Acid−Amide Intermolecular Hydrogen Bonding

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Abstract: A 2,2-dimethylbutynoic acid with a pyridone terminus (**1**) acts as its self-complement in molecular recognition to form an intermolecularly hydrogen-bonded dimer with hydrogen bonding between the amide and carboxylic acid group. The dimer is found in crystals of **1** by X-ray diffraction, in chloroform solution by ^{1}H-NMR experiments and vapor pressure osmometry, and in the gas phase by FAB-MS.

Introduction

Hydrogen bonds[2−5] are among the more important of the weak electrostatic binding interactions found in nucleic acid structure,[2−6] protein conformation,[2−5,7] and supramolecular chemistry.[8−10] Although hydrogen bonds may be formed from many different types of components,[2−10] the amide and carboxylic acid functional groups, either of which can act as proton donor and acceptor, are among the most studied.[2−5,10] Acetic acid, for example, has been shown to form an intermolecularly hydrogen-bonded dimer in CCl_4 solvent, with an association constant of K_{assoc}= 2370 M^{-1} at 24 °C,[11] and δ-valerolactam forms a dimer, with K_{assoc} = 206 M^{-1} at 30 °C.[12] Many other examples of complementary acid−acid (Figure 1A) and amide−amide (Figure 1B) association complex formation have been recognized,[2−10] with the latter being among the most frequently encountered in molecular recognition studies.[10,13] Surprisingly, there were few well-documented examples of carboxylic acid to amide hydrogen bonding (Figure 1C) prior to its observation in the bile pigment, bilirubin (Figure 1E).[14]

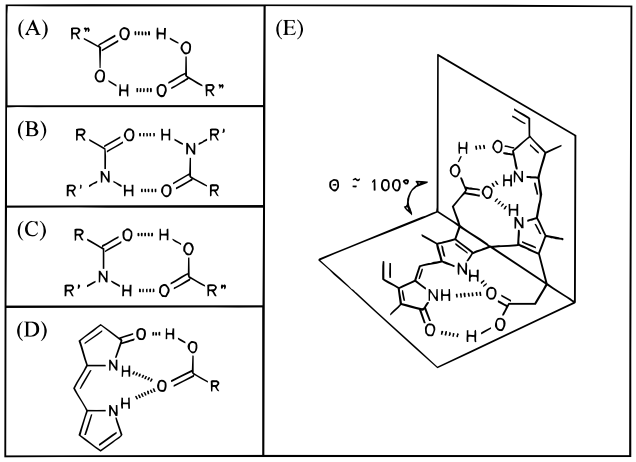

Figure 1. (A) Carboxylic acid−carboxylic acid hydrogen bonds. (B) Amide−amide hydrogen bonds. (C) Amide−carboxylic acid hydrogen bonds. (D) Dipyrrinone to carboxylic acid hydrogen bonds. (E) Bilirubin-IXα held in a ridge-tile conformation by intramolecular amide-carboxylic acid hydrogen bonds.

The three-dimensional structure of bilirubin in the crystal[14] and in solution[14−16] is dominated by a ridge-tile-shaped conformation stabilized by *intra*molecular hydrogen bonding between propionic acid groups and lactam NHC═O and pyrrole NH components of the opposing dipyrrinones. Recently, this unusual carboxylic acid to dipyrrinone *inter*molecular hydrogen bonding (Figure 1D) has been detected in solutions of certain dipyrrinone acids, which in nonpolar solvents adopt a π-facial dimer structure.[17] In both cases, carboxylic acid to amide hydrogen bonding (Figure 1C) is probably further stabilized by additional hydrogen bonding from the pyrrole NH to the acid carbonyl oxygen.

More recently, amide to carboxylic acid hydrogen bonds have become important in molecular recognition chemistry, where amide hosts have been designed and constructed for binding

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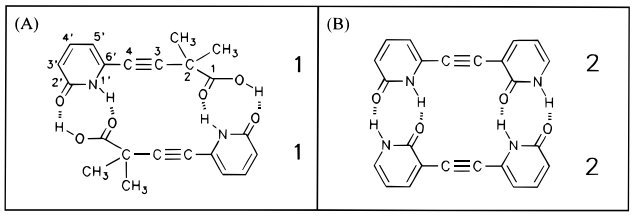


Figure 2. (A) Pyridone acid **1** dimer formed by intermolecular carboxylic acid to amide hydrogen bonds. (B) Bispyridone **2** dimer formed by intermolecular amide−amide hydrogen bonds.

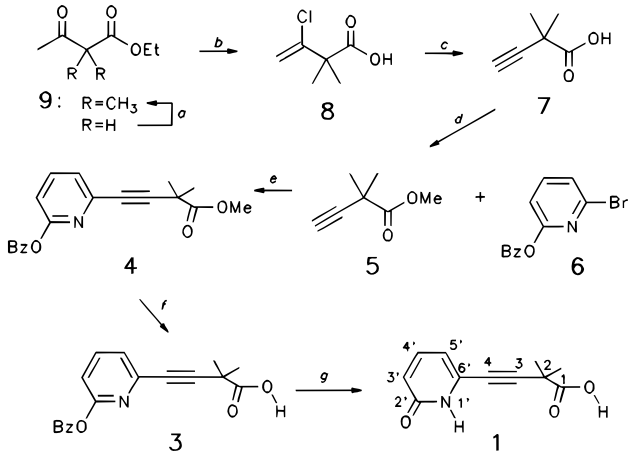
carboxylic acid[18] and carboxylate ion[19] guests. However, in only two examples[18b,c] is the amide carbonyl designed to be a part of the hydrogen bonding motif (as in Figure 1C). In one of the two relevant examples[18c] the acid carbonyl is hydrogen bonded to two amide N−H groups—an arrangement similar to that observed in dipyrrinones (Figure 1, parts D and E). There are extremely few examples of carboxylic acid to amide hydrogen bonding of the type shown in Figure 1C; among them are several cyclic amide−carboxylic acid complexes.[13b,18f−h,20c] One such arrangement is the linkage between two molecules of 6-methyluracil-5-acetic acid.[18h] Another is the involuntary intramolecular carboxylic acid to amide (Figure 1C) hydrogen bonding studied by Rebek and coworkers[13b] in a cleverly-designed system involving a monoamide derivative of *m*-xylidenediamine bis(Kemp's triacid) imide.

When bilirubin and its analogs constituted the only well-documented examples of carboxylic acid to amide hydrogen bonding, we designed a very different model compound (**1**), a carboxylic acid possessing an amide terminus, that we expected would exhibit strong *inter*molecular hydrogen bonding in a dimer formed when the termini are oriented head-to-tail (Figure 2A). Inspiration for **1** came from the work of Wuest *et al.*,[20a] who showed that bis-pyridone **2** forms an extraordinarily stable dimer in $CHCl_3$ ($-\Delta G° > 6.5$ kcal/mol) with *inter*molecular amide−amide hydrogen bonds (Figure 2B). In the following, we report on the synthesis and characterization of **1** and show by X-ray crystallography, vapor pressure osmometry, mass spectrometry, and ^{1}H-NMR that it forms a very stable association dimer.

Results and Discussion

Synthesis. Adopting the methodology employed by Wuest *et al.*[20] for coupling 2-(benzyloxy)bromopyridines to acetylenes, we identified the two key synthetic intermediates to be used in the preparation of **1**: methyl 2,2-dimethyl-3-butynoate (**5**) and 2-(benzyloxy)-6-bromopyridine (**6**). The parent acid (**7**) of the former was prepared by the method of Engel and Schexnayder[21] from ethyl acetoacetate, as outlined in Scheme 1. Pyridine **6** was prepared from 2,6-dibromopyridine by the method of Duggan *et al.*[22] by reaction with benzyl alcohol with KOH and 18-crown-6 in dry toluene. Previously, we reported on the $Pd(PPh_3)_4$ catalyzed coupling of **6** and **7**, which led to a furanone through intramolecular cyclization of the carboxyl and acetylene groups.[23] Coupling of **5** and **6**, however, led smoothly to **4**, which was first saponified and then deprotected using TFA to give **1**. Crystallization of **1** from dichloromethane−toluene gave small, thin needles. Needles suitable for X-ray crystallography were grown in chloroform with ethyl acetate added by vapor diffusion at room temperature.

Scheme 1[a−g]



[a] Potassium *tert*-butoxide, CH_3I. [b] PCl_5, then NaOH. [c] $NaNH_2$. [d] CH_2N_2. [e] $Pd(PPh_3)_4$, CuI, Et_3N. [f] NaOH. [g] CF_3CO_2H.

Molecular Structure. The structure assigned to **1** is consistent with its spectroscopic properties, in particular, with its ^{13}C-NMR spectrum, in which all carbon resonances were assigned by long-range ^{1}H{^{13}C}-COSY experiments. X-ray crystallography confirmed the constitutional structure of **1** and clearly indicated that it is a hydrogen-bonded dimer (Figures 2A and 3). In the crystal, H atoms are well located, and two sets of two nearly linear hydrogen bonds, directed approximately toward receptor C=O lone pairs, complete the 8-membered ring arrangement (Figures 1C, 2A, and 3). The H-bond geometry is shown in Table 1, where the same parameters for other cyclic amide−carboxyl pairs[18f−h,20c] are given for comparison. The O···O and N···O distances in **1** (2.55 and 2.79 Å) may also be compared to the intramolecular mean values of 2.61 and 2.64 Å (O···O) and 2.84 and 2.87 Å (N···O) in bilirubin[14b] and mesobilirubin,[14c] respectively. Similar (amide) H···O (carboxyl) distances, 1.88−2.14 Å, are found in the complexes of bis(amidopyridines) with dicarboxylic acids of varying chain length;[18e] in these complexes, the second H-bond in the 8-membered ring is (carboxyl) H···N (pyridine), 1.60−2.33 Å. The lactam−carboxyl cyclic grouping found in **1** implies stronger intermolecular hydrogen bonds than those in lactam dimers, in which typical N···O distances are about 2.82 Å.[23]

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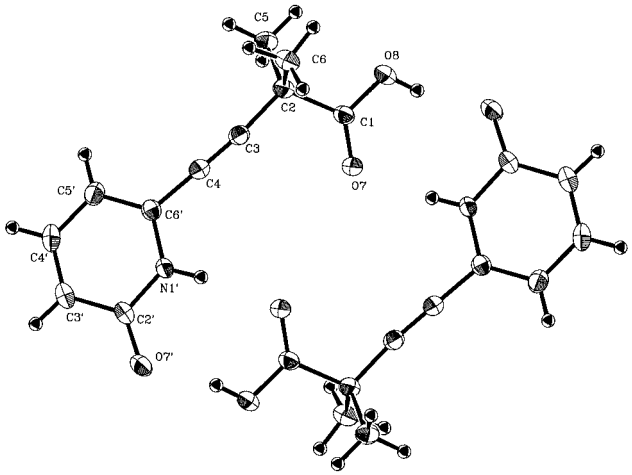

Figure 3. Drawing of the dimer of **1** in the crystal. Ellipsoids are drawn at the 50% probability level; H atoms are represented by spheres of arbitrary radius. The numbered molecule is related to its partner by the symmetry operation $1 - x, -y, 2 - z$.

Table 1. Hydrogen-Bond Distances (Å) and Angles (deg) in the Dimer[a] of **1** in the Crystal and in Four Other Cyclic Amide−Carboxylic Acid Structures

	compound				
distance (Å) or angle (deg)	**1**	ref 18f	ref 18g	ref 18h	ref 20c
(lactam) O7′··· O8 (carboxyl)	2.554(2)	2.60	2.62	2.67	2.66
O7′··· H8	1.75(2)	1.66	1.62	1.71	1.70
O7′···H8−O8	165(2)	176	166	174	170
(lactam) N1′··· O7 (carboxyl)	2.791(2)	2.84	2.83	2.80	2.77
H1′···O7	1.95	1.94	1.84	1.93	1.86
N1′−H1′···O7	167	166	161	171	173

[a] The hydrogen bonds in **1** are all intermolecular, the second molecule being related to the first by the symmetry operation $1 - x, -y, 2 - z$. See Figure 3.

Table 2. Dilution and Temperature Effects on the ^{1}H-NMR[a] Chemical Shifts of **1**[b] in $CDCl_3$

		^{1}H-NMR Chemical Shift for H at					
temp (°C)	concn (M)	CO_2H	NH	CH_3	3′	4′	5′
20	2.44×10^{-2}	15.52	12.96	1.668	6.599	7.476	6.533
20	4.68×10^{-2}	15.50	12.80	1.669	6.600	7.477	6.534
50	8.04×10^{-2}			1.667	6.512	7.456	6.587
40	8.04×10^{-2}	15.32	12.89	1.666	6.519	7.464	6.591
0	8.04×10^{-2}	15.70	12.99	1.661	6.552	7.495	6.605
−72	8.04×10^{-2}	16.03	13.10	1.653	6.624	7.566	6.650

[a] Reported in δ (ppm) downfield from $(CH_3)_4Si$. [b] See synthetic scheme or Figure 2A for numbering system used.

Evidence for a predominantly dimeric structure of **1** in solution comes from vapor pressure osmometry studies in $CHCl_3$ at 37 °C, which gave an average molecular weight of 409[24] —almost exactly twice the molecular weight (205) of the monomer. Further evidence for the dimeric structure in chloroform solution comes from ^{1}H-NMR spectroscopy. The very strong deshieldings (Table 2) seen for the carboxylic acid (∼15.5 ppm) and amide (∼13 ppm) hydrogens are characteristic of strong hydrogen bonding,[17,25,26] as might be found in the dimeric structure shown in Figure 2C. Consistent with such a dimer structure for **1**, a strong nOe is found between the lactam and carboxylic acid hydrogens. Finally, in the FAB-mass spectrum of **1** (glycerol matrix), a prominent *m/z* 411 peak is found for the parent ion dimer in addition to the *m/z* 206 base peak of the parent ion monomer.

Monomer−Dimer Equilibrium. We attempted to determine the extent of dimerization of **1** using ^{1}H-NMR spectroscopy to follow changes in position of the chemical shifts (δ_{obs}) of sensitive reporting groups such as NH and CO_2H. At high dilution, the monomer concentration can be expected to increase, while the dimer concentration decreases. One should therefore expect to observe a shift in δ_{obs} to higher field with increasing dilution.[27] However, this was not observed for any of the C*H* signals over the concentration range 0.024 to 0.00047 M in $CDCl_3$. Only very minor changes were seen for δ_{obs}(N*H*) [12.96 ppm at 2.44×10^{-2} M and 12.80 ppm at 4.68×10^{-4} M] and $\delta_{obs}(CO_2H)$ [15.52 ppm at 2.44×10^{-2} M and 15.50 ppm at 4.68×10^{-4} M]. The data suggest a very large self-association constant, K_{assoc}= [dimer]/[monomer]^2 M^{-1}, for **1** in $CDCl_3$, exceeding 10^4 M^{-1}.[27] Consequently, K_{assoc} was determined by ^{1}H-NMR spectroscopy[27,28] in a solvent mixture in which dimerization is less extensive: $CDCl_3$ with 3% by volume $(CD_3)_2SO$. The added $(CD_3)_2SO$, which is an excellent hydrogen bond (acceptor) solvent,[27] interferes to some extent with dimerization of **1** by forming hydrogen bonds competitively with it.[27,28] We used the method of Horman and Dreux,[28] developed for caffeine dimerization studies, to determine K_{assoc}(∼510 M^{-1}) of **1** from the ^{1}H-NMR chemical shifts of its amide hydrogens in 3% by volume $(CD_3)_2SO$ in $CDCl_3$ at 25 °C. For calibration, we used the same method to determine K_{assoc} values for 2-pyridone in pure $CDCl_3$ (540 M^{-1}) and in 3% by volume $(CD_3)_2SO$ in $CDCl_3$ (50 M^{-1}) at 25 °C. There is wide variability in K_{assoc} values reported for 2-pyridone: ∼13 000 M^{-1} in benzene-d_6 at 8 °C (^{1}H-NMR),[29] 7100 M^{-1} in CCl_4 at 25 °C (IR),[30] and 100 M^{-1} in $CDCl_3$ at 25 °C (ultrasonic measurements).[31] The method of Horman and Dreux[28] has been used recently by Moore *et al.*[32] for determining K_{assoc} of phenylacetylene macrocycles. In a related experiment, Zimmerman and Duerr[33] were able to determine K_{assoc} = 20 000 M^{-2} for amide self-trimerization in 10% $(CD_3)_2SO$−90% $CDCl_3$.

In an attempt to perturb the monomer ⇄ dimer equilibrium by heating, we examined the ^{1}H-NMR δ_{obs} over the range −72 to +50 °C for all of the hydrogens of **1** (Table 2). While no large shifts occurred that might be attributed to displacing a monomer ⇄ dimer equilibrium, we noticed that the N*H* and CO_2H signals broadened upon going from −72 to +50 °C, and that $\delta_{obs}(CO_2H)$ at 40 °C was ∼0.7 ppm more shielded than at −72 °C and δ_{obs}(N*H*) was ∼0.2 ppm more shielded (Figure 4). Equilibrium with a small amount of monomer with significantly different chemical shifts might produce the observed broadening. The C−H signals, however, did not broaden particularly, and they were slightly more deshielded (by ∼0.1 ppm) at −72 °C than at 50 °C. Since small deshieldings of C−H resonances attend the shift from pyridone (δ_{C-3}= 6.59 ppm, δ_{C-4} = 7.48 ppm, δ_{C-5} = 6.29 ppm, and δ_{C-6} = 7.39 ppm in $CDCl_3$) to hydroxypyridine (2-ethoxypyridine, δ_{C-3} = 6.71 ppm, δ_{C-4} =

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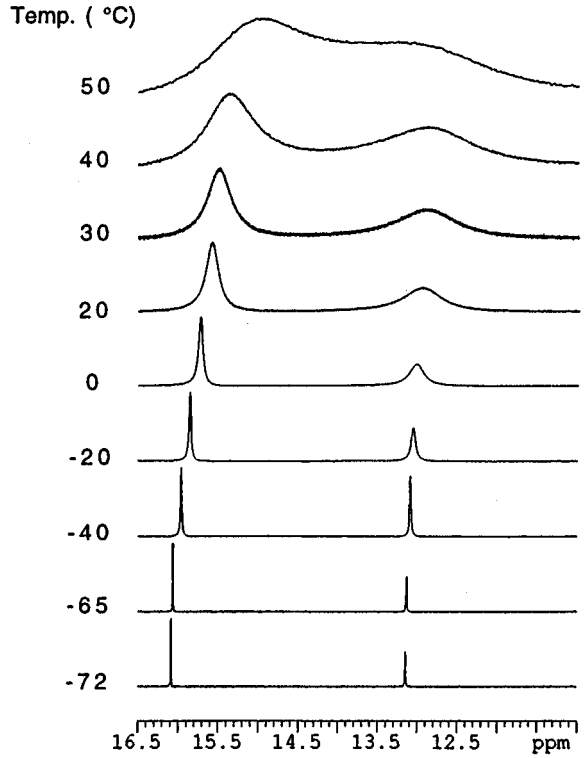

Figure 4. Temperature dependence of NH and OH ^{1}H-NMR chemical shifts of 0.08 M **1** in $CDCl_3$ from +50 (top) to −72 °C (bottom). Temperatures are indicated on each spectrum.

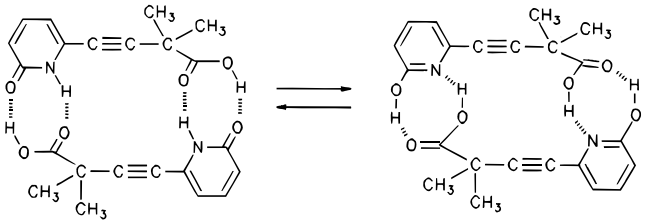

Figure 5. Lactam (left)−lactim (right) tautomerism in the hydrogen-bonded dimer of **1**. The tautomerism shown in both hydrogen bonded pairs might also occur in just one pair.

7.55 ppm, $\delta_{C-5} = 6.84$ ppm, and $\delta_{C-6} = 8.14$ ppm in $CDCl_3$) tautomers, the data might also be interpreted in terms of a lactam−lactim tautomerization in the dimer where one or both pyridones (Figure 5) adopt the hydroxypyridine tautomeric structure at low temperatures.

Concluding Comments

Pyridone acid **1** forms an intermolecularly hydrogen-bonded dimer in the crystal and in solutions in nonpolar organic solvents such as chloroform, where the dimerization constant exceeds 10^4 M^{-1}. The dimer of **1** thus constitutes one of the rare examples of strong carboxylic acid to amide hydrogen bonding.

Experimental Section

General Procedures. All nuclear magnetic resonance (NMR) spectra were measured in $CDCl_3$ and reported in δ (ppm) downfield from $(CH_3)_4Si$ on a GE QE-300, unless otherwise indicated. Infrared spectra were recorded on a Perkin-Elmer model 1610 FT instrument. Low-resolution mass spectra (MS) were measured on a Hewlett Packard 5970 or a Finnigan MAT SSQ 710 spectrometer. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Combustion analyses were carried out at Desert Analytics, Tucson, AZ. Chromatography was carried out on silica gel (60−200 mesh, column chromatography grade, Schoofs, Inc.).

NMR spectral data were obtained in spectral grade solvents from Cambridge Isotope Laboratories. Deuterated chloroform and dimethyl sulfoxide ($(CD_3)_2SO$) were distilled from calcium hydride. Ethyl acetoacetate, methyl iodide, trifluoroacetic acid, cuprous iodide and triethylamine were obtained from Aldrich or Fisher and used as received unless otherwise specified. Palladium tetrakis(triphenylphosphine) was synthesized from $PdCl_2$.[34]

Crystal Structure. Compound **1**, formula $C_{11}H_{11}NO_3$, formula weight 205.21, was crystallized from chloroform by vapor diffusion with ethyl acetate. The crystal used for diffraction measurements was a colorless, cut needle: 0.2 × 0.2 × 0.5 mm, space group $P2_1/c$ (no. 14), $a = 9.3619(6)$ Å, $b = 5.9057(4)$ Å, $c = 18.5810(10)$ Å, $\beta = 95.566(2)^\circ$, $V = 1022.47(11)$ Å, $Z = 4$. Intensities were measured at 156 K on a modified Picker FACS-1 diffractometer with Mo Kα radiation; 3633 reflections were collected with $0 < \Theta \leq 30°$. Data collection and reduction, as well as other necessary calculations, were performed with the UCLA Crystallographic Package.[35] The structure was solved with SHELXS86[36a] and refined on F^2 by full-matrix least squares with SHELXL.[36b] All non-H atoms were refined anisotropically. The four hydrogen atoms attached to C and N in the lactam moiety were riding on their attached atoms with fixed distances (default values, N−H = 0.86 Å, C−H = 0.93 Å)[36b] and a common isotropic displacement parameter. Methyl hydrogens were treated as rigid groups with C−H = 0.96 Å and a common isotropic displacement parameter. Positional and isotropic displacement parameters for the carboxyl H were refined independently. The final $R(F)$ for 142 parameters is 0.094 for all 3008 unique reflections and 0.043 for the 1833 reflections with $I \geq 2\sigma(I)$, $R_w(F^2)$ is 0.128, and the "goodness-of-fit" S is 1.04. In the crystal, **1** forms dimers, joined in $R_2^2(8)$ patterns (8-membered rings with 2 donors and 2 acceptors)[37] by N−H···O and O−H···O hydrogen bonds, across a center of symmetry (see Figure 3[38]). Coordinates for the compounds in refs 18g and 20c for use in Table 1 were obtained from the Cambridge Structural Database.[39]

Ethyl 2,2-Dimethyl-3-oxobutanoate (**7**). The ester was prepared in 75% yield by the method of Schexnayder and Engel:[21] bp 71−73 °C (10 mmHg) [lit.[40] bp 180−184 °C (atm)]; ^{1}H-NMR δ 1.24 (t, 3H, $J = 7.2$ Hz), 1.34 (s, 6H), 2.14 (s, 3H), 4.17 (q, 2H, $J = 7.2$ Hz) ppm; ^{13}C-NMR δ 13.98 (q), 21.80 (q), 55.68 (t), 61.27 (s), 173.6 (s), 205.9 (s) ppm; IR (film) ν 1740, 1716 cm^{-1}; mass spectrum (*m*/*z*, rel intensity) 158 (0.3) [$M^{\bullet+}$], 116 (86), 88 (100), 73 (68), 57 (19) amu.

2,2-Dimethyl-3-chloro-3-butenoic Acid (**6**). The chloro acid was prepared in 50% yield from **7** in two steps as described previously: mp 62−64 °C (lit.[21] mp 60.5−63 °C); ^{1}H-NMR δ 1.48 (s, 6H), 5.37 (d, 1H, $J = 2.1$ Hz), 5.39 (d, 1H, $J = 2.1$ Hz), 11.73 (br s, 1H) ppm; ^{13}C-NMR δ 24.44 (q), 50.29 (s), 112.64 (t), 144.8 (s), 180.4 (s) ppm; IR (film) ν 2902, 1704, 1686 cm^{-1}; mass spectrum (*m*/*z*, rel intensity) 148 (9) [$M^{\bullet+}$], 133 (52), 103 (41), 67 (100), 53 (32) amu.

2,2-Dimethyl-3-butynoic Acid (**5**). The alkyne acid was prepared in 80% yield as described previously: bp 80−82 °C (8 mmHg) [lit.[21] bp 77−78 °C (5 mmHg)]; ^{1}H-NMR δ 1.53 (s, 6H), 2.31 (s, 1H), 10.66 (br s, 1H) ppm; ^{13}C-NMR δ 26.93 (q), 38.15 (s), 70.45 (d), 85.47 (s), 179.9 (s) ppm; IR (film) ν 3298, 3099, 2119, 1713 cm^{-1}; mass spectrum (*m*/*z*, rel intensity) 112 (4) [$M^{\bullet+}$], 97 (7), 67 (100), 51 (32) amu.

Methyl 2,2-Dimethyl-3-butynoate (**4**). Acid **5** was methylated in ether with diazomethane generated in ether from *N*-methyl-*N*-nitrosourea. The ether solution was evaporated to leave **4** as a clear liquid (4.34 g, 0.034 mol, 96%): ^{1}H-NMR δ 1.48 (s, 6H), 2.26 (s, 1H), 3.74 (s, 3H) ppm; ^{13}C-NMR δ 27.13 (q), 37.99 (s), 52.79 (q), 69.88 (d), 86.2 (s), 173.9 (s) ppm; IR (film) ν 3290, 2119, 1743 cm^{-1}; mass

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spectrum (*m*/*z*, rel intensity) 126 (4) [M$^{\bullet+}$], 125 (23), 111 (35), 83 (13), 67 (100), 51 (31) amu.

Methyl 2,2-Dimethyl-4-(2-(benzyloxy)-6-pyridyl)-3-butynoate (3). Diethylamine (30 mL) was added to a glass pressure tube followed by the alkyne-ester **4** (0.5 g, 4.0 mmol) and 2-(benzyloxy)-6-bromopyridine[22] (1.15 g, 4.4 mmol). Cuprous iodide (50 mg, 0.26 mmol) was then added followed by palladium tetrakis(triphenylphosphine) (302 mg, 0.26 mmol) after which the tube was sealed under argon and heated to 75 °C overnight. The contents were then poured into 100 mL of water and extracted with ether (2 × 100 mL). The combined organic fractions were then dried over anhydrous magnesium sulfate and evaporated to leave a yellow oil. The oil was passed through a small column of silica gel (ether eluent) to remove trace catalyst and yielded compound **3** as a light-yellow oil (1.16 g, 3.76 mmol, 95%): ^{1}H-NMR δ 1.62 (s, 6H), 3.79 (s, 3H), 5.39 (s, 2H), 6.74 (d, 1H, J = 8.4 Hz), 7.06 (d, 1H, J = 7.2 Hz), 7.32−7.48 (m, 5H), 7.52 (dd, 1H, J = 7.9, 8.1 Hz) ppm; ^{13}C-NMR δ 27.12 (q), 38.67 (s), 52.85 (q), 67.94 (t), 81.50 (s), 91.19 (s), 111.1 (d), 121.0 (d), 127.7 (d), 128.2 (d), 128.4 (d), 137.1 (s), 138.6 (d), 140.1 (s), 163.2 (s), 173.9 (s) ppm; IR (film) ν 2231, 1741 cm^{-1}; mass spectrum (*m*/*z*, rel intensity) 309 (40) [M$^{\bullet+}$], 250 (15), 232 (11), 203 (9), 143 (10), 91 (100), 65 (31) amu.

Anal. Calcd for $C_{19}H_{19}NO_3$ (309.4): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.63; H, 6.04; N, 4.42.

2,2-Dimethyl-4-(2-(benzyloxy)-6-pyridyl)-3-butynoic Acid (2). Sodium hydroxide (2 N, 20 mL) was added to methyl ester **3** (200 mg, 0.65 mmol) followed by sufficient 95% ethanol to form a solution. The resulting creme-colored solution was heated at reflux for 2 h, after which it was acidified (concentrated HCl) and extracted with methylene chloride (2 × 40 mL). The combined organic fractions were dried over anhydrous magnesium sulfate and evaporated to leave a tan oil which was purified by passage through a small column of silica gel (methylene chloride eluent) to leave a clear viscous oil, which solidified upon standing (180 mg, 0.61 mmol, 94%): mp 73−75 °C; ^{1}H-NMR δ 1.66 (s, 6H), 5.39 (s, 2H), 6.75 (d, 1H, J = 8.4 Hz), 7.07 (d, 1H, J = 7.2 Hz), 7.32−7.40 (m, 5H), 7.52 (dd, 1H, J = 7.5, 7.8 Hz), 10.81 (br s, 1H) ppm; ^{13}C-NMR δ 26.87 (q), 38.71 (s), 68.06 (t), 81.76 (s), 90.64 (s), 111.3 (d), 121.1 (d), 127.9 (d), 128.2 (d), 128.4 (d), 137.0 (s), 138.7 (d), 139.8 (s), 163.2 (s), 178.9 (s) ppm; IR (film) ν 2976, 2234, 1712 cm^{-1}; mass spectrum (*m*/*z*, rel intensity) 295 (4) [M$^{\bullet+}$], 252 (3), 225 (10), 145 (33), 91 (100), 65 (26) amu.

Anal. Calcd for $C_{18}H_{17}NO_3$ (295.3): C, 73.20; H, 5.80; N, 4.74. Found: C, 73.00; H, 5.78; N, 4.71.

2,2-Dimethyl-4-(2-oxo-1*H*-6-pyridyl)-3-butynoic acid (1). Benzyl ether (**2**) (64 mg, 0.22 mmol) was stirred in neat trifluoroacetic acid (TFA) for 2 days, after which excess TFA was removed by azeotroping with toluene. The white crystalline residue was taken up in a minimal amount of methylene chloride. Toluene was then added and recrystallization occurred overnight. Compound **1** crystallized as small thin needles (37 mg, 0.18 mmol, 83%) with mp 190−193 °C: ^{1}H-NMR δ 1.67 (s, 6H, CH_3), 6.54 (dd, 1H, J = 0.6, 6.9 Hz, C_6−H), 6.62 (dd, 1H, J = 0.6, 9.0 Hz, C_4−H), 7.48 (dd, 1H, J = 6.9, 9.2 Hz, C_5−H), 12.95 (br s, 1H, NH), 15.50 (br s, 1H, COOH) ppm; ^{13}C-NMR δ, 26.91 (CH_3), 40.55 (C_2), 75.27 (C_4), 98.33 (C_3), 112.7 ($C_{3'}$), 119.6 ($C_{5'}$), 129.4 ($C_{6'}$), 142.6 ($C_{4'}$), 165.1 ($C_{2'}$, CONH), 179.1 (C_1, COOH) ppm; IR (film) ν 2932, 2233, 1686, 1658 cm^{-1}; mass spectrum (*m*/*z*, rel intensity): 205 (70) [M$^{\bullet+}$], 160 (100), 130 (10), 117 (19), 89 (7), 65 (6) amu. ^{13}C-NMR assignments are from long-range H−C COSY experiments; ^{1}H-NMR are from H−C COSY.

Anal. Calcd for $C_{11}H_{11}NO_3$ (205.2): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.15; H, 5.38; N, 6.49.

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Supporting Information Available: Listings of positional and displacement parameters and bond distances, angles and torsion angles for the crystal structure of **1** (2 pages). See any current masthead page for ordering and Internet access instructions.

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