

## Supporting Information

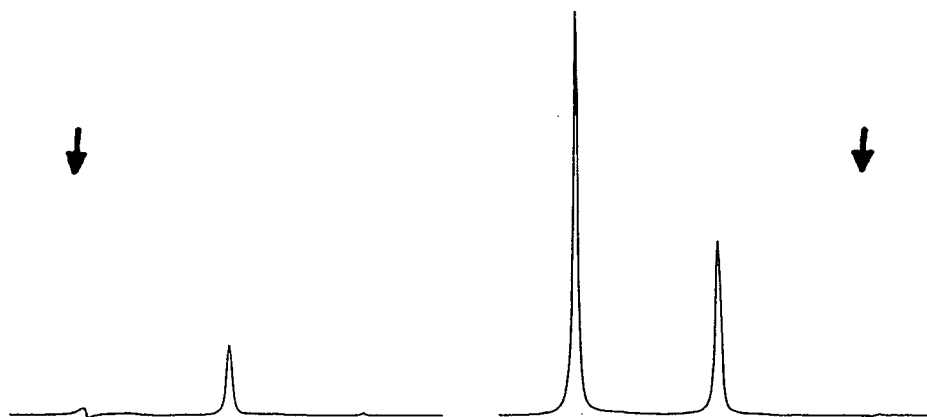
**General Methods.** NMR spectra were recorded on a Varian Unity Plus 500 MHz spectrometer. Proton and carbon chemical shifts were referenced to residual solvent peaks, and spectra run in  $\text{CCl}_4$  were locked on an external standard of  $d_6$ -acetone. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer. All reagents were commercially available (Aldrich) and were used without prior purification. NMR solvents were used as obtained, except that  $\text{CDCl}_3$  was dried over 4 Å molecular sieves and run through basic alumina immediately prior to use, and  $\text{CCl}_4$  was purified by filtration through silica gel. Dichloromethane was distilled from  $\text{CaH}_2$  immediately prior to use.

**Saturation Transfer Experiments.** The rate of amide rotation was determined by applying a saturating decoupling pulse to the *trans* resonance of a methyl or methylene group and then measuring the transfer of saturation to the *cis* resonance, as well as the associated apparent spin-lattice relaxation rate. For example, the minimum power needed to fully saturate the *trans* N-methyl signal of amide 3 was applied, and the peak height of the *cis* resonance,  $I_1$ , was measured. 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  $90^\circ$  observation pulse was applied. The initial intensity of the *cis* N-methyl resonance,  $I_0$ , was determined by measuring the peak height with off-resonance decoupling a distance of  $|\delta_{\text{cis}} - \delta_{\text{trans}}|$  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 the saturation transfer experiment of amide 3 at 25 °C in  $\text{CD}_3\text{CN}$ .

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## Supporting Figure 1.



**Supporting Figure 1.** The  $^1\text{H}$  saturation transfer experiment of amide 3 in  $\text{CD}_3\text{CN}$  at 25  $^\circ\text{C}$ . The arrows represent the location of homonuclear decoupling. Both spectra are scaled equally, so the visible reduction in the height of the *cis* resonance is evidence of transfer of saturation from the irradiated *trans* resonance.

The apparent spin-lattice relaxation time,  $T_1$ , of the *cis* N-methyl peak was then measured by the inversion-recovery method while the *trans* site was under irradiation. Homonuclear decoupling was applied during the preacquisition delay, and during the  $\tau$  delay of the  $T_1$  measurement, but was switched off during acquisition. The apparent  $T_1$  value was determined by a manual plot 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 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 be easily applied to 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 then determined by equations 2 and 3:

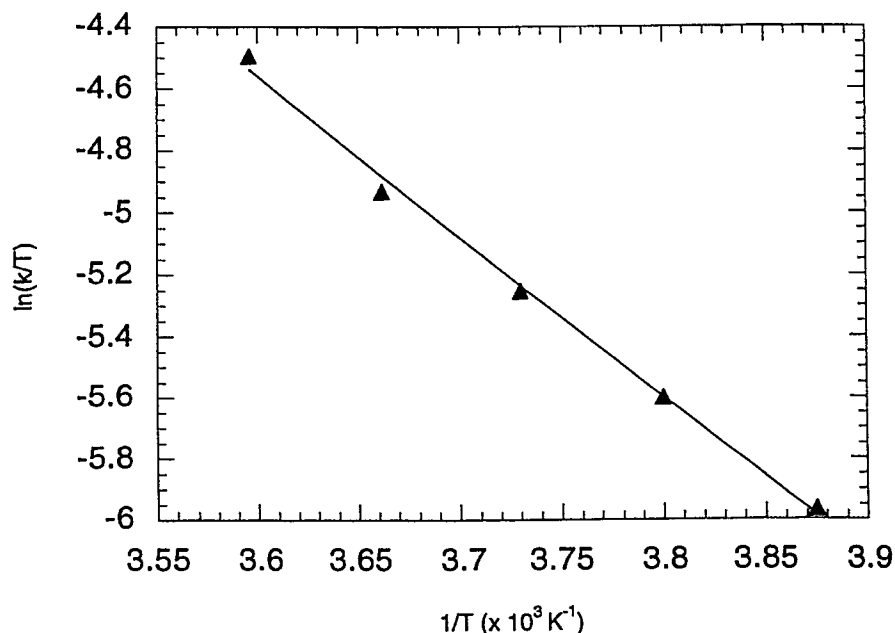
$$k = \frac{\% \Delta}{T_1} \quad (2) \quad \% \Delta = \frac{I_0 - I_1}{I_0} \quad (3)$$

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  $\leq 0.1^\circ\text{C}$ .

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  $\pm 0.1$  kcal/mol for individual  $\Delta G^\ddagger$  measurements. A value of  $\pm 0.2$  kcal/mol is reported in the Tables to allow for systematic errors. However, since we are interested only 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  $20^\circ\text{C}$ . 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 disappears 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.  $1/T$  ( $\times 10^3 \text{ K}^{-1}$ ) and standard equations were solved to determine  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ . The correlation of the line was always at least 0.99. The reported errors in  $\Delta H^\ddagger$  were determined from the least squares analysis of the Eyring plot. Although the errors in  $\Delta S^\ddagger$  determined from the least squares analysis were normally  $\pm 2$  cal/mol·K, we report the error limits as  $\pm 4$  cal/mol·K (see note 14 in the text). A representative Eyring plot of carbamate **4** is included as Supporting Figure 2.

## Supporting Figure 2.



**Supporting Figure 2.** Eyring plot of carbamate 4 in 50%  $\text{D}_2\text{O}/\text{MeOD}$ . The equation of the line is  $y = -5.182 + 14.095x$  and  $R = 0.998$ . Analysis of this line yields  $\Delta H^\ddagger = 10.3 \text{ kcal/mol}$  and  $\Delta S^\ddagger = -20 \text{ cal/mol}\cdot\text{K}$ .

**General Amide or Carbamate Synthesis.** To 1 equivalent of amine stirring at  $-78^\circ\text{C}$  under nitrogen in about 20 mL  $\text{CH}_2\text{Cl}_2$  was slowly added 1 equivalent of acyl chloride (1,3) or chloroformate (2, 4-7), followed by 1.2 equivalents of  $\text{Et}_3\text{N}$ . The mixture was allowed to warm to room temperature and stir for approximately 2 h. The reaction was quenched with 50 mL 1.0 M HCl and extracted with 3 x 50 mL  $\text{CH}_2\text{Cl}_2$ . The organic extracts were combined and washed again with 2 x 50 mL 1.0 M HCl. The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated by rotary evaporation. The crude material was then purified by flash column chromatography with EtOAc/hexanes as the eluent. The yields reported are purified, and none of the reactions were optimized.

**(L)-N-Benzoylproline Methyl Ester (1).** 1.2 g L-proline methyl ester hydrochloride; 0.84 mL benzoyl chloride; 2.22 mL  $\text{Et}_3\text{N}$  (2.2 eq). Chromatography with 10-50% EtOAc/hexanes

provided 1.39g (82%) of a colorless oil whose NMR and IR were identical to previously prepared racemic material.<sup>1</sup>

**(L)-N-Benzylloxycarbonylproline Methyl Ester (2).** 1.5 g L-proline methyl ester hydrochloride; 1.30 mL benzyl chloroformate; 2.78 mL Et<sub>3</sub>N (2.2 eq). Chromatography with 5-25% EtOAc/hexanes provided 1.72g (72%) of a colorless oil which was identical to previously prepared material.<sup>2</sup>

**N-benzyl-N-methylacetamide (3).** 3 mL N-benzylmethylamine; 1.65 mL acetyl chloride; 3.90 mL Et<sub>3</sub>N. Chromatography with 25-50% EtOAc/hexanes provided 3.2g (84%) of a colorless oil which was identical to previously prepared material.<sup>3</sup>

**Methyl N-benzyl-N-methylcarbamate (4).** 3 mL N-benzylmethylamine; 1.80 mL methyl chloroformate; 3.90 mL Et<sub>3</sub>N. Chromatography with 10-25% EtOAc/hexanes provided 4.2g (79%) of a colorless oil which was identical to previously prepared material.<sup>4</sup>

**Ethyl N-benzyl-N-methylcarbamate (5).** 1.0 mL N-benzyl-methylamine; 0.72 mL ethyl chloroformate; 1.3 mL Et<sub>3</sub>N. Chromatography with 10-25% EtOAc/hexanes provided 1.2g (81%) of a colorless oil. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.4-7.2 (m, 5H), 4.5 (s, 2H), 4.2 (q, 3H), 2.9 (s, 0.95H), 2.8 (s, 1.05H) 1.3 (s, 3H) ppm; <sup>13</sup>C-NMR (125.7 MHz, CDCl<sub>3</sub>) δ 137.4, 128.3, 127.5, 127.0, 61.1, 52.1, 51.9, 33.9, 33.2, 14.5 ppm; IR (neat) 1700 cm<sup>-1</sup>; C<sub>11</sub>H<sub>15</sub>NO<sub>2</sub> requires C, 68.37; H, 7.82; N, 7.25. Found: C, 68.61; H, 7.88; N, 7.12.

**Benzyl N-benzyl-N-methylcarbamate (6).** 1.0 mL N-benzylmethylamine; 1.1 mL benzyl chloroformate; 1.3 mL Et<sub>3</sub>N. Chromatography with 10-25% EtOAc/hexanes provided 1.64g (83%) of a colorless oil which was identical to previously prepared material.<sup>5</sup>

**Isobutyl N-benzyl-N-methylcarbamate (7).** 3 mL N-benzylmethylamine; 3.01 mL isobutyl chloroformate; 3.90 mL Et<sub>3</sub>N. Chromatography with 5-25% EtOAc/hexanes provided 4.58g (89%) of a colorless oil which was identical to previously prepared material.<sup>6</sup>

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