Supporting Information for:

Intramolecular Acid-Catalyzed Amide Isomerization in Aqueous Solution

Christopher Cox and Thomas Lectka*

General. Reactions were carried out in oven- or flame-dried glassware under nitrogen, unless otherwise specified. All reagents used are commercially available from Sigma/Aldrich. Solvents were reagent grade and purified by standard techniques. Reactions were magnetically stirred and monitored by thin layer chromatography on Macherey-Nagel 0.25 mm precoated plastic silica gel plates (Alltech). Flash chromatography was performed with EM Science silica gel 60 (particle size 0.040-0.063 mm). Yields reported are for isolated, spectroscopically pure compounds unless otherwise indicated. No reactions were optimized for yield. NMR spectra were recorded on a Varian Unity Plus 400 or 500 MHz spectrometer. Proton and carbon chemical shifts were referenced to residual solvent peaks or internal TMS, and fluorine shifts were referenced to external $CFCl_3$. As a result of two conformations being present in the reported compounds at room temperature, the ^{13}C NMR spectra have many more lines than expected, and the ^{1}H NMR spectra are often very complicated. Part of the complicated nature of the ^{1}H spectra involves the fact that a peak may represent a fraction of one proton, and we account for this by reporting the integration as a decimal value. Solution phase IR were recorded with a CaF_2 flow-cell on a Bruker IFS-55 FTIR spectrometer and UV-Visible spectra were acquired on a Hewlett Packard Model 8453 spectrometer. High resolution mass spectra were provided by the Mass Spectral Laboratory at the University of Illinois, and elemental analyses were provide by Atlantic Microlabs, Norcross, Georgia.

Saturation Transfer Experiments. Rates of amide isomerization were followed by applying a saturating decoupling pulse to the trans isomer's resonance of the fluorine atom and then measuring the transfer of saturation to the cis isomer's fluorine resonance, as well as the associated apparent spin-lattice relaxation rate of the cis isomer. For example, the minimum power needed to fully saturate the trans resonance of **2** was applied, and the peak height of the cis resonance was used to determine the intensity, I_1. Peak heights were found to be in

fairly close agreement with the alternative integration method, which was used to confirm the reliability of the results. A preacquisition delay of at least $7T_1$ was employed to allow for complete equilibration before the 90° observation pulse was applied. The initial intensity of the cis resonance, I_0, was determined by measuring the peak height with off-resonance decoupling a distance of $[\delta_{trans} - \delta_{cis}]$ on the opposite side of the cis resonance in order to negate any effect on this peak due to overlap of the decoupler's frequency bandwidth. Supporting Figure 1 shows a representative saturation transfer experiment.

The apparent spin-lattice relaxation time, T_1, of the cis resonance was then measured by the inversion-recovery method while the trans resonance was under irradiation. Homonuclear decoupling was applied during the preacquistion delay, and during the τ delay of the T_1 measurement, but was switched off during acquisition. Apparent T_1 values were determined by manual plots of the data from the inversion-recovery experiment. This method supplies results in very good agreement with those computed by the NMR software, unless the baseline is uneven, as is the case when we are near the fast-exchange limit of detection. In this case, we assume that our manual method is more accurate due to the correction which can easily applied for the uneven baseline by visual inspection; this assumption is validated by the excellent reproducibility we find in our manual methods versus the nonreproducible computer generated ones.

The rate constant for isomerization, k, was determined by equations 1 and 2:

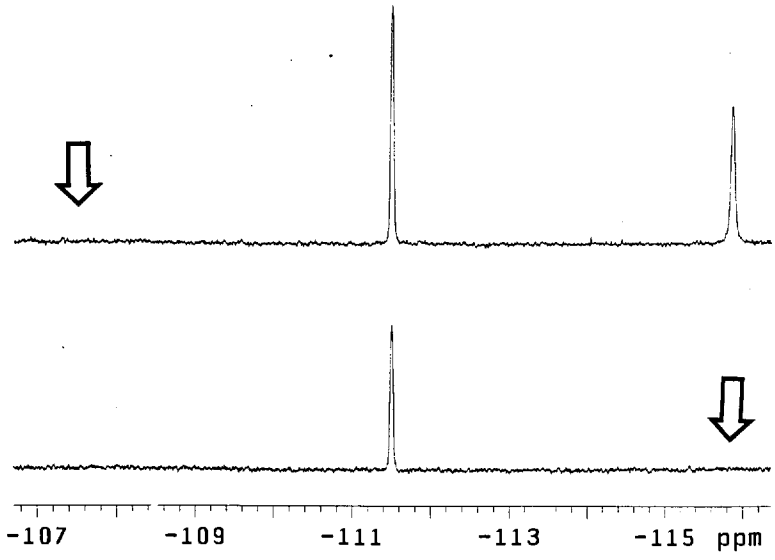
$$k = \frac{\%\Delta}{T_1} \quad (1) \qquad \%\Delta = \frac{I_0 - I_1}{I_0} \quad (2)$$

Once the rate constant was determined, the free energy of activation ($\Delta G^{\ddagger}$) for the rotational process was readily available from the Eyring equation, and $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were available from a standard Eyring plot. All samples were allowed to equilibrate at least 15 minutes after probe temperature changes, and the actual probe temperature was determined by peak separation of an ethylene glycol or methanol sample. Probe temperature fluctuations during the acquisition of data were ≤ 0.1°C.

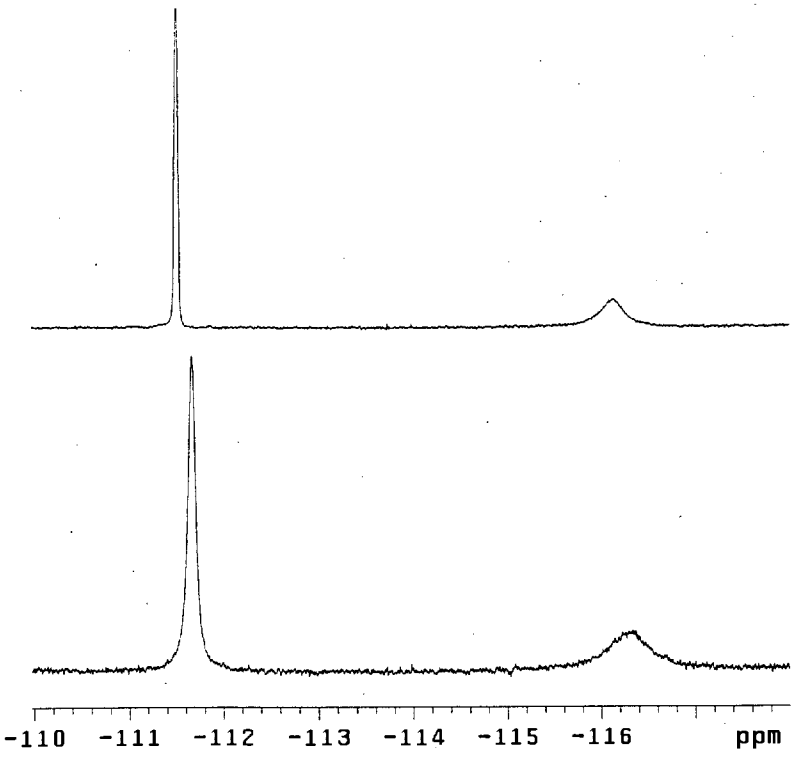
The number of scans necessary for each sample was determined by the signal-to-noise ratio, but was usually between 16-32. The reliability of the rate measurements was determined by performing the experiments in triplicate under identical conditions, which led to reproducibility of at least ± 0.1 kcal/mol for individual $\Delta G^{\ddagger}$ measurements. A value of ± 0.2 kcal/mol is reported in the Tables to allow for any small systematic errors.

However, since we are usually interested in $\Delta(\Delta G^{\ddagger})$, the absolute values are not important and any systematic errors are assumed to mostly cancel.

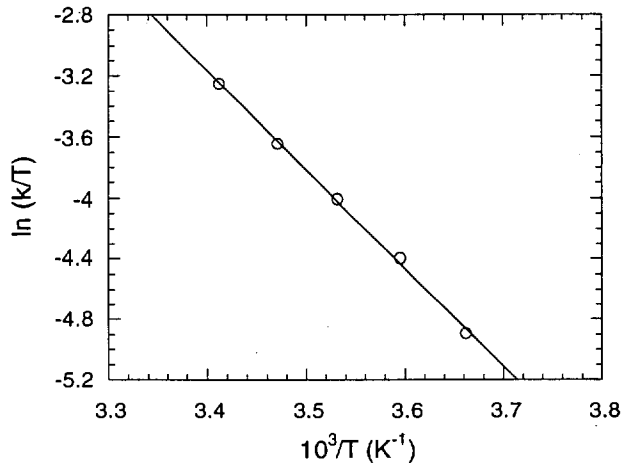
Eyring Plots. Eyring plots were created by carefully measuring the rate constants of isomerization for the same sample at a minimum of five temperatures over a range of at least 20 °C. The number of points obtained was determined by the range over which the saturation transfer method yielded meaningful results; at the high temperature limit, the cis resonance is completely saturated and sinks into the baseline, and at the low temperature limit, there is no difference in the initial and final height of the peak. The plots were created by graphing ln(k/T) vs. 1/T (K^{-1} x 10^3) and standard equations were solved to determine $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. The correlation of the line was always at least 0.985, and often was 0.995 or better. The reported errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were determined from least squares analysis of the Eyring plot. A representative Eyring plot of **2** plus 0.5 equiv CAA is included as Supporting Figure 3.



Supporting Figure 1. Result of ^{19}F ST NMR experiment on **2** at 75°C in 50/50 EtOH/D_2O. The arrows indicate the location of homonuclear decoupling.



Supporting Figure 2. ^{19}F NMR spectra of **2** in 50/50 EtOH/D_2O before (top) and after (bottom) addition of 0.5 equiv CAA.



Supporting Figure 3. Eyring plot of **2** plus 0.5 equiv CAA in 50/50 EtOH/D_2O (y = -6.48x + 18.866; R = 0.999).

Synthesis of 1-[*N*-(2-Fluorobenzoyl)-*N*-methyl]amino-8-(*N*,*N*-dimethyl)aminonaphthalene (2). To 500 mg (2.5 mmol) of 8-methylamino-1-dimethylamino-naphthalene[1] stirring in the dark at -78°C in 20 mL CH_2Cl_2 was added 0.30 mL (2.5 mmol) 2-fluorobenzoyl chloride followed by 0.38 mL (2.8 mmol) triethylamine. The reaction was allowed to warm to rt and stir until judged complete by TLC. The reaction mixture was then concentrated by rotary evaporation and the crude material was purified directly by flash column chromatography with 5-40% EtOAc/hexanes to yield 540 mg (67%) of **2** as a white solid (m.p. 104-105°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8 (m, 0.55 H), 7.6-7.1 (m, 6.9 H), 7.0 (m, 0.55 H), 6.9 (m, 1 H), 6.6-6.4 (m, 1 H) 3.85 (s, 1.35 H), 3.15 (s, 1.65 H), 2.9 (s, 1.65 H), 2.85 (s, 1.35 H), 2.8 (s, 1.65 H), 2.65 (s, 1.35 H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 166.7, 159.6, 159.3, 157.1, 156.8, 150.2, 149.7, 140.0, 138.5, 137.2, 136.2, 131.1, 131.0, 130.5, 130.4, 129.7, 129.6, 128.9, 128.4, 127.7, 125.8, 125.7, 125.65, 125.60, 125.55, 125.50, 124.8, 124.7, 124.65, 124.6, 124.5, 124.0, 123.7, 123.1, 122.6, 122.55, 116.9, 116.0, 115.8, 115.3, 114.9, 114.7, 48.5, 48.0, 43.8, 43.5, 40.8, 39.6 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.0 (m, 0.45 F), -114.8 (bs, 0.55 F) ppm; IR (CH_2Cl_2) 2947, 1640, 1578, 1455, 1390 cm^{-1}; Anal. Calcd for $C_{20}H_{19}FN_2O$: C, 74.51; H, 5.94; N, 8.69. Found: C, 74.77; H, 5.89; N, 8.73.

5-Methylamino-1-dimethylaminonaphthalene (4). 1,5-Diaminonaphthalene (20g, 126 mmol) was suspended in 300 mL of 1M NaOH, and 37.2 mL (392 mmol) dimethyl sulfate was slowly added with efficient stirring. The mixture was placed on a steam bath for 30 min and then allowed to cool to room temperature. The reaction was diluted with 300 mL H_2O and extracted with Et_2O (4 x 150 mL). The organic phases were combined, washed with water (1 x 250 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The crude product was then purified by flash column chromatography (5-20% Et_2O/petroleum ether): The first spot to elute was the tetramethylated material, and the second spot (2.6 g) was collected and identified as the desired trimethylated product (**4**) as a redish-orange oil (10% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6 (m, 1 H), 7.5-7.3 (m, 3 H), 7.0 (m, 1 H), 6.55 (m, 1 H), 4.3 (bs, 1 H), 2.85 (s, 3 H), 2.65 (s, 6 H) ppm; ^{13}C NMR (101

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(1) Alder, R. W.; Bryce, M. R.; Goode, N. C.; Miller, N.; Owen, J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2840-2847.

MHz, $CDCl_3$) δ 151.3, 144.9, 129.4, 125.8, 124.6, 124.5, 114.5, 113.9, 113.3, 103.7, 45.2, 31.0 ppm; IR ($CDCl_3$) 3455, 2943, 1589, 1526, 1411 cm^{-1}; HRMS (FAB+) calcd mass 200.1313. Found: 200.1313.

1-[*N*-(2-Fluorobenzoyl)-*N*-methyl]amino-5-(*N*,*N*-dimethyl)aminonaphthalene (3). 2-Fluorobenzoyl chloride and 5-methylamino-1-dimethylaminonaphthalene (**4**) were coupled as described above for the synthesis of **2**, and chromatography with 10-25% EtOAc/hexanes yielded 77% of **3** as a beige solid (m.p. 117-118°C). ^1H NMR (500 MHz, $CDCl_3$) δ 8.3 (m, 0.1 H), 8.1 (m, 0.9 H), 7.7-7.0 (m, 7 H), 6.75 (m, 2 H), 3.6 (s, 2.7 H), 3.4 (s, 0.3 H), 2.9 (s, 0.6 H), 2.85 (s, 5.4 H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 159.2, 157.3, 151.3, 139.8, 131.4, 130.55, 130.50, 129.8, 128.0, 127.9, 127.05, 127.00, 125.7, 125.2, 125.1, 125.0, 124.9, 124.7, 124.3, 123.3, 123.2, 117.1, 115.4, 115.2, 114.6, 114.5, 45.2, 45.1, 37.5 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ -113.8 (m, 0.9 F), -114.9 (bs, 0.1 F) ppm; IR (CH_2Cl_2) 2944, 1648, 1410 cm^{-1}; Anal. Calcd for $C_{20}H_{19}FN_2O$: C, 74.51; H, 5.94; N, 8.69. Found: C, 74.37; H, 5.91; N, 8.78.