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Amide Bond Cleavage: Acceleration Due to a 1,3-Diaxial Interaction with a Carboxylic Acid

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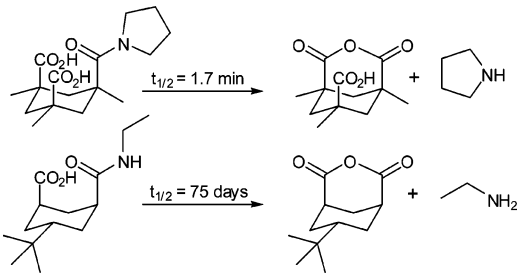


To independently assess the contribution of ground-state pseudoallylic strain to the enormous rates of amide bond cleavage in tertiary amide derivatives of Kemp's triacid, we have studied four amide derivatives of (1α-3α-5*β*)-5-*tert*-butyl-1,3-cyclohexanedicarboxylic acid. Our results demonstrate that absent pseudoallylic strain, a 1,3-diaxial interaction of an amide with a carboxylic acid leads to only a 2400-fold increase in the rate of amide bond cleavage as compared with the rate of hydrolysis of an unactivated peptide bond.

In 1988, Menger and Ladika[1] reported that the pyrrolidyl amide of Kemp's triacid (**1a**, Figure 1) undergoes intramolecular acylolysis with a half-life of 8 min at pD 7.05 and 21.5 °C. Only one of the two carboxylic acid functionalities directly participates in the reaction, as evidenced by, for example, the fact that the acid−ester−amide derivative **1b** undergoes amide cleavage at a rate only slightly slower than diacid−amide **1a**. The second acid functionality in **1a** does, however, perturb the pK_a of the first so that an appreciable concentration of reactive conjugate acid is present at neutrality. The anhydride **2** initially generated rapidly hydrolyzes, and thus the net transformation is formally the hydrolysis of an unactivated amide bond.

At neutral pH and 25 °C, the hydrolysis of an unactivated peptide bond has a half-life of roughly 500 years.[2,3] The reaction

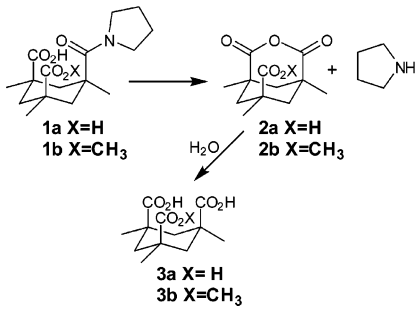
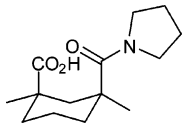


FIGURE 1. Pyrrolidyl amide cleavage.

is independent of buffer catalysis and likely involves the direct attack of water. Under these conditions, the rate of amide cleavage in Kemp's triacid derivative **1a** is approximately 33 million times faster, an increase that was initially attributed primarily to the "sustained proximity" of the carboxylic acid and amide functionalities.[1]

That only one carboxylic acid functionality is required for rapid amide cleavage was directly confirmed in 1990, when Menger and Ladika reported that monoacid−amide derivative **4** reacts at a rate comparable to that of **1a** and **1b**.[4]



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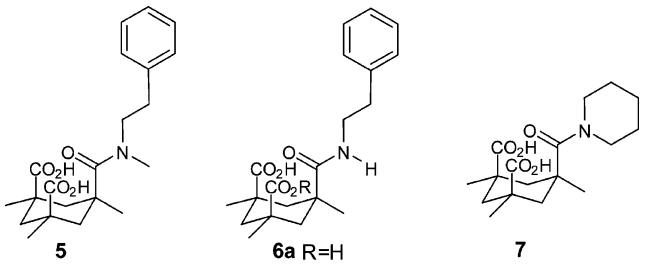
In 1994, Curran et al.[5] demonstrated that the tertiary methylphenethyl amide of Kemp's triacid **5** undergoes intramolecular amide cleavage at a rate similar to that of Kemp's derivatives **1a** and **1b** but that the secondary phenethyl amide **6a** reacts 10^2−10^4 times more slowly, depending upon pH. These workers therefore proposed that an important factor in the reactivity of the tertiary amide derivatives was the relief of "pseudoallylic (pseudo $A^{1,3}$) strain" (the nonbonded interactions between the amide substituent *trans* to the carbonyl group and the neighboring methyl group on the cyclohexyl ring) upon intramolecular attack of the amide bond. (In accord with the earlier results noted above, the cleavage rate of **6a** was found to be only slightly faster than that of the monomethyl ester **6b**.)



5 **6a** R=H **6b** R=CH_3 **7**

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(1) Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* **1988**, *110*, 6794−6796.
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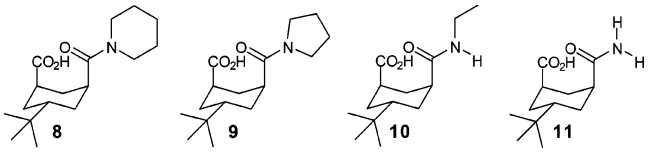
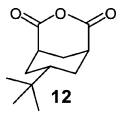
To investigate further the reactivity of Kemp's diacid−amides, our group[6] synthesized the piperidyl amide of Kemp's triacid (**7**). This derivative undergoes amide bond cleavage approximately four-times more quickly than pyrrolidyl derivative **1a**. Molecular mechanics calculations suggested, consistent with the proposal of Curran et al.,[5] that this increase in rate is due to greater pseudoallylic strain in the amide ground state of derivative **7** as a result of increased nonbonded interactions with the pseudo-chair conformation of the piperidyl ring.

Given the potential significance of Menger and Ladika's observations to the catalytic mechanism of some proteases and to the design of artificial enzymes, we wished to independently probe the role of pseudoallylic strain in these systems. We report here the syntheses and reactivities of the *tert*-butylcyclohexyl acid−amide derivatives **8**−**11**. In comparison to amide derivatives of Kemp's triacid, pseudoallylic strain is reduced in these *tert*-butyl derivatives, due to the absence of a methyl group geminal to the amide functionality; in particular, steric contacts are greatly minimized in secondary amide derivative **10** and primary amide derivative **11**. The presence of the *trans tert*-butyl group assures, of course, that the acid and amide functionalities in derivatives **8**-**11** are maintained in the 1,3-diaxial geometry.[7]



The above acid−amides were all synthesized directly from the *trans*-*tert*-butylcyclohexyl anhydride **12**[7,8] and the corresponding amine.



Compounds **8**−**11** were each dissolved in a small amount of DMSO-d_6 and introduced into buffered D_2O (at pD ∼2.5, ∼5.0, and either ∼6.5 for derivatives **10** and **11** or ∼7.5 for derivatives **8** and **9**), and the rate of amide-bond cleavage was monitored by ^{1}H NMR. The kinetic data obtained at pD 5.5 for the *tert*-butyl derivatives **9** are plotted in Figure 2. (The rate constants measured at each pD for all of the derivatives **8**−**11** are listed in the Supporting Information.)

For derivatives **8**−**11**, the pD-independent rate constant (k_{ind}) and the apparent dissociation constant for the carboxylic acid functionality (K_a) were determined from a nonlinear Levenberg−Marquardt fit of the pD−rate data to the equation utilized by Curran et al.:[5]

$$\log(k_{obs}) = \log[(k_{ind}L)/(K_a + L)]$$

where $L = D_3O^+$ concentration. The pD−rate profile for the cleavage of derivative **9** is shown in Figure 3 (the rates were measured at pD 3.0, 5.5, and 7.7, and the data fit to the above equation). Although the pK_as of the Kemp's *di*acid−amide and the *tert*-butyl *mono*acid−amide derivatives may vary considerably (for example, Menger and Ladika[1] estimated that the second pK_a of Kemp's derivative **1a** is 6.9 in D_2O), the values of k_{ind} allow for a direct comparison of cleavage rates for the reactive conjugate acid protonation state. The k_{ind} and K_a parameters obtained for derivatives **8**−**11** are listed in Table 1. Immediately evident from these data are the slow reaction rates for the sterically unencumbered *tert*-butyl derivatives **10** and **11**. Although not critical to the issue of pseudoallylic strain, the K_as obtained, including somewhat larger values for the tertiary amide derivatives, correspond well to the results obtained by Curran et al.[5]

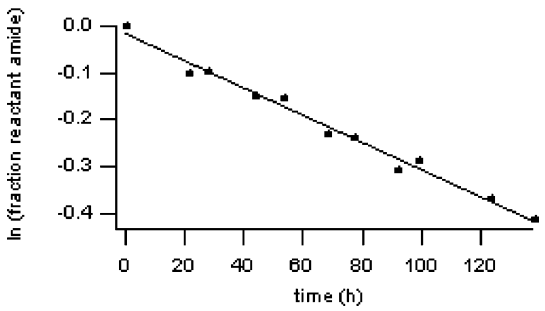


FIGURE 2. Reaction kinetics of *tert*-butyl acid−pyrrolidyl amide **9** at pD 5.5.

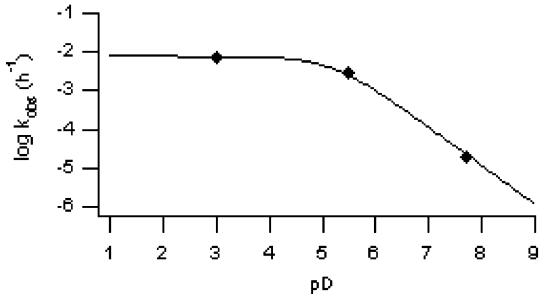


FIGURE 3. Plot of log k (h^{-1}) vs pD for *tert*-butyl acid−pyrrolidyl amide **9**.

TABLE 1. Data for *tert*-Butyl Derivatives 8−11

compd	rate constant (k_{ind}) (h^{-1})	$t_{1/2}$ (h)	K_a (in D_2O)	pK_a (in D_2O)
tert-butyl acid−piperidyl amide **8**	0.32 (± 0.04)	2.2	7.8 (± 1.4) × 10^{-6}	5.1
tert-butyl acid−pyrrolidyl amide **9**	7.70 (± 1.5) × 10^{-3}	90	6.7 (± 1.9) × 10^{-6}	5.2
tert-butyl acid−ethyl amide **10**	3.85 (± 0.2) × 10^{-4}	1800	1.1 (± 0.1) × 10^{-6}	6.0
tert-butyl acid−primary amide **11**	2.14 (± 0.2) × 10^{-3}	324	1.5 (± 0.3) × 10^{-6}	5.8

To explore further the structural features of the *tert*-butylcyclohexyl derivatives **8**−**11**, as well as of the Kemp's triacid derivatives **1a**, **5**, **6a**, **6b**, and **7** discussed above, we employed molecular modeling calculations. Consistent with the earlier calculations of Menger and Ladika,[1] the lowest energy conformation found for all nine compounds has a carboxylic-acid carbonyl oxygen positioned near the amide−carbonyl carbon. Shown in Figure 4 are the minimized structures of Kemp's diacid−pyrrolidyl amide **1a** and the corresponding *tert*-butylcyclohexyl acid−pyrrolidyl amide **9**. Note that in comparison to the Kemp's triacid derivative **1a**, the conformations of the

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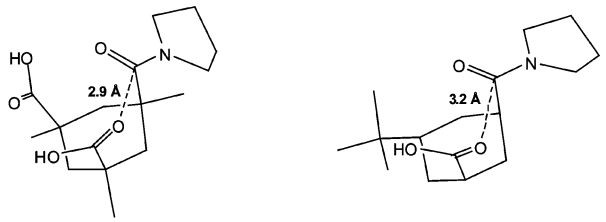


Kemp's diacid-pyrrolidyl amide derivative **1a** | *tert*-butyl acid-pyrrolidyl amide derivative **9**

FIGURE 4. Conformations of pyrrolidyl derivatives **1a** and **9**.

TABLE 2. Amide−Cyclohexyl Close Contact Distances

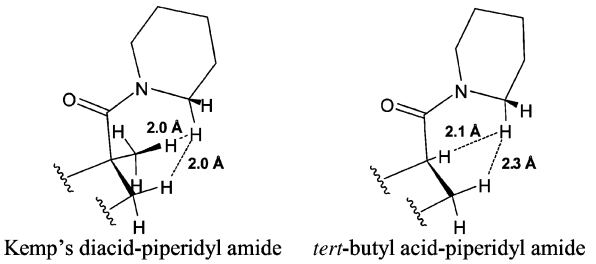
compd	$t_{1/2}$	relative reaction rate	H−H close contact(s)[a] (Å)	extent of steric clash(es)[b] (Å)
Kemp's diacid−piperidyl amide **7**	∼0.5 min[c]	216 000	2.0, 2.0[d]	0.4, 0.4
Kemp's diacid−methylphenethyl amide **5**	∼1 min[e]	108 000	2.0, 2.2, 2.3[d]	0.4, 0.2, 0.1
Kemp's diacid−pyrrolidyl amide **1a**	1.7 min[f]	63 529	2.0, 2.2, 2.4[d]	0.4, 0.2, 0.0
tert-butyl acid−piperidyl amide **8**	2.2 h	818	2.1, 2.3	0.3, 0.1
Kemp's diacid−phenethyl amide **6a**	∼6 h[e]	300	*2.0, 2.2*	*0.2, 0.0*
Kemp's acid−ester−phenethyl amide **6b**	14 h[f]	129	*2.0, 2.2*	*0.2, 0.0*
tert-butyl acid−pyrrolidyl amide **9**	90 h	20	2.2	0.2
tert-butyl acid−primary amide **11**	324 h	6	*2.1*	*0.1*
tert-butyl acid−ethyl amide **10**	75 days (1800 h)	1	*2.1*	*0.1*

[a] C−H:C−H distances of less than 2.4 Å (twice the van der Waals radius of a C−H hydrogen[9,10]) and C−H:N−H distances of less than 2.2 Å (the sum of 1.2 Å, the van der Waals radius of a C−H hydrogen, and 1.0 Å, the van der Waals radius of a N−H hydrogen[9,10]); C−H:N−H distances are shown in italics. [b] The distance(s) under 2.4 Å for C−H:C−H and under 2.2 Å for C−H:N−H (in italics). [c] Estimated through extrapolation of data in ref 6. [d] Reference 6. [e] Estimated through extrapolation of data in ref 5. [f] Reference 5.

carboxylic acid and amide functionalities are altered in the *tert*-butyl derivative **9**—absent the steric constraints afforded by the geminal methyl groups, these two substituents have rotated away from each other, and the distance between the carboxylic-acid carbonyl oxygen and the amide-carbonyl carbon has increased by 0.3 Å. A comparable increase in distance holds for all of the *tert*-butylcyclohexyl derivatives **8**−**11**.

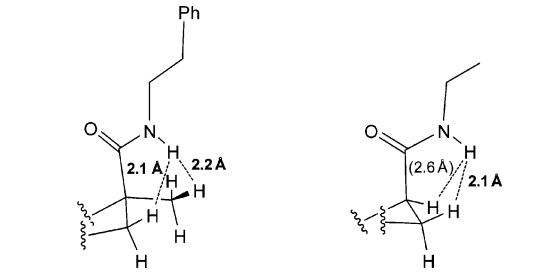
The nonbonded interactions for each of the four *tert*-butyl and five Kemp's triacid derivatives are given in Table 2 (the data are listed by derivative in order of increasing half-life for amide cleavage, as calculated from k_{ind}). For many of the derivatives, a number of low-energy conformations were found, differing only in the position of the amide substituent—the close contact distances listed in Table 2 derive from the low-energy conformation with the least-severe nonbonded interactions. Note as well that a second conformation, likely the reactive one,[1] with the carboxylic acid hydroxyl group poised to both protonate and attack the amide functionality lies at slightly higher energy (1−3 kcal/mol) for all of the derivatives; the nonbonded interactions in these conformations are essentially identical to those listed in Table 2.

To determine the extent of the nonbonded interactions, we employed the values of 1.2 Å for the van der Waals radius of a hydrogen bound to carbon and 1.0 Å for hydrogen bound to nitrogen ("polar hydrogen") utilized by the Richardson group in their studies of amide side chain orientation in protein interiors.[9,10] For all nine derivatives listed in Table 2, the data indicate that the number and severity of hydrogen−hydrogen close contact distances correlate well to the rate of amide cleavage. Shown in Figure 5, for example, are the nonbonded interactions in the minimized structures of the tertiary amide derivatives **7** and **8**. The Kemp's triacid derivative **7**, in which the two nonbonded interactions are more severe, reacts approximately 250-times more quickly than the corresponding *tert*-butyl derivative **8**.



Kemp's diacid-piperidyl amide derivative **7** | *tert*-butyl acid-piperidyl amide derivative **8**

FIGURE 5. Nonbonded interactions in piperidyl derivatives **7** and **8**.



Kemp's diacid-phenethyl amide derivative **6a** | *tert*-butyl acid-ethyl amide derivative **10**

FIGURE 6. Nonbonded interactions in secondary amide derivatives **6a** and **10**.

A similar conclusion is reached from consideration of the nonbonded interactions in the secondary amide derivatives **6a** and **10** shown in Figure 6. The Kemp's triacid derivative **6a** reacts approximately 300 times more quickly than the *tert*-butyl derivative **10**. Both derivatives have a small nonbonded interaction of 2.1 Å, but the Kemp's triacid derivative has a second interaction on the cusp of a steric clash—the kinetic data suggest that this second interaction is enough to increase the cleavage rate significantly.

Finally, while other structural features in the above derivatives might be expected to lead to increased rates of amide cleavage, we have been unable to find factors other than steric contacts that correlate with the kinetic data. For example, although each of the derivatives has a small out-of-plane distortion of the amide bond,[11] no pattern is evident. Similarly, the "attack" distance between the carboxylic-acid carbonyl oxygen and the amide-carbonyl carbon (as shown in Figure 4 for derivatives **1a** and

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9) does not parallel reaction rate—in particular, the distance for *tert*-butylcyclohexyl pyrrolidyl amide derivative **9** is almost 0.2 Å longer than for the slower-reacting Kemp's phenethyl amide derivative **6a**. (The values for the out-of-plane distortions and attack distances for each of the derivatives in Table 2 are provided in the Supporting Information.)

In conclusion, the results presented here on the *tert*-butyl amide derivatives **8**−**11** further support the conclusion of Curran et al.[5] that ground-state pseudoallylic strain plays an important role in the extraordinary reactivity of Kemp's diacid−tertiary amide derivatives. Moreover, our data allow us to estimate the rate increase of amide bond cleavage afforded by a 1,3-diaxial interaction with a carboxylic acid group in the absence of additional strain. Compared with the Kemp's diacid−pyrrolidyl amide **1a** originally reported by Menger and Ladika,[1] which has significant pseudoallylic strain, the *tert*-butylcyclohexyl ethyl amide derivative **10**, which has just a single, small nonbonded interaction, reacts 65 000 times more slowly (Table 2). In comparison with the rate of hydrolysis of an unactivated peptide bond (half-life of approximately 500 years at pH 5−9[2,3]), derivative **10** reacts only 2400 times more quickly, a small increase indeed given that enzyme-catalyzed peptide bond hydrolysis can occur with a rate acceleration of over 10^{13}-fold.[12]

Experimental Section

General Procedure for the Synthesis of the *tert*-Butyl Derivatives 8 and 9. To *tert*-butylcyclohexyl anhydride **12** (42 mg, 0.20 mmol) in 1.5 mL of CH_2Cl_2 were added the appropriate amine (0.22 mmol) and triethylamine (70 μL, 0.50 mmol). The mixture was stirred at room temperature for 12 h under nitrogen. The reaction solution was then diluted with 10 mL of CH_2Cl_2 and washed with 3 × 5 mL of 1 M HCl. The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent removed by evaporation under reduced pressure to yield the product.

(1α,3α,5β)-5-*tert*-Butyl-3-(1-piperidylcarbonyl)cyclohexanecarboxylic Acid (8). Yield: 20.1 mg (67.9%). Clear colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.66−3.41 (m, 4H), 2.95 (m, 1H), 2.77 (m, 1H), 2.23−2.08 (m, 2H), 1.90−1.78 (m, 2H), 1.72−1.46 (m, 7H), 1.44−1.31 (m, 2H), 0.90 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.8 (2C), 47.1, 43.3, 39.2, 34.9, 32.8, 28.3, 27.73, 27.67, 27.4, 27.1, 26.8, 25.8, 24.8. IR ($CHCl_3$, cm^{-1}): 1228, 1446, 1586, 1617, 1705, 2863, 2946. HRMS (TOF ES+): calcd for $C_{17}H_{29}NO_3$ (M + H)$^+$ 296.2225, found 296.2214.

(1α,3α,5β)-5-*tert*-Butyl-3-(1-pyrrolidylcarbonyl)cyclohexanecarboxylic Acid (9). Yield: 12.5 mg (44.3%). Clear colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.47 (m, 4H), 2.80 (m, 2H), 2.18−2.07 (m, 2H), 1.96 (m, 2H), 1.90−1.79 (m, 4H), 1.75−1.56 (br s, 1 H), 1.41 (m, 2H), 0.88 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.4 (2C), 46.9, 46.4, 39.0, 37.2, 32.8, 27.8, 27.7, 26.6, 26.5, 24.4. IR ($CHCl_3$, cm^{-1}): 1228, 1441, 1586, 1617, 1711, 2873, 2967. HRMS (TOF ES+): calcd for $C_{16}H_{27}NO_3$ (M + H)$^+$ 282.2069, found 282.2070.

(1α,3α,5β)-5-*tert*-Butyl-3-(1-ethylaminocarbonyl)cyclohex1anecarboxylic Acid (10). To *tert*-butylcyclohexyl anhydride **12** (7.5 mg, 36 μmol) in 0.50 mL of CH_2Cl_2 were added a 2.0 M solution of ethylamine in THF (20 μL, 40 μmol of $EtNH_2$) and triethylamine (14 μL, 100 μmol). The mixture was stirred under nitrogen for 6 h at room temperature and the product worked up as described above to yield 6.8 mg (74.3%) of a clear, colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.95 (br s, 1H), 7.80 (t, J = 4.8 Hz, 1H), 3.15 (m, 2H), 2.62 (m, 1H), 2.50 (m, 1H), 1.95−1.62 (m, 5H), 1.51 (m, 2H), 1.11 (t, J = 7.3 Hz, 3H), 0.97 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 176.5, 174.5, 38.7, 37.9, 37.4, 33.3, 32.6, 28.8, 27.63, 27.55, 26.3, 14.7. IR ($CHCl_3$, cm^{-1}): 1224, 1516, 1662, 1704, 2874, 2958, 3445. HRMS (TOF ES+): calcd for $C_{14}H_{25}NO_3$ (M + H)$^+$ 256.1912, found 256.1924.

(1α,3α,5β)-5-*tert*-Butyl-3-carbamoylcyclohexanecarboxylic Acid (11). To *tert*-butylcyclohexyl anhydride **12** (10.5 mg, 50 μmol) of in 0.75 mL of CH_2Cl_2 was added a 0.5 M solution of NH_3 in dioxane (150 μL, 75 μmol NH_3) and triethylamine (21 μL, 150 μmol). The mixture was stirred under nitrogen for 6 h at room temperature; the contents were then diluted with 10 mL of CH_2Cl_2 and washed with 3 × 5 mL of 1 M HCl. The CH_2Cl_2 layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to yield a clear, colorless oil. This oil was subsequently washed with 3 × 1 mL $CDCl_3$ and the residue retained to yield 2.5 mg (21.9%) of a clear oil. ^{1}H NMR (DMSO-d_6/$CDCl_3$, 400 MHz): δ 11.88 (s, 1H), 7.14 (s, 1H), 6.59 (s, 1H), 2.49 (m, 1H), 2.41 (m, 1H), 1.71 (m, 4H), 1.53 (m, 1H), 1.41 (m, 2H), 0.86 (s, 9H). ^{13}C NMR (DMSO-d_6/$CDCl_3$, 100 MHz): δ 177.0, 176.5, 38.6, 37.7, 37.3, 32.4, 27.7, 27.6, 27.0, 26.2. IR (KBr pellet, cm^{-1}): 1233, 1256, 1656, 1703, 2956, 3210, 3426. HRMS (TOF ES+): calcd for $C_{12}H_{21}NO_3$ (M + H)$^+$ 228.1599, found 228.1604.

Kinetic Measurements. Reactions were initiated by adding 60 μL of a DMSO-d_6 solution containing approximately 1 mg of the *tert*-butyl acid−amide to 540 μL of buffer solution in D_2O (125 or 250 mM phosphate for pD ∼2.5, ∼6.5, and ∼7.5; 125 or 250 mM mellitic acid for pD ∼5.0; the ionic strength for all buffers was adjusted to 1 or 2 using sodium chloride). Narrow-range pH paper was used to measure the pD of each solution. The pD was taken as the "pH" indicated plus 0.5, the correction factor for a "well-behaved" buffer.[6,13] The samples were maintained at 20(±1) °C in a thermostatted room. The extent of each reaction was typically determined by integrating resolved signals of the reactant relative to product. For some reactions, the product amine was integrated relative to the residual protonated DMSO in the deuterated solvent. Data analysis and curve-fitting were performed using IGOR Pro, Version 4.0 for Windows (WaveMetrics, Inc.).

Computational Details. Molecular mechanics calculations were performed using HyperChem Release 5.11 Pro for Windows (Hypercube, Inc.). The MM+ force field with the block-diagonal Newton−Raphson algorithm was employed, and all minimizations were terminated at a RMS gradient of 0.05 kcal/(Å mol) or less.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and IR spectra of compounds **8**−**12**; synthetic details for *tert*-butyl anhydride **12**; and tables of the amide-cleavage rate constants at each pD for the derivatives **8**−**11** and the amide out-of-plane deformation parameters and the carbonyl-oxygen−amide-carbon attack distances for all of the derivatives in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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