

**Activation Parameters for Base-Catalyzed Hydrolysis and  $^{18}\text{O}=\text{C}$  Exchange for Amides Having Amine Portions of Reduced Basicity. *N*-Ethyl-*N*-(trifluoroethyl)toluamide and *N*-Toluoyl-3,3,4,4-tetrafluoropyrrolidine Exchange Faster than They Hydrolyze**

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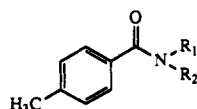
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The carbonyl  $^{18}\text{O}$  exchange and hydrolysis kinetics of *N*-ethyl-*N*-(trifluoroethyl)toluamide (4) and *N*-toluoyl-3,3,4,4-tetrafluoropyrrolidine (5) have been studied in basic media as a function of temperature. For these two amides, the rate constant for  $^{18}\text{O}=\text{C}$  exchange exceeds the rate constant for hydrolysis in the  $[\text{OH}^-]$  domain where both processes are first order in  $[\text{OH}^-]$ . For  $^{18}\text{O}$  exchange, the rate-limiting step is  $k_1$ , referring to the addition of hydroxide, while for hydrolysis, the rate-limiting step is  $k_2$  ( $k_2'$ ), referring to the breakdown of the anionic tetrahedral intermediates. The observed  $\Delta H^*_{\text{ex}}$ ,  $\Delta H^*_{\text{hyd}}$  for 4 are 17.3 (0.3) and 17.3 (0.4) kcal/mol, while those for 5 are 14.5 (0.3) and 16.7 (0.2) kcal mol $^{-1}$ , respectively. The observed  $\Delta S^*_{\text{ex}}$  and  $\Delta S^*_{\text{hyd}}$  values for 4 are -26.2 (0.8) and -33.2 (1.1) cal·K $^{-1}$ ·mol $^{-1}$  while those corresponding to 5 are -25.0 (0.8) and -23.0 (0.6) cal·K $^{-1}$ ·mol $^{-1}$ , respectively. The activation parameters are discussed in terms of the restriction of solvent in the transition states leading to and away from the anionic tetrahedral intermediates and a change in mechanism for product formation between 4 and 5.

### Introduction

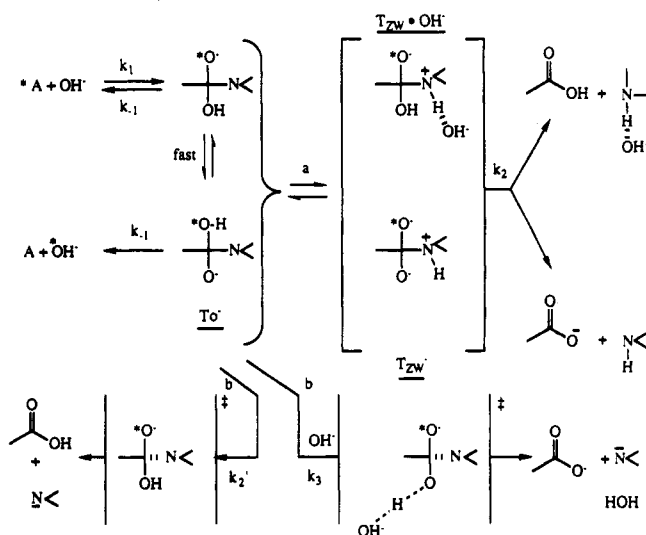
Recent studies of  $\text{OH}^-$ -promoted hydrolysis of amides 1-6 have revealed that there are well-defined mechanistic changes that occur as the basicity of the amine portion decreases.<sup>1</sup> Detailed carbonyl  $^{18}\text{O}$  exchange and  $\text{D}_2\text{O}$



- 1  $\text{R}_1 = \text{R}_2 = \text{CH}_3$
- 2  $\text{R}_1 = \text{R}_2 = -(\text{CH}_2)_4-$
- 3  $\text{R}_1 = \text{R}_2 = -(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$
- 4  $\text{R}_1 = \text{CH}_2\text{CF}_3$ ;  $\text{R}_2 = \text{CH}_2\text{CH}_3$
- 5  $\text{R}_1 = \text{R}_2 = -\text{CH}_2(\text{CF}_2)_2\text{CH}_2-$
- 6  $\text{R}_1 = \text{R}_2 = -\text{CH}=\text{CH}-\text{CH}=\text{CH}-$

solvent kinetic isotope effect studies<sup>1</sup> support the generalized hydrolytic processes<sup>2</sup> for these amides presented in Scheme I. For amides with relatively basic amine portions, the path leading to product formation (path a,  $k_2$ ) involves monoanionic but fully *N*-protonated intermediates ( $\text{T}_{\text{ZW}}$  or  $\text{T}_{\text{ZW}}\cdot\text{OH}^-$ ).<sup>1</sup> For those amides, e.g., 1 and 2, installation of the requisite  $\text{N}^+\text{H}$  is facile, and  $k_2$  is large so that the  $k_{\text{ex}}/k_{\text{hyd}}$  ratios are small. Reduction of the amine basicity increases the energy of the *N*-protonated forms as well as any transition states involving them and produces increasing amounts of  $^{18}\text{O}$ -exchange. For example, the  $k_{\text{ex}}/k_{\text{hyd}}$  ratios for 3 and 4 ( $T = 100^\circ\text{C}$ ,  $\mu = 1.0$ ) are 0.13<sup>3</sup> and ~33 while the respective  $\text{pK}_a$  values for their ammonium ions are 8.33 and 6.3, respectively.<sup>1</sup> Further reduction in amine basicity so raises the energy of  $\text{T}_{\text{ZW}}$ - and/or  $\text{T}_{\text{ZW}}\cdot\text{OH}^-$  that C-N cleavage cannot involve those species and new pathways must become important. These involve expul-

### Scheme I<sup>a</sup>



<sup>a</sup> Key: \* =  $^{18}\text{O}$ ; products refer to those initially formed after C-N cleavage.

sion of the amide anion directly from  $\text{To}^-$  (path b, Scheme I), perhaps with some general assistance of the solvent ( $k_2'$ ) or involvement of a second  $\text{OH}^-$  in assisting in the expulsion of amide anion from  $\text{To}^-$  ( $k_3$ ). To the extent that further reductions in amine basicity favor the expulsion of amide anion from  $\text{To}^-$ , the  $k_{\text{ex}}/k_{\text{hyd}}$  ratios fall.<sup>1a</sup> Our most recent study<sup>1a</sup> suggests that the point of mechanistic transition from path a for C-N cleavage, to path b, occurs when the amine basicity is someplace between that of 4 and 5 ( $\text{pK}_a$ , ammonium ion of tetrafluoropyrrolidine is 4.05,<sup>4</sup>  $k_{\text{ex}}/k_{\text{hyd}}$  for 5 is 9,  $T = 73^\circ\text{C}$ ).<sup>1a</sup>

The comprehensive hydrolytic process can be described by eq 1 from which can be derived eqs 2 and 3 which

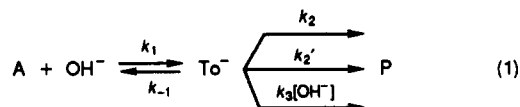
(1) (a) Brown, R. S.; Bennet, A. J.; Slebocka-Tilk, H.; Jodhan, A. J. *Am. Chem. Soc.* 1992, 114, 3092. (b) Slebocka-Tilk, H.; Bennet, A. J.; Hogg, H. J.; Brown, R. S. *J. Am. Chem. Soc.* 1991, 113, 1288. (c) Slebocka-Tilk, H.; Bennet, A. J.; Keillor, J. W.; Brown, R. S.; Guthrie, J. P.; Jodhan, A. J. *Am. Chem. Soc.* 1990, 112, 8507.

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describe the  $^{18}\text{O}$  exchange and hydrolysis kinetic constants,  $k_{\text{ex}}$  and  $k_{\text{hyd}}$ . The factor of 2 in eq 2 arises from the fact that only half the reversal by  $k_{-1}$  leads to  $^{18}\text{O}$  exchange.



$$k_{\text{ex}} = k_1 k_{-1} [\text{OH}^-] / 2(k_2 + k_2' + k_3[\text{OH}^-] + k_{-1}) \quad (2)$$

$$k_{\text{hyd}} = k_1 [\text{OH}^-] (k_2 + k_2' + k_3[\text{OH}^-]) / (k_2 + k_2' + k_3[\text{OH}^-] + k_{-1}) \quad (3)$$

Only amides 5 and 6 with relatively nonbasic amine portions have been shown<sup>1a</sup> to exhibit terms in their hydrolysis profiles that are second order in  $[\text{OH}^-]$ , but at low  $[\text{OH}^-]$ , the second-order term ( $k_3[\text{OH}^-]$ ) is unimportant. Thus, for the entire set of amides (1–6) conditions can be found where the exchange and hydrolysis kinetics are given as:

$$k_{\text{ex}} = k_1 k_{-1} [\text{OH}^-] / 2(k_2 + k_2' + k_{-1}) \quad (4)$$

$$k_{\text{hyd}} = k_1 [\text{OH}^-] (k_2 + k_2') / (k_2 + k_2' + k_{-1}) \quad (5)$$

$$k_{\text{ex}}/k_{\text{hyd}} = k_{-1} / 2(k_2 + k_2') \quad (6)$$

Amides 4 and 5 stand alone among presently investigated amides in that their  $k_{\text{ex}}/k_{\text{hyd}}$  ratios are large enough that the pathways leading to exchange and hydrolysis are kinetically isolated and therefore are amenable to individual analysis. Also, the fact that there appears to be a break in the  $k_{\text{ex}}/k_{\text{hyd}}$  ratios in passing from 3  $\rightarrow$  4  $\rightarrow$  5 suggests that there is a change in the mechanism of breakdown from the  $k_2$  pathway (Scheme I) to the  $k_2'$  pathway as the amine basicity is reduced to the point where its departure as an anion is favored. In order to offer some insight into this mechanistic change, we determined the activation parameters,  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ , for the exchange and hydrolysis processes for amides 4 and 5.

### Experimental Section

(a) **Materials.** *N*-Ethyl-*N*-(trifluoroethyl)toluamide (4)<sup>1b</sup> and *N*-toluoyl-3,3,4,4-tetrafluoropyrrolidine (5)<sup>1a</sup> were prepared as previously described, as were their 50%  $^{18}\text{O}$ -labeled analogues.

(b) **Kinetics.** The rate of hydrolysis of 4 at various temperatures were determined by HPLC analysis. Conventional UV/vis spectrophotometry cannot be used because the amine product decomposes in the reaction medium and gives colored products. NaOH solutions were prepared under  $\text{CO}_2$ -free conditions in an Ar-filled drybox and stored under Ar. The concentrations were determined by titration with standardized HCl (phenolphthalein indicator).  $\text{H}_2\text{O}$  was prepared  $\text{CO}_2$  and  $\text{O}_2$  free by passing distilled  $\text{H}_2\text{O}$  through an Osmonics Aries water purification system consisting of two MR-1 mixed bed cartridges and one MROX-1 mixed bed, organic, and  $\text{O}_2$  removal cartridge. For each temperature set, 11  $\mu\text{L}$  (12.9 mg) of 4 in 1 mL of DME was added to 24 mL of 1.08 M NaOH solution (4% v/v DME for solubility) such that the final [amide] was 2.10 mM. The solution was divided into five or six portions, each being placed in an 8-mL Teflon FEP centrifuge tube which was then sealed with a Nalgene leak-proof cap having a Teflon liner. The sealed tubes were thermostated at 72.0, 79.0, 86.0, 93.0 (water circulating bath), and 100  $^\circ\text{C}$  (boiling  $\text{H}_2\text{O}$  vapor). The tube corresponding to zero time ( $t_0$ ) was removed after a 15-min equilibration period. The other tubes were removed after various times and cooled in an ice bath, and a precisely measured 0.50-mL portion was removed

Table I. Pseudo-First-Order Rate Constants for Hydrolysis and  $^{18}\text{O}$  Exchange of Amide 4<sup>a</sup>

temp ( $^\circ\text{C}$ )	$k_{\text{hyd}}$ ( $\text{s}^{-1} \times 10^5$ ) <sup>b</sup>	$k_{\text{ex}}$ ( $\text{s}^{-1} \times 10^6$ ) <sup>c</sup>	$k_{\text{ex}}/k_{\text{hyd}}$ <sup>d</sup>
72.0	0.49 $\pm$ 0.02	1.37 $\pm$ 0.01	31.7
79.0	0.78 $\pm$ 0.01	2.28 $\pm$ 0.01	33.3
86.0	1.28 $\pm$ 0.06	3.74 $\pm$ 0.04	33.2
93.0	2.20 $\pm$ 0.04	5.94 $\pm$ 0.16	30.7
100.0	3.43 $\pm$ 0.04	10.0 $\pm$ 0.1	33.1

<sup>a</sup> Errors from standard deviations of slopes of plots of  $\ln$  [residual amide] or  $\ln(I_{M^{+2}}/(I_{M^{+2}} + I_{M^+}))$  vs time where  $I_{M^+}$  and  $I_{M^{+2}}$  are mass spectrometric peak intensities of parent and parent + 2 ions. <sup>b</sup> At 1.08 M NaOH. <sup>c</sup> At 0.095 M NaOH ( $\mu = 1.0$  (KCl)). <sup>d</sup>  $k_{\text{ex}}$  and  $k_{\text{hyd}}$  converted to second-order rate constants to determine  $k_{\text{ex}}/k_{\text{hyd}}$  ratio.

Table II. Pseudo-First-Order Rate Constants for Hydrolysis and  $^{18}\text{O}$  Exchange of Amide 5<sup>a</sup>

temp ( $^\circ\text{C}$ )	$k_{\text{hyd}}$ ( $\text{s}^{-1} \times 10^5$ )	$k_{\text{ex}}$ ( $\text{s}^{-1} \times 10^6$ )
33.1		2.12 $\pm$ 0.02
40.1	0.28 $\pm$ 0.01	3.57 $\pm$ 0.10
47.0		6.41 $\pm$ 0.13
50.0	0.671 $\pm$ 0.01	
54.0		10.6 $\pm$ 0.2
57.0	1.15 $\pm$ 0.02	
61.3		16.9 $\pm$ 0.2
64.0	1.97 $\pm$ 0.03	
70.1	3.30 $\pm$ 0.13	
71.5	3.74 $\pm$ 0.05	
72.6	4.05 $\pm$ 0.05	
75.0	4.58 $\pm$ 0.04	
77.5	5.79 $\pm$ 0.07	
80.0	6.52 $\pm$ 0.10	
82.5	7.83 $\pm$ 0.14	
85.0	8.52 $\pm$ 0.17	

<sup>a</sup>  $[\text{NaOH}] = 0.0219$  M,  $\mu = 1.0$  (KCl).

and quenched by injection into 0.75 mL of MeOH containing enough HOAc to neutralize the base. Twenty  $\mu\text{L}$  of this solution was subjected to HPLC analysis to determine quantitatively the amount of residual amide: flow, 1.38 mL/min, 60/40 MeOH/ $\text{H}_2\text{O}$  degassed with He for 10 min before run; Waters 8 MB C18 radial pak column; UV detection 254 nm; amide retention time, 10.7 min. For each temperature two independent samples were analyzed, and each was subjected to three HPLC determinations of the amount of residual amide. The  $k_{\text{hyd}}$  value was determined as the slope of a plot of  $\ln$  (amide area) vs time: the averages of the so-determined pseudo-first-order rate constants for the hydrolyses of 4 are presented in Table I. The rate of hydrolysis of 5 at 40.2, 50.0, 57.0, 64.0, 70.1, 71.5, 72.6, 75.0, 77.5, 80.0, 82.5, and 85.0  $^\circ\text{C}$  (external MGW Lauda RM20 water circulating bath) was measured by observing the rate of increase in absorbance at 235 nm of  $1 \times 10^{-4}$  M aqueous solutions of 5 (containing 4% DME for solubility) using a Cary 210 UV/vis spectrophotometer. The NaOH concentration was 0.0219 M ( $\mu = 1.0$  (KCl)), and all solutions were  $\text{CO}_2$  free and made up in an Ar-filled drybox. Observed pseudo-first-order rate constants ( $k_{\text{hyd}}$ ) were obtained by fitting the absorption vs time curves to a standard exponential model. Given in Table II are the  $k_{\text{hyd}}$  values for hydrolysis of 5 (average of three runs). The  $^{18}\text{O}$  exchange kinetics for 50%  $^{18}\text{O}$  labeled amides were determined as previously described<sup>1a,b</sup> at five different temperatures for each amide. The pseudo-first-order rate constants for exchange ( $k_{\text{ex}}$ ) for 4 and 5 are reported in Tables I and II.

### Results and Discussion

The pseudo-first-order rate constants for base-catalyzed hydrolysis and carbonyl  $^{18}\text{O}$  exchange of amides 4 and 5 shown in Tables I and II were converted to second-order ones and then plotted according to the Eyring equation in the usual way against  $1/T$  to give the activation parameters shown in Table III.

Because  $k_{\text{ex}} > k_{\text{hyd}}$  for these two amides, reversal from the anionic tetrahedral intermediate ( $k_{-1}$ ) must be large

**Table III. Activation Parameters for Base-Catalyzed Hydrolysis and Carbonyl  $^{18}\text{O}$  Exchange of Amides 4 and 5<sup>a</sup>**

parameter	amide 4		amide 5	
	exchange	hydrolysis <sup>b</sup>	exchange	hydrolysis
$\Delta H^\ddagger$ (kcal·mol <sup>-1</sup> )	17.3 ± 0.3	17.3 ± 0.4	14.5 ± 0.3	16.7 ± 0.2
$\Delta S^\ddagger$ (cal·K <sup>-1</sup> ·mol <sup>-1</sup> )	-26.2 ± 0.8	-33.2 ± 1.1	-25.0 ± 0.8	-23.0 ± 0.6
$\Delta G^\ddagger$ (100 °C) (kcal·mol <sup>-1</sup> )	27.1 ± 0.6	29.7 ± 0.8	23.8 ± 0.6	25.3 ± 0.4

<sup>a</sup> Determined from Eyring plots of  $\ln(kh/k_B T)$  vs  $1/T$  where  $h$  = Planck's constant,  $k_B$  = Boltzmann's constant, and  $k$  = second-order exchange or hydrolysis rate constant; duplicate runs of five temperatures for exchange and hydrolysis of 4 and exchange for 5; triplicate runs of 12 temperatures for hydrolysis of 5. <sup>b</sup> Previously determined<sup>1b</sup>  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  for hydrolysis of 4  $16.4 \pm 0.6$  kcal·mol<sup>-1</sup>,  $35.5 \pm 1.5$  cal·K<sup>-1</sup>·mol<sup>-1</sup>; by  $^1\text{H}$  NMR, three temperatures.

relative to product formation ( $k_2$  or  $k_2'$ ). Thus, the expressions for  $k_{\text{ex}}$  and  $k_{\text{hyd}}$  are simplified to:

$$k_{\text{ex}} = k_1[\text{OH}^-]/2 \quad (7)$$

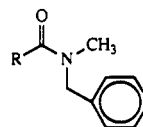
$$k_{\text{hyd}} = k_1(k_2 + k_2')[\text{OH}^-]/k_{-1} = K(k_2 + k_2')[\text{OH}^-] \quad (8)$$

where  $K = k_1/k_{-1}$ . As such,  $k_{\text{ex}}$  and its associated activation parameters pertain only to the transition state corresponding to  $\text{OH}^-$  attack, while the rate-limiting step(s) pertaining to hydrolysis are those involving  $k_2$  and/or  $k_2'$  corresponding to breakdown of the anionic intermediate.

Inspection of the activation parameters given in Table III reveals that for amide 4 the  $\Delta H^\ddagger$  for both hydrolysis and exchange are essentially equal (17.3 kcal·mol<sup>-1</sup>) while the  $\Delta S^\ddagger$  values are both negative, with the one associated with hydrolysis being somewhat more negative. This has two important ramifications, namely: (1) it is the entropy term that retards the hydrolysis and allows exchange to predominate, and (2) since the  $\Delta H^\ddagger$  for exchange and hydrolysis are experimentally the same, the  $k_{\text{ex}}/k_{\text{hyd}}$  ratio will not change significantly as a function of temperature. That the  $\Delta S^\ddagger_{\text{hyd}}$  is more negative than the  $\Delta S^\ddagger_{\text{ex}}$  is probably a consequence of the greater restriction of waters of solvation in the transition state required for breakdown of the highly charged separated  $\text{T}_{\text{ZW}}^-$  or  $\text{T}_{\text{ZW}}\text{-OH}^-$  relative to the transition state required for simple addition to  $\text{OH}^-$  to form  $\text{To}^-$  from 4.

In the case of amide 5 where  $k_{\text{ex}}/k_{\text{hyd}} = k_{-1}/2k_2' = 9$  at 73 °C,<sup>1a</sup> the entropies for exchange and hydrolysis are similar which means that  $^{18}\text{O}$  exchange exceeds hydrolysis because the  $\Delta H^\ddagger_{\text{ex}}$  is lower than  $\Delta H^\ddagger_{\text{hyd}}$  by roughly 2 kcal·mol<sup>-1</sup>. The similarity of the  $\Delta S^\ddagger_{\text{ex}}$  and  $\Delta S^\ddagger_{\text{hyd}}$  values is consistent with the proposed mechanism shown in Scheme I where the transition states controlling exchange ( $k_1$ ) and hydrolysis ( $k_2'$ ) are both close to  $\text{To}^-$  and involve similar restriction of solvent in the expulsion/addition of the mono anionic groups,  $\text{OH}^-$  or  $\text{NR}_1\text{R}_2$ . The fact that  $\Delta H^\ddagger_{\text{ex}} < \Delta H^\ddagger_{\text{hyd}}$  means that the  $k_{\text{ex}}/k_{\text{hyd}}$  ratio will decrease as the temperature increases. From the activation parameters given in Table III,  $k_{\text{ex}}/k_{\text{hyd}}$  ratios of 12.9 and 7.4 at 40 and 100 °C are calculated, respectively.

A similar sort of dissection of the activation parameters controlling exchange and hydrolysis has been attempted previously by Deslongchamps et al.<sup>5</sup> in order to lend support to his theory of stereoelectronic control of the cleavage of tetrahedral intermediates formed during hydrolysis reactions. However, the data presented in the original paper<sup>5a</sup> for hydrolysis and  $^{18}\text{O}$  exchange for amides 7–9 indicate that the  $k_{\text{ex}}/k_{\text{hyd}}$  ratios vary from 0.28 to 0.48



7 R = H

8 R = CD<sub>3</sub>9 R = CD<sub>2</sub>CH<sub>3</sub>

( $T = 10\text{--}45$  °C), 0.10–0.30 ( $T = 40\text{--}85$  °C), and 0.18–0.43 ( $T = 60\text{--}90$  °C), respectively, which means that the  $k_{-1}$  and  $k_2$  transition states are of comparable energy. Therefore, the appropriate equations for describing the exchange and hydrolysis kinetics for 7–9 are not the reported ones<sup>5</sup> which are equivalent to eqs 7 and 8, but rather eqs 4 and 5 where the  $k_3[\text{OH}^-]$  term is omitted from the generalized hydrolysis pathway of eq 1. Moreover, in such cases because the exchange and hydrolysis processes are of comparable energy, they are not kinetically isolated, so that any activation parameters determined are those corresponding to the virtual transition states associated with partitioning of the intermediate.<sup>6</sup> In the reported cases, it was observed that  $k_{\text{ex}}/k_{\text{hyd}}$  ratios increased with temperature, which is required since  $\Delta H^\ddagger_{\text{ex}} > \Delta H^\ddagger_{\text{hyd}}$ .

**Conclusions.** For amides 4 and 5 where  $^{18}\text{O}$  exchange is far more prominent than hydrolysis, the exchange and hydrolysis transition states are kinetically isolated and therefore analyzable in terms of their activation parameters. The important consequence of these findings is that for a given amide  $k_{\text{ex}}/k_{\text{hyd}}$  may increase,<sup>5</sup> decrease, or remain unchanged as a function of temperature, but this is controlled by the  $\Delta H^\ddagger$  of the competing transition states which is not immediately predictable in any given situation.

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(5) (a) Deslongchamps, P.; Bartlett, R.; Taillefer, R. J. *Can. J. Chem.* 1980, 58, 2167. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983; pp 111–116.

(6) According to Deslongchamps' analysis<sup>5a</sup> of eq 1, "because there is isotope exchange with solvent,  $k_2$  must be the rate determining step and since an OH group is a better leaving group than an  $\text{R}_2\text{N}$  group, we must have  $k_{-1} \gg k_2$  and hence  $k_{\text{hyd}} = Kk_2$  where  $K = k_1/k_{-1}$ , the equilibrium constant for tetrahedral intermediate formation". This assumption is only true if  $k_{\text{ex}} \gg k_{\text{hyd}}$  as is the situation for amides 4 and 5 studied herein, but is not warranted for amides 7–9. Any conclusions based on such assumptions that relate to the support of the stereoelectronic theory<sup>5</sup> as pertains to tetrahedral intermediate partitioning must be viewed with skepticism.