroxylamine (0,05M) at pH 8.5 (Tris) and ionic strength 1.0 M

Temperature, K	$10^3 k_{obs}$, s^{-1}
293.15	0.96
303.15	1.77
313.15	3.06
323.15	5.33

Activation parameters were calculated using Equations 1-3 for the reaction of hydroxylamine with Aspirin giving values of ΔS = -32.0 e.u. and ΔH=+10.1 kcal mol^{-1}, therefore, a value of ΔG=+19.6 kcal mol^{-1} at 25°C was obtained.

$$\ln\left(\frac{k_{obs}}{T}\right) = \left[\ln\left(\frac{k_b}{h}\right) + \frac{\Delta S^{\neq}}{R}\right] - \frac{\Delta H^{\neq}}{R}\left(\frac{1}{T}\right) \quad \textbf{(S5)}$$

$$\Delta G^{\mp} = \ln\left(\frac{k_2 h}{k_B T}\right) \times RT \quad \textbf{(S6)}$$

$$\Delta G^{\mp} = \Delta H^{\mp} - T\Delta S^{\mp} \quad \textbf{(S7)}$$

2. N-acetylhydroxylamine

Table S8. Yields of *N*-acetylhydroxylamine (acetohydroxamic acid) from the reactions of hydroxylamine (0.05M) with substituted aspirins, at pH 8.50, 0.01M Tris and 25.0 °C

Aspirin	% *N*-acetylhydroxylamine
5-MeO	30
H	25
5-F	21
5-Cl	26
5-NO_2	55

3. Computational data: Cartesian coordinates

hydroxylamine

H	1.043066000	0.816133000	-0.348836000
N	0.691105000	-0.000050000	0.154629000
H	1.043047000	-0.815927000	-0.349340000
O	-0.724675000	0.000056000	-0.140823000
H	-1.126454000	-0.000299000	0.742354000

MP4(SDQ) energy: -131.356838 ht
DeltaG (solv): -2.91 kcal/mol
Thermal correction to Gibbs Free Energy= 0.01792 ht

aspirin

C	-0.828443000	0.588634000	-0.048087000
C	-2.467732000	-1.732142000	-0.074673000
C	-0.310877000	-0.679914000	-0.352919000
C	-2.200972000	0.651189000	0.240653000
C	-3.014621000	-0.483711000	0.241596000
C	-1.108480000	-1.825165000	-0.379115000
H	-2.607710000	1.636627000	0.448881000
H	-4.073679000	-0.394926000	0.478983000
H	-0.649743000	-2.776923000	-0.635095000
H	-3.090068000	-2.625202000	-0.086004000
C	0.004054000	1.902761000	-0.025484000
O	1.248156000	1.769780000	0.126839000
O	-0.668544000	2.955405000	-0.149884000
O	1.022512000	-0.822849000	-0.752450000

C	1.992040000	-0.813924000	0.215693000
O	1.797889000	-1.143246000	1.364702000
C	3.322615000	-0.432977000	-0.377346000
H	3.453635000	-0.878160000	-1.369504000
H	4.130369000	-0.739676000	0.291641000
H	3.311590000	0.657031000	-0.484459000

MP4(SDQ) energy: -646.354211 ht
DeltaG (solv): -52.05 kcal/mol
Thermal correction to Gibbs Free Energy= 0.1049 ht

TS-OH

O	1.966150000	-1.653293000	0.329441000
C	1.923100000	-0.662061000	-0.404780000
C	3.078071000	-0.210800000	-1.274501000
O	0.709979000	-0.313008000	-1.096416000
C	-0.493772000	-0.628688000	-0.508974000
C	-0.879039000	-1.971320000	-0.378585000
C	-2.133634000	-2.296582000	0.133586000
C	-3.024010000	-1.280137000	0.499900000
C	-2.643935000	0.051897000	0.348112000
C	-1.372353000	0.404463000	-0.134161000
C	-1.073158000	1.892813000	-0.264855000
O	0.107126000	2.329653000	0.069714000
O	-1.983354000	2.634116000	-0.647075000
O	1.909216000	0.862080000	0.776767000
N	1.806154000	0.424772000	2.128944000
H	2.922360000	0.804410000	-1.646512000
H	3.998050000	-0.250717000	-0.686427000
H	3.170608000	-0.896601000	-2.128441000
H	-0.176328000	-2.740866000	-0.676465000
H	-2.418050000	-3.341970000	0.239609000
H	-4.009242000	-1.525148000	0.891754000
H	-3.329936000	0.856679000	0.595324000
H	1.576617000	-0.577041000	2.044723000
H	2.774337000	0.429994000	2.464772000
H	0.887954000	1.593960000	0.445148000

MP4(SDQ) energy: -777.713513 ht
DeltaG (solv): -43.94 kcal/mol

Thermal correction to Gibbs Free Energy= 0.14297 ht

TS-O-

O	-1.862974000	-1.363969000	-0.893702000
C	-1.941995000	-0.774754000	0.193655000
C	-2.990936000	-1.065927000	1.242523000
O	-0.753141000	-0.313107000	0.832135000
C	0.489745000	-0.642785000	0.315373000
C	0.820122000	-1.990097000	0.102705000
C	2.102056000	-2.348920000	-0.309504000
C	3.076632000	-1.359730000	-0.485189000
C	2.747355000	-0.026212000	-0.246039000
C	1.452108000	0.366756000	0.134761000
C	1.214872000	1.873594000	0.325482000
O	0.302307000	2.410576000	-0.393270000
O	1.990032000	2.460716000	1.101054000
O	-2.694523000	0.964936000	-0.247045000
N	-1.857840000	1.280622000	-1.318120000
H	-3.018767000	-0.271155000	1.991537000
H	-3.965350000	-1.155798000	0.757364000
H	-2.743656000	-2.015063000	1.737531000
H	0.057398000	-2.746580000	0.253310000
H	2.339833000	-3.397359000	-0.480796000
H	4.085645000	-1.627467000	-0.793914000
H	3.500761000	0.751229000	-0.342443000
H	-1.657310000	0.390093000	-1.817776000
H	-2.340208000	1.921406000	-1.954281000
H	-0.926826000	1.721574000	-0.959687000

MP4(SDQ) energy: -777.704007 ht
DeltaG (solv): -52.41 kcal/mol
Thermal correction to Gibbs Free Energy= 0.14607 ht

TS-NH2

O	2.238105000	-1.739426000	-0.046984000
C	1.888466000	-0.555212000	-0.375564000
C	2.861713000	0.292317000	-1.205485000
O	0.586416000	-0.372085000	-1.149034000
C	-0.609313000	-0.618678000	-0.536539000
C	-1.070853000	-1.941456000	-0.422717000

C	-2.325801000	-2.207828000	0.125359000
C	-3.141652000	-1.151022000	0.547030000
C	-2.685208000	0.162927000	0.426035000
C	-1.411821000	0.456480000	-0.086750000
C	-0.993498000	1.931776000	-0.137620000
O	0.186864000	2.246483000	0.299319000
O	-1.834237000	2.746509000	-0.538925000
H	2.493074000	1.310417000	-1.361964000
H	3.836853000	0.321671000	-0.709577000
H	2.977321000	-0.202085000	-2.175168000
H	-0.419038000	-2.735671000	-0.772543000
H	-2.670127000	-3.236914000	0.213506000
H	-4.128418000	-1.348901000	0.961339000
H	-3.315396000	0.996279000	0.724836000
N	1.522951000	0.244431000	0.940062000
O	2.659338000	0.207154000	1.793662000
H	0.980225000	1.296324000	0.699484000
H	0.817747000	-0.341349000	1.400216000
H	3.003007000	-0.695692000	1.572648000

MP4(SDQ) energy: -777.705476 ht
DeltaG (solv): -45.35 kcal/mol
Thermal correction to Gibbs Free Energy= 0.1441 ht

OAcet

O	0.551505000	-0.752378000	0.000996000
C	-0.441381000	0.170004000	-0.016405000
C	-1.795715000	-0.489175000	-0.000415000
O	-0.232091000	1.367793000	-0.016565000
N	1.884637000	-0.196507000	0.126372000
H	-2.459884000	0.043728000	-0.685793000
H	-2.214952000	-0.404977000	1.008947000
H	-1.735992000	-1.545644000	-0.270173000
H	1.746413000	0.814245000	0.009591000
H	2.339212000	-0.540103000	-0.721696000

MP4(SDQ) energy: -283.596995 ht
DeltaG (solv): -2.13 kcal/mol
Thermal correction to Gibbs Free Energy= 0.048917 ht

Nacet

C	0.432871000	0.155024000	-0.009269000
C	1.816338000	-0.449054000	0.021651000
H	1.806286000	-1.542588000	-0.030076000
H	2.322331000	-0.134062000	0.940083000
H	2.390630000	-0.060729000	-0.825417000
O	0.204611000	1.366695000	-0.001914000
N	-0.607177000	-0.725942000	-0.115797000
H	-0.566201000	-1.651191000	0.293314000
O	-1.892379000	-0.185005000	0.036047000
H	-1.695913000	0.780828000	0.085326000

MP4(SDQ) energy: -283.590963 ht
DeltaG (solv): -3.57 kcal/mol
Thermal correction to Gibbs Free Energy= 0.049216 ht

