Nucleophilic Catalysis of Amide Isomerization

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Studies on the Brønsted acid-catalyzed cis–trans isomerization of amides have served as an elegant testing ground for a number of classical NMR techniques in physical organic chemistry.1 A potentially complementary process, the nucleophilic catalysis of amide isomerization, whereby the formation of a tetrahedral intermediate disrupts amide resonance and facilitates rotation about the C–N bond (eq 1), remains uncharacterized although a number

\[
\text{R} \quad \text{O} \quad \text{N} \quad \text{R}_1 \quad \text{Nu}^- \quad \text{O} \quad \text{N} \quad \text{R}_2 \quad \text{R}_3 \quad \text{Nu}^- \quad \text{O} \quad \text{N} \quad \text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \quad \text{O} \quad \text{N} \quad \text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \quad \text{O}
\]

(1)

of intriguing proposals imply its biological significance. For example, the human PP-Iase Pin1, and the closely related Ess1 in yeast, are essential in the regulation of mitosis2 and are thus potential therapeutic targets for cancer chemotherapy. Noel and co-workers have recently suggested a nucleophilic component in the mechanism of Pin1 catalysis based on the X-ray structure of a Pin1–AlaPro dipeptide complex, as well as on site-directed mutagenesis data.3 These authors propose that the active site His59 catalyzes cis–trans isomerization; however, no direct evidence was provided to support this hypothesis. In this report, we unveil a model system in which nucleophilic catalysis of amide isomerization is characterized for the first time, as well as the first X-ray structure of an anionic tetrahedral intermediate resulting from nucleophilic attack on an amide carbonyl.4

We postulated that amide 1, following deprotonation of the amino proton, would produce tetrahedral intermediate 2. If formation and breakdown of 2 are faster than the rate of uncatalyzed amide isomerization, interconversion of cis and trans 1 will be catalyzed (eq 2). The 1H and 13C NMR spectra of 1a in CD3CN indicated a predominance of one species (cis/trans > 20:1), and the 13C shift of the labeled carbon at 172.5 ppm was as expected for an amide carbonyl. Additionally, the IR spectrum of 1b in CD3CN showed a typical amide carbonyl stretch at 1657 cm−1. However, upon addition of 1 equiv of potassium hexamethyldisilazane (KHMDS), 13C NMR revealed a single resonance at 102.5 ppm, and no carbonyl stretch was visible in the IR. The


(8) We believe that the cis forms of 1 and 3 are thermodynamically favored, in which case the barriers reported throughout represent the cis-to-trans isomerization of the amide bond. This conclusion is based on several pieces of data: (1) previous experimental (Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. J. Am. Chem. Soc. 1992, 114, 10649) and theoretical (Saito, S.; Toriumi, Y.; Tomioka, N.; Itai, A. J. Am. Chem. Soc. 1995, 117, 6715) results indicate that N-methylnitrides are more stable in the cis conformation; (2) single-crystal X-ray structures of related 1,8-disubstituted naphthyl amides indicate that cis is the favored form in the solid state (Cox, C.; Wack, H.; Lectka, T. Angew. Chem., Int. Ed. Engl. 1999, 38, 798).

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little deprotonation of the thiol, and a stronger base was required to increase the catalytic effect. The potassium salt of imidazole (K-Im) was found to be an excellent base that did not promote transacylation under strictly anhydrous conditions.

Upon addition of 1 equiv of K-Im to 3b in CD$_3$CN, the $^1$H NMR remained essentially unaltered with the exception of a modest change in the cis/trans ratio. The IR stretch of the carbonyl moved ~20 cm$^{-1}$ to 1636, consistent with increased electron density of the naphthyl system due to deprotonation of the thiol. All attempts to observe the putative tetrahedral intermediate 4a by $^{13}$C NMR were unsuccessful, presumably due to its extremely short lifetime and/or small population. Nevertheless, kinetic analysis of cis-trans isomerization (3b) with 1 equiv of K-Im was straightforward: $\Delta G^\circ = 16.2 \pm 0.3 \text{ kcal mol}^{-1}$ at 25 °C, $\Delta H^\circ = 5.8 \pm 0.3 \text{ kcal mol}^{-1}$, and $\Delta S^\circ = -35 \pm 4 \text{ cal mol}^{-1} \text{ K}^{-1}$, indicating a 2.8 kcal mol$^{-1}$ lowering of $\Delta G^\circ$ (110-fold rate increase) due to nucleophilic catalysis (entries 1 and 3). The large negative $\Delta S^\circ$ is indicative of a highly ordered transition state and is consistent with rapid formation and breakdown of putative tetrahedral intermediate 4b as being the catalytically competent mechanism of action. The concentration of charge from the delocalized thiocarboxylic anion $\overline{5}$ to the oxygen

in 4, with attendant strengthening of solvent and counterion coordination, may also be in part responsible for the magnitude of $\Delta S^\circ$. The amount of catalysis was proportional to the quantity of base added, as 1 equiv of K-Im produced an approximately 3-fold greater rate increase than 0.25 equiv of K-Im. Additionally, if we analyze the results at ~25 °C (entries 4 and 5), a sizable 4.3 kcal mol$^{-1}$ reduction in $\Delta G^\circ$ is observed. Control compound 6 in the presence of potassium thiophenoxide or K-Im showed no lowering of $\Delta G^\circ$ (entries 6–8), suggesting that the well-defined intramolecular nature of 3 is paramount to the success of the catalytic interaction.

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**Supporting Information Available:** Experimental procedures including the synthesis and characterization of compounds reported herein, X-ray data for 3c, plus details of saturation transfer experiments and Eyring analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) This change is most likely due to an electronic effect of the deprotonated sulfur atom. The original cis/trans ratio is re-established immediately upon the addition of H0Ac to the NMR tube.

(12) IR analysis indicated that 1 equiv of K-Im deprotonates only 75% of 3b under these conditions. As a control, we synthesized thiol 7 and noted a similar shift of ~12 cm$^{-1}$ (from 1651 to 1639 cm$^{-1}$) upon treatment with K-Im.

(13) We investigated control amide 7 in CD$_3$CN by $^{19}$F ST NMR and found no change in $\Delta G^\circ$ upon addition of 1 equiv of K-Im, and an increase of 1.0 kcal mol$^{-1}$ upon addition of 2 equiv of K-Im.


(15) We also found the rate of isomerization in 3b with 1 equiv of K-Im to be the first-order in substrate concentration between 5 and 20 mg/mL, further suggesting an intramolecular interaction.

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**Figure 1.** X-ray crystal structure of the potassium salt of tetrahedral intermediate 2c (50% ellipsoids; the potassium cation coordinated to the oxygen has been excluded for clarity. The structure is perfectly symmetrical, with atoms C5, C6, C8, O1, C9–C14, and By1 in a plane that bisects the naphthyl ring. Selected bond distances (Å): N1–C8, 1.517(3); O1–C8, 1.314(4). Selected angles (deg): O1–C8–N1, 110.3(2); N1–C8–C9, 109.3(2).**

**Scheme 1**

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**Table 1.** Kinetic Parameters for the Catalyzed and Uncatalyzed Amide Isomerization of 3 and 6

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>$T$ (°C)</th>
<th>additive</th>
<th>$\Delta G^b$ (kcal mol$^{-1}$)</th>
<th>cis/trans ratio</th>
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<tbody>
<tr>
<td>1</td>
<td>3b</td>
<td>25</td>
<td>1 equiv of PS</td>
<td>19.0</td>
<td>7:1</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>25</td>
<td>1 equiv of K-Im</td>
<td>16.2</td>
<td>12:1</td>
</tr>
<tr>
<td>3</td>
<td>3b</td>
<td>25</td>
<td>1 equiv of K-Im</td>
<td>14.5</td>
<td>20:1</td>
</tr>
<tr>
<td>4</td>
<td>3b</td>
<td>25</td>
<td>1 equiv of K-Im</td>
<td>17.8</td>
<td>7:1</td>
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<tr>
<td>5</td>
<td>3b</td>
<td>25</td>
<td>1 equiv of K-Im</td>
<td>17.6</td>
<td>7:1</td>
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<tr>
<td>6</td>
<td>3b</td>
<td>25</td>
<td>1 equiv of PS+ K$^+$</td>
<td>17.8</td>
<td>7:1</td>
</tr>
</tbody>
</table>

* Kinetic measurements were performed at 10 mg/mL in CD$_3$CN by $^1$H ST NMR. *cis-to-trans ± 0.2 kcal mol$^{-1}$. *PS = Proton Sponge. *Calculated from the Eyring plot; ±0.3 kcal mol$^{-1}$.

**Scheme 1**

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"sofa I"       "planar*"       "sofa II"
trans-3        cis-3

5 R = 2-FC$_6$H$_4$  6 R = 2-FC$_6$H$_4$  7 R = 2-FC$_6$H$_4$

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(10) The term “sofa” has been used for a six-membered ring conformation in which five of the ring atoms lie approximately in a plane. For an interesting discussion of the genesis of the “sofa” moniker, see: Nickon, A.; Silversmith, E. F. Organic Chemistry: The Name Game. Modern Coined Terms and their Origins; Pergamon Press: New York, 1987; Chapter 7.