

## SUPPORTING INFORMATION

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### O-Acylation of Hydroxyproline Residues: Effect on Peptide Bond Isomerization and Collagen Stability

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## X-Ray Diffraction Analysis of AcHyp(C(O)CH<sub>3</sub>)OMe (2)

**Data Collection.** A colorless crystal of AcHyp(C(O)CH<sub>3</sub>)OMe (**2**) with approximate dimensions  $0.5 \times 0.3 \times 0.3$  mm<sup>3</sup> was selected under oil under ambient conditions and attached to the tip of a glass capillary. The crystal was mounted in a stream of cold nitrogen at 173(2) K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker CCD-1000 diffractometer with Mo K $\alpha$  ( $\lambda = 0.71073$  Å) radiation and the diffractometer to crystal distance of 4.9 cm.

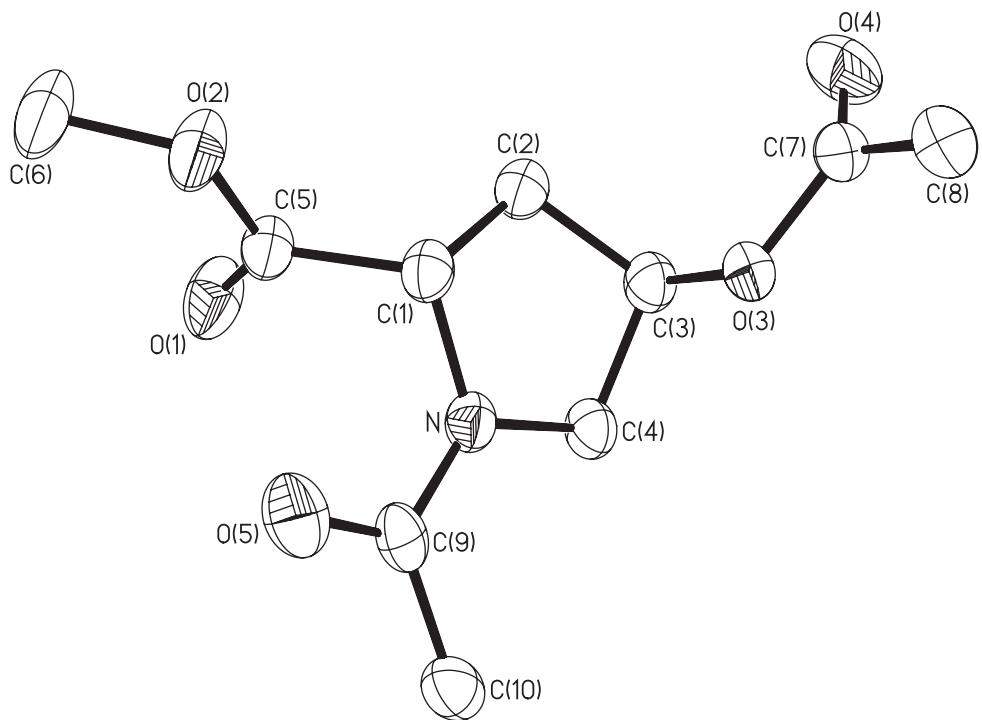
The initial cell constants were obtained from three series of  $\omega$  scans at different starting angles. Each series consisted of 20 frames collected at intervals of 0.3° in a 6° range about  $\omega$  with the exposure time of 10 s per frame. A total of 55 reflections was obtained. The reflections were successfully indexed by an automated indexing routine built in the SMART program. The final cell constants were calculated from a set of 2599 strong reflections from the actual data collection.

Data were collected by using the hemisphere data collection routine. The reciprocal space was surveyed to the extent of a full sphere to a resolution of 0.80 Å. A total of 3185 data were harvested by collecting two sets of frames with 0.3° scans in  $\omega$  with an exposure time 30 s per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements.<sup>1</sup>

**Structure Solution and Refinement.** The systematic absences in the diffraction data were consistent for the space group  $P2_1/m$  and  $P2_1$ . The  $E$ -statistics strongly suggested the non-centrosymmetric space group  $P2_1$  that yielded chemically reasonable and computationally stable results of refinement.<sup>2</sup> A successful solution by the direct methods provided most non-hydrogen atoms from the E-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The H-atoms of the C(8) methyl group are equally disordered over two positions each. The absolute configuration of the molecule could be unequivocally established by the X-ray single crystal diffraction techniques.

The final least-squares refinement of 148 parameters against 2087 data resulted in residuals  $R$  (based on  $F^2$  for  $I \geq 2\sigma$ ) and  $wR$  (based on  $F^2$  for all data) of 0.0290 and 0.0784, respectively. The final difference Fourier map was featureless.

The ORTEP diagram was drawn with 50% probability ellipsoids.



**Figure S-1. The crystal structure of  $\text{AcHyp}(\text{C}(\text{O})\text{CH}_3)\text{OMe}$  (**2**).** The Supporting Information uses the nomenclature in this figure.

**Table S-I Crystal data and structure refinement for AcHyp(C(O)CH<sub>3</sub>)OMe (2)**

Identification code	rai02	
Empirical formula	C <sub>10</sub> H <sub>15</sub> NO <sub>5</sub>	
Formula weight	229.23	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2 <sub>1</sub>	
Unit cell dimensions	$a = 6.8636(6)$ Å $b = 6.5172(6)$ Å $c = 13.1028(11)$ Å	$\alpha = 90^\circ$ $\beta = 101.516(2)^\circ$ $\gamma = 90^\circ$
Volume	574.31(9) Å <sup>3</sup>	
Z	2	
Density (calculated)	1.326 Mg/m <sup>3</sup>	
Absorption coefficient	0.107 mm <sup>-1</sup>	
<i>F</i> (000)	244	
Crystal size	0.50 × 0.30 × 0.30 mm <sup>3</sup>	
Theta range for data collection	3.03 to 26.37°	
Index ranges	$-8 \leq h \leq 7, -8 \leq k \leq 8, -16 \leq l \leq 14$	
Reflections collected	3177	
Independent reflections	2087 [ <i>R</i> (int) = 0.0140]	
Completeness to theta = 26.37°	98.2%	
Absorption correction	Empirical with SADABS	
Max. and min. transmission	0.9687 and 0.9486	
Refinement method	Full-matrix least-squares on <i>F</i> <sup>2</sup>	
Data / restraints / parameters	2087 / 1 / 148	
Goodness-of-fit on <i>F</i> <sup>2</sup>	1.038	
Final <i>R</i> indices [ <i>I</i> > 2σ( <i>I</i> )]	<i>R</i> 1 = 0.0290, <i>wR</i> 2 = 0.0784	
<i>R</i> indices (all data)	<i>R</i> 1 = 0.0296, <i>wR</i> 2 = 0.0790	
Absolute structure parameter	N/A	
Largest diff. peak and hole	0.157 and -0.119 e.Å <sup>-3</sup>	

**Table S-II Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for crystalline AcHyp(C(O)CH<sub>3</sub>)OMe (2)**

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq) <sup>a</sup>
O(1)	-3605(2)	8272(2)	8543(1)	49(1)
O(2)	-3847(2)	10362(2)	7177(1)	43(1)
O(3)	2045(1)	6066(2)	6706(1)	33(1)
O(4)	955(2)	4040(2)	5329(1)	54(1)
O(5)	351(2)	11059(2)	8936(1)	45(1)
N	524(2)	7821(2)	8417(1)	29(1)
C(1)	-1056(2)	8194(2)	7510(1)	30(1)
C(2)	-1351(2)	6089(2)	6980(1)	35(1)
C(3)	694(2)	5101(2)	7291(1)	32(1)
C(4)	1400(2)	5765(2)	8413(1)	31(1)
C(5)	-2946(2)	8937(2)	7832(1)	31(1)
C(6)	-5721(3)	11093(3)	7379(2)	52(1)
C(7)	1966(2)	5439(3)	5719(1)	37(1)
C(8)	3308(3)	6704(3)	5207(1)	49(1)
C(9)	1137(2)	9364(2)	9092(1)	31(1)
C(10)	2781(2)	8895(3)	10004(1)	38(1)

<sup>a</sup> *U*(eq) is defined as one third of the trace of the orthogonalized *U*<sup>ij</sup> tensor.

**Table S-III Bond lengths [Å] and angles [°]  
for crystalline AcHyp(C(O)CH<sub>3</sub>)OMe (2)**

O(1)–C(5)	1.1948(18)
O(2)–C(5)	1.3305(17)
O(2)–C(6)	1.4445(18)
O(3)–C(7)	1.3477(17)
O(3)–C(3)	1.4577(19)
O(4)–C(7)	1.197(2)
O(5)–C(9)	1.2286(18)
N–C(9)	1.3502(19)
N–C(1)	1.4605(18)
N–C(4)	1.4686(17)
C(1)–C(5)	1.5210(18)
C(1)–C(2)	1.532(2)
C(2)–C(3)	1.5237(19)
C(3)–C(4)	1.516(2)
C(7)–C(8)	1.491(3)
C(9)–C(10)	1.501(2)
C(5)–O(2)–C(6)	115.34(12)
C(7)–O(3)–C(3)	117.76(12)
C(9)–N–C(1)	119.53(12)
C(9)–N–C(4)	127.42(12)
C(1)–N–C(4)	112.75(11)
N–C(1)–C(5)	111.29(11)
N–C(1)–C(2)	103.23(11)
C(5)–C(1)–C(2)	111.59(12)
C(3)–C(2)–C(1)	103.08(11)
O(3)–C(3)–C(4)	105.81(11)
O(3)–C(3)–C(2)	109.04(12)
C(4)–C(3)–C(2)	103.71(11)
N–C(4)–C(3)	102.26(11)
O(1)–C(5)–O(2)	123.81(13)
O(1)–C(5)–C(1)	125.25(13)
O(2)–C(5)–C(1)	110.84(11)
O(4)–C(7)–O(3)	123.31(16)
O(4)–C(7)–C(8)	125.94(14)
O(3)–C(7)–C(8)	110.75(14)
O(5)–C(9)–N	119.47(13)
O(5)–C(9)–C(10)	123.40(14)
N–C(9)–C(10)	117.13(13)

**Table S-IV Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for AcHyp(C(O)CH<sub>3</sub>)OMe (2)<sup>a</sup>**

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{23}$	$U^{13}$	$U^{12}$
O(1)	43(1)	59(1)	51(1)	23(1)	26(1)	17(1)
O(2)	40(1)	51(1)	44(1)	19(1)	21(1)	21(1)
O(3)	30(1)	39(1)	30(1)	-8(1)	8(1)	4(1)
O(4)	60(1)	58(1)	42(1)	-21(1)	8(1)	-4(1)
O(5)	54(1)	30(1)	52(1)	-6(1)	17(1)	4(1)
N	29(1)	28(1)	31(1)	1(1)	8(1)	6(1)
C(1)	29(1)	31(1)	31(1)	4(1)	11(1)	5(1)
C(2)	28(1)	38(1)	38(1)	-5(1)	7(1)	3(1)
C(3)	32(1)	28(1)	36(1)	-3(1)	8(1)	4(1)
C(4)	35(1)	26(1)	33(1)	1(1)	8(1)	7(1)
C(5)	31(1)	31(1)	33(1)	5(1)	11(1)	7(1)
C(6)	42(1)	60(1)	59(1)	17(1)	21(1)	27(1)
C(7)	34(1)	46(1)	31(1)	-9(1)	4(1)	12(1)
C(8)	39(1)	76(1)	34(1)	-6(1)	12(1)	5(1)
C(9)	33(1)	30(1)	34(1)	-3(1)	18(1)	-2(1)
C(10)	36(1)	44(1)	35(1)	-7(1)	12(1)	-6(1)

<sup>a</sup> The anisotropic displacement factor exponent takes the form:  $-2\pi^2[h^2a^{*2}U^{11} + \dots + 2hka^*b^*U^{12}]$ .

**Table S-V** Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for AcHyp(C(O)CH<sub>3</sub>)OMe (2)

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq)
H(1)	-607	9216	7037	36
H(2A)	-2372	5279	7239	42
H(2B)	-1746	6230	6215	42
H(3)	648	3575	7210	39
H(4A)	901	4832	8899	37
H(4B)	2870	5821	8600	37
H(6A)	-5496	11789	8055	78
H(6B)	-6620	9928	7388	78
H(6C)	-6317	12056	6831	78
H(8A)	3564	8022	5569	74
H(8B)	2675	6945	4478	74
H(8C)	4568	5976	5238	74
H(8D)	3641	5940	4621	74
H(8E)	4529	7017	5712	74
H(8F)	2636	7985	4952	74
H(10A)	2419	7694	10376	56
H(10B)	2988	10077	10475	56
H(10C)	4008	8608	9755	56

**Table S-VI Torsion angles [°] for AcHyp(C(O)CH<sub>3</sub>)OMe (2)**


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C(9)–N–C(1)–C(5)	–58.24(16)
C(4)–N–C(1)–C(5)	127.53(12)
C(9)–N–C(1)–C(2)	–178.06(12)
C(4)–N–C(1)–C(2)	7.71(15)
N–C(1)–C(2)–C(3)	–28.41(14)
C(5)–C(1)–C(2)–C(3)	–148.03(12)
C(7)–O(3)–C(3)–C(4)	168.52(11)
C(7)–O(3)–C(3)–C(2)	–80.48(15)
C(1)–C(2)–C(3)–O(3)	–73.44(14)
C(1)–C(2)–C(3)–C(4)	38.94(15)
C(9)–N–C(4)–C(3)	–157.42(13)
C(1)–N–C(4)–C(3)	16.25(14)
O(3)–C(3)–C(4)–N	81.10(12)
C(2)–C(3)–C(4)–N	–33.61(14)
C(6)–O(2)–C(5)–O(1)	0.3(2)
C(6)–O(2)–C(5)–C(1)	176.71(14)
N–C(1)–C(5)–O(1)	–41.6(2)
C(2)–C(1)–C(5)–O(1)	73.11(19)
N–C(1)–C(5)–O(2)	142.00(12)
C(2)–C(1)–C(5)–O(2)	–103.27(15)
C(3)–O(3)–C(7)–O(4)	–5.6(2)
C(3)–O(3)–C(7)–C(8)	174.98(13)
C(1)–N–C(9)–O(5)	0.3(2)
C(4)–N–C(9)–O(5)	173.55(13)
C(1)–N–C(9)–C(10)	–179.37(12)
C(4)–N–C(9)–C(10)	–6.1(2)

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## X-Ray Diffraction Analysis of Achyp(C(O)CH<sub>3</sub>)OMe (5)

**Data Collection.** A yellow air-sensitive crystal of Achyp(C(O)CH<sub>3</sub>)OMe (**5**) with approximate dimensions 0.5 × 0.4 × 0.3 mm<sup>3</sup> was selected under oil under ambient conditions and attached to the tip of a glass capillary with epoxy glue. The crystal was mounted on the diffractometer at room temperature and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker CCD-1000 diffractometer with Mo K $\alpha$  ( $\lambda = 0.71073 \text{ \AA}$ ) radiation and the diffractometer to crystal distance of 4.9 cm.

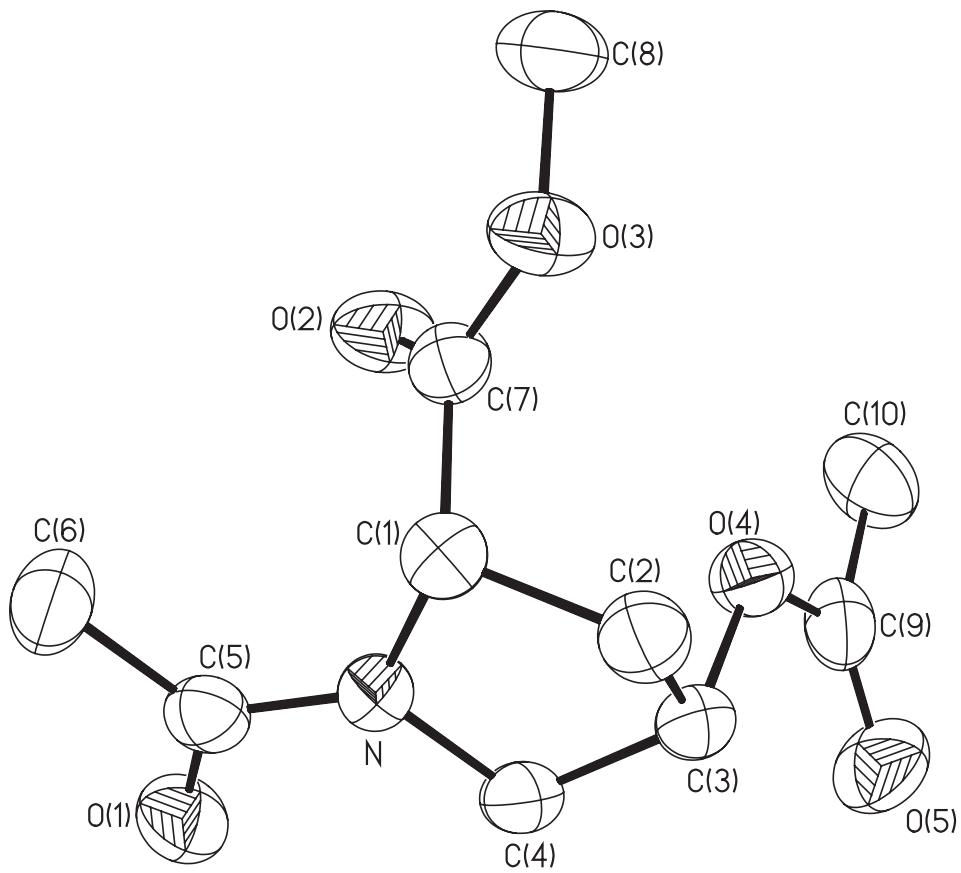
The initial cell constants were obtained from three series of  $\omega$  scans at different starting angles. Each series consisted of 20 frames collected at intervals of 0.3° in a 6° range about  $\omega$  with the exposure time of 10 s per frame. A total of 83 reflections was obtained. The reflections were successfully indexed by an automated indexing routine built in the SMART program. The final cell constants were calculated from a set of 2321 strong reflections from the actual data collection.

The data were collected by using the hemisphere data collection routine. The reciprocal space was surveyed to the extent of a full sphere to a resolution of 0.80 Å. A total of 7570 data were harvested by collecting five sets of frames with 0.3° scans in  $\omega$  with an exposure time 20 s per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements.<sup>1</sup>

**Structure Solution and Refinement.** The systematic absences in the diffraction data were uniquely consistent for the space group  $P2_12_12_1$  that yielded chemically reasonable and computationally stable results of refinement.<sup>2</sup> A successful solution by the direct methods provided most non-hydrogen atoms from the E-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The hydrogen atoms at C(10) are equally disordered over two positions each. The absolute configuration of **5** could not be unequivocally assigned based on the crystallographic data.

The final least-squares refinement of 149 parameters against 2314 data resulted in residuals  $R$  (based on  $F^2$  for  $I \geq 2\sigma$ ) and  $wR$  (based on  $F^2$  for all data) of 0.0379 and 0.0703, respectively. The final difference Fourier map was featureless.

The ORTEP diagram is drawn with 40% probability ellipsoids.



**Figure S-2. The crystal structure of Achyp(C(O)CH<sub>3</sub>)OMe (5).** The Supporting Information uses the nomenclature in this figure.

**Table S-VII Crystal data and structure refinement for Achyp(C(O)CH<sub>3</sub>)OMe (5)**

Identification code	rai01
Empirical formula	C <sub>10</sub> H <sub>15</sub> NO <sub>5</sub>
Formula weight	229.23
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Unit cell dimensions	$a = 8.4173(8)$ Å $\alpha = 90^\circ$ $b = 8.9062(8)$ Å $\beta = 90^\circ$ $c = 15.2409(15)$ Å $\gamma = 90^\circ$
Volume	1142.55(19) Å <sup>3</sup>
Z	4
Density (calculated)	1.333 Mg/m <sup>3</sup>
Absorption coefficient	0.107 mm <sup>-1</sup>
<i>F</i> (000)	488
Crystal size	0.50 × 0.40 × 0.30 mm <sup>3</sup>
Theta range for data collection	2.65 to 26.41°
Index ranges	$-10 \leq h \leq 10, -11 \leq k \leq 10, -18 \leq l \leq 17$
Reflections collected	7570
Independent reflections	2314 [ <i>R</i> (int) = 0.0319]
Completeness to theta = 26.41°	99.1%
Absorption correction	Empirical with SADABS
Max. and min. transmission	0.9685 and 0.9483
Refinement method	Full-matrix least-squares on <i>F</i> <sup>2</sup>
Data / restraints / parameters	2314 / 0 / 149
Goodness-of-fit on <i>F</i> <sup>2</sup>	1.062
Final R indices [ <i>I</i> > 2σ( <i>I</i> )]	<i>R</i> 1 = 0.0379, <i>wR</i> 2 = 0.0703
<i>R</i> indices (all data)	<i>R</i> 1 = 0.0624, <i>wR</i> 2 = 0.0750
Absolute structure parameter	N/A
Largest diff. peak and hole	0.105 and -0.119 e.Å <sup>-3</sup>

**Table S-VIII** Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for crystalline Achyp(C(O)CH<sub>3</sub>)OMe (**5**)

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq) <sup>a</sup>
O(1)	6509(2)	11655(1)	3042(1)	67(1)
O(2)	8782(2)	7727(1)	2481(1)	65(1)
O(3)	8221(2)	6391(1)	1286(1)	62(1)
O(4)	9951(2)	9892(1)	783(1)	57(1)
O(5)	11051(2)	12070(2)	381(1)	81(1)
N	6929(2)	10125(1)	1910(1)	46(1)
C(1)	6905(2)	8699(2)	1431(1)	46(1)
C(2)	7278(2)	9198(2)	494(1)	55(1)
C(3)	8390(2)	10507(2)	616(1)	53(1)
C(4)	7776(2)	11295(2)	1423(1)	54(1)
C(5)	6347(2)	10408(2)	2711(1)	51(1)
C(6)	5488(3)	9189(2)	3183(2)	69(1)
C(7)	8090(2)	7586(2)	1802(1)	46(1)
C(8)	9326(3)	5249(2)	1581(2)	74(1)
C(9)	11196(3)	10816(2)	657(1)	60(1)
C(10)	12720(3)	10069(3)	902(2)	80(1)

<sup>a</sup> *U*(eq) is defined as one third of the trace of the orthogonalized *U*<sup>ij</sup> tensor.

**Table S-IX Bond lengths [Å] and angles [°] for crystalline Achyp(C(O)CH<sub>3</sub>)OMe (**5**)**

O(1)–C(5)	1.227(2)
O(2)–C(7)	1.194(2)
O(3)–C(7)	1.328(2)
O(3)–C(8)	1.450(2)
O(4)–C(9)	1.346(2)
O(4)–C(3)	1.446(2)
O(5)–C(9)	1.200(2)
N–C(5)	1.340(2)
N–C(4)	1.464(2)
N–C(1)	1.465(2)
C(1)–C(7)	1.516(3)
C(1)–C(2)	1.527(3)
C(2)–C(3)	1.507(3)
C(3)–C(4)	1.507(3)
C(5)–C(6)	1.490(3)
C(9)–C(10)	1.493(3)
C(7)–O(3)–C(8)	115.57(15)
C(9)–O(4)–C(3)	116.83(14)
C(5)–N–C(4)	120.36(14)
C(5)–N–C(1)	127.77(14)
C(4)–N–C(1)	111.81(14)
N–C(1)–C(7)	111.80(14)
N–C(1)–C(2)	102.18(13)
C(7)–C(1)–C(2)	113.79(16)
C(3)–C(2)–C(1)	103.73(15)
O(4)–C(3)–C(2)	107.04(14)
O(4)–C(3)–C(4)	110.19(15)
C(2)–C(3)–C(4)	104.37(16)
N–C(4)–C(3)	104.40(14)
O(1)–C(5)–N	120.31(17)
O(1)–C(5)–C(6)	121.00(19)
N–C(5)–C(6)	118.69(16)
O(2)–C(7)–O(3)	123.87(17)
O(2)–C(7)–C(1)	125.14(16)
O(3)–C(7)–C(1)	110.94(16)
O(5)–C(9)–O(4)	122.6(2)
O(5)–C(9)–C(10)	126.2(2)
O(4)–C(9)–C(10)	111.20(18)

**Table S-X Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for Achyp(C(O)CH<sub>3</sub>)OMe (5)**

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{23}$	$U^{13}$	$U^{12}$
O(1)	75(1)	56(1)	70(1)	-11(1)	8(1)	5(1)
O(2)	76(1)	57(1)	61(1)	-4(1)	-17(1)	12(1)
O(3)	73(1)	45(1)	66(1)	-8(1)	-8(1)	6(1)
O(4)	48(1)	54(1)	71(1)	13(1)	10(1)	5(1)
O(5)	87(1)	68(1)	87(1)	21(1)	9(1)	-14(1)
N	50(1)	42(1)	47(1)	3(1)	7(1)	2(1)
C(1)	45(1)	46(1)	48(1)	-2(1)	-3(1)	-5(1)
C(2)	53(1)	61(1)	51(1)	1(1)	-4(1)	7(1)
C(3)	52(1)	54(1)	52(1)	13(1)	6(1)	12(1)
C(4)	54(1)	44(1)	63(1)	10(1)	7(1)	7(1)
C(5)	44(1)	52(1)	57(1)	3(1)	-3(1)	6(1)
C(6)	77(2)	71(1)	59(1)	6(1)	15(1)	-10(1)
C(7)	47(1)	42(1)	50(1)	-1(1)	1(1)	-5(1)
C(8)	90(2)	50(1)	83(2)	0(1)	0(1)	17(1)
C(9)	62(2)	65(1)	53(1)	-4(1)	15(1)	-7(1)
C(10)	53(1)	86(2)	101(2)	-9(1)	10(1)	6(1)

**Table S-XI Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for Achyp(C(O)CH<sub>3</sub>)OMe (5)**

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq)
H(1)	5834	8268	1453	55
H(2A)	7786	8397	166	66
H(2B)	6320	9503	189	66
H(3)	8389	11172	104	63
H(4A)	8645	11699	1768	64
H(4B)	7064	12108	1265	64
H(6A)	6244	8512	3439	103
H(6B)	4828	8651	2777	103
H(6C)	4840	9618	3636	103
H(8A)	10363	5684	1648	111
H(8B)	9371	4454	1156	111
H(8C)	8977	4853	2134	111
H(10A)	12595	8999	865	120
H(10B)	13002	10342	1491	120
H(10C)	13544	10385	508	120
H(10D)	13499	10818	1044	120
H(10E)	13092	9476	418	120
H(10F)	12550	9432	1402	120

**Table S-XII Torsion angles [°] for Achyp(C(O)CH<sub>3</sub>)OMe (**5**)**

C(5)–N–C(1)–C(7)	–73.9(2)
C(4)–N–C(1)–C(7)	103.15(17)
C(5)–N–C(1)–C(2)	164.04(18)
C(4)–N–C(1)–C(2)	–18.9(2)
N–C(1)–C(2)–C(3)	33.56(18)
C(7)–C(1)–C(2)–C(3)	–87.13(18)
C(9)–O(4)–C(3)–C(2)	161.03(16)
C(9)–O(4)–C(3)–C(4)	–86.07(19)
C(1)–C(2)–C(3)–O(4)	80.32(18)
C(1)–C(2)–C(3)–C(4)	–36.49(18)
C(5)–N–C(4)–C(3)	173.96(15)
C(1)–N–C(4)–C(3)	–3.3(2)
O(4)–C(3)–C(4)–N	–89.89(17)
C(2)–C(3)–C(4)–N	24.71(18)
C(4)–N–C(5)–O(1)	0.5(3)
C(1)–N–C(5)–O(1)	177.29(18)
C(4)–N–C(5)–C(6)	179.82(18)
C(1)–N–C(5)–C(6)	–3.4(3)
C(8)–O(3)–C(7)–O(2)	–2.2(3)
C(8)–O(3)–C(7)–C(1)	–179.91(16)
N–C(1)–C(7)–O(2)	11.5(3)
C(2)–C(1)–C(7)–O(2)	126.6(2)
N–C(1)–C(7)–O(3)	–170.81(15)
C(2)–C(1)–C(7)–O(3)	–55.7(2)
C(3)–O(4)–C(9)–O(5)	–3.5(3)
C(3)–O(4)–C(9)–C(10)	176.65(17)

## Kinetics of Amide Bond Isomerization of 1–6

The isomerization rates of **1–6** were determined using the method described by Led and Gesmar.<sup>3,4</sup> The <sup>1</sup>H and <sup>13</sup>C NMR inversion transfer experiments were conducted on a Bruker NMR spectrometer operating at 300.00 MHz for <sup>1</sup>H NMR (Samples **1**, **3**, and **6**) or at 74.43 MHz for <sup>13</sup>C NMR using a 5-mm broadband probe (Samples **1**, **2**, **4**, and **5**). Identical results were obtained for **1** using either <sup>1</sup>H or <sup>13</sup>C NMR. NMR samples of each hydroxyproline derivative (**1–6**) were prepared at concentrations of 10 mM of in 1,4-dioxane-*d*<sub>8</sub> (99 atom %). Doubling or halving the concentration of **1** and **3** in the sample did not alter the rates. Experiments were performed using a temperature range of 313–333 K. The temperature settings of the spectrometer were calibrated to within 1°C by reference to a 100% ethylene glycol standard. The peak heights for each resonance from spectra acquired using the inversion transfer pulse sequence (eq 1) were plotted against  $\tau$  [s].

$$(\pi/2)x - {}^1_2\Delta\delta - (\pi/2)x - \tau - (\pi/2)x - \text{acquire} \quad (1)$$

sigma Plot 2001 was used to fit the inversion transfer data to eq 2 and 3:

$$M_a(t) = C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t} + M_a^\infty \quad (2)$$

$$M_b(t) = C_3 e^{\lambda_1 t} + C_4 e^{\lambda_2 t} + M_b^\infty \quad (3)$$

The “a” subscript refers to the upfield resonance and the “b” subscript refers to the downfield resonance. The complementary experiments were performed at each temperature, in which both the upfield and subsequently the downfield peak were each placed on resonance. Both experiments were fitted to the same equations, except that the *trans* constants were denoted as  $C_1^*$ ,  $C_2^*$ ,  $C_3^*$ ,  $C_4^*$ ,  $\lambda_{1a}$ , and  $\lambda_{2a}$ . The values of  $k_{1a}$  and  $k_{1b}$  were extracted from eq 4 and 5, and the rate constants  $k_a$  and  $k_b$  were determined using eq 6 and 7, where  $\alpha$  is the ratio of the upfield and downfield linewidths.

$$k_{ia} = \frac{(C_1^* \lambda_{1a} + C_2^* \lambda_{2a})(C_3 + C_4) - (C_1 \lambda_1 + C_2 \lambda_2)(C_3^* + C_4^*)}{(C_1 + C_2)(C_3^* + C_4^*) - (C_3^* + C_2^*)(C_3 + C_4)} \quad (4)$$

$$k_{ib} = \frac{(C_1 + C_2)(C_3^* \lambda_{1a} + C_4^* \lambda_{2a}) - (C_1^* + C_2^*)(C_3 \lambda_1 + C_4 \lambda_2)}{(C_1^* + C_2^*)(C_3 + C_4) - (C_1 + C_2)(C_3^* + C_4^*)} \quad (5)$$

$$k_a = \frac{(C_3\lambda_1 + C_4\lambda_2) + k_{ib}(C_3 + C_4)}{\alpha(C_1 + C_2)} \quad (6)$$

$$k_b = \frac{\alpha(C_1\lambda_1 + C_2\lambda_2) + k_{ia}(C_1 + C_2)}{C_3 + C_4} \quad (7)$$

Individual data points were collected in duplicate. For individual experiments, the value of  $k_a$  or  $k_b$  was determined to be within 3%. The 37°C isomerization rate constants were calculated by

extrapolation of the linear least squares fit from Eyring plots.<sup>5</sup> An error value of 10% is reported for  $k_a$  and  $k_b$  to account for systematic errors. The values of  $\Delta G^\ddagger$ ,  $\Delta H^\ddagger$ , and  $\Delta S^\ddagger$  derived from the temperature-dependent rate data are listed in Table S-XIII, along with rates of isomerization extrapolated to 37°C.

**Table S-XIII Activation Parameters and Amide Bond Isomerization Rates of 1–6**

Compound	Process	$\Delta H^\ddagger$ (kcal/mol)	$\Delta S^\ddagger$ [cal/(mol·deg)]	$\Delta G^\ddagger$ (kcal/mol)	$k$ (37°C) (s <sup>-1</sup> )
<b>1</b>	cis-to-trans	33.45 ± 2.94	48.70 ± 8.73	18.35 ± 1.84	0.74 ± 0.07
	trans-to-cis	36.69 ± 1.86	42.93 ± 10.62	18.65 ± 1.87	0.46 ± 0.05
<b>2</b>	cis-to-trans	17.21 ± 1.15	1.19 ± 3.53	17.21 ± 1.72	4.73 ± 0.47
	trans-to-cis	23.77 ± 1.89	17.87 ± 5.80	18.23 ± 1.82	0.19 ± 0.02
<b>3</b>	cis-to-trans	35.75 ± 2.60	58.23 ± 8.02	17.69 ± 1.77	2.15 ± 0.21
	trans-to-cis	19.30 ± 1.96	5.02 ± 6.13	17.75 ± 1.78	1.99 ± 0.20
<b>4</b>	cis-to-trans	24.19 ± 0.06	21.81 ± 2.25	17.43 ± 1.74	3.34 ± 0.33
	trans-to-cis	19.62 ± 0.35	4.18 ± 1.18	18.32 ± 1.83	0.78 ± 0.08
<b>5</b>	cis-to-trans	20.43 ± 1.15	11.05 ± 3.59	17.01 ± 1.70	6.57 ± 0.66
	trans-to-cis	18.34 ± 0.75	1.61 ± 2.34	17.84 ± 1.78	1.71 ± 0.17
<b>6</b>	cis-to-trans	28.02 ± 2.54	32.06 ± 8.01	18.08 ± 1.80	1.16 ± 0.12
	trans-to-cis	19.84 ± 0.95	4.24 ± 3.00	18.53 ± 1.85	0.59 ± 0.06

**References and Notes**

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