

Supplementary Material

The Reaction of Hydroxylamine with Aspirin

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Table of Contents

| | |
|--|----|
| 1. Kinetic data | S2 |
| 2. N-acetylhydroxylamine | S4 |
| 3. Computational data: Cartesian coordinates | S4 |

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 $\mu = 1.0$ M

| $[\text{NH}_2\text{OH}]_{\text{neutral}}$ mol/L | $10^3 k_{\text{obs}}, \text{s}^{-1}$ 5-MeO | $10^3 k_{\text{obs}}, \text{s}^{-1}$ H | $10^3 k_{\text{obs}}, \text{s}^{-1}$ 5-F | $10^3 k_{\text{obs}}, \text{s}^{-1}$ 5-Cl | $10^3 k_{\text{obs}}, \text{s}^{-1}$ 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, $([\text{NH}_2\text{OH}] + [\text{NH}_3^+\text{OH}]) = 0.3$ M and $\mu = 1.0$ M (KCl)

| pH | $10^4 k_{\text{obs}}, \text{s}^{-1}$ | $10^4 k_{\text{obs}}, \text{s}^{-1}$ | $10^4 k_{\text{obs}}, \text{s}^{-1}$ | $10^4 k_{\text{obs}}, \text{s}^{-1}$ |
|------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| | H | 5-F | 5-Cl | 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: ClCH₂COOH (pH 2.00-3.00), CH₃COOH (pH 4.00-5.00), NH₂OH (pH 6.00-7.00) and TRIS (pH 8.00-9.00).

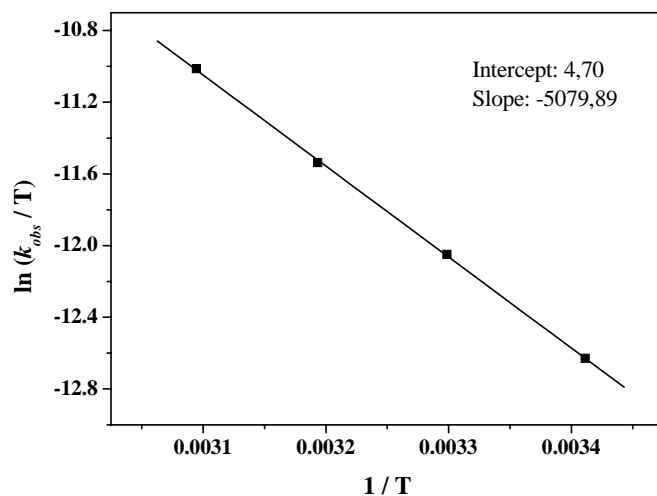


Figure S3. Eyring plot for reaction of aspirin with hydroxylamine (0.05 M), pH=8.50(Tris), and $\mu= 1.0$ M (KCl).

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 $\Delta S = -32.0$ e.u. and $\Delta H = +10.1$ kcal mol⁻¹, therefore, a value of $\Delta G = +19.6$ kcal mol⁻¹ at 25°C was obtained.

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

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

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

2. N-acetylhydroxylamine

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

| Aspirin | % <i>N</i> -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