greater than 100:1 in favor of C-N cleavage for the hydroxyl derivatives **5** and **6** (the T^0 formed from dimethylbenzamide).[2,18] Several reasons for the partitioning difference were advanced by McClelland,[20] the most reasonable being a hydrogen bonding stabilization of the remaining OH group in **5** or **6** with solvent (not possible with **4**) that develops in the TS for C-N cleavage. Our observation of SKIE effects near unity for the breakdown of T^0 produced from **2a** or *N*,2,4-trimethylacetanilide[3] supports that rationale and extends it to accommodate a solvent-promoted proton removal from the OH group concurrent with the C-N cleavage.

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Base-Catalyzed Hydrolysis and $^{18}O{=}C$ Exchange Kinetics for Toluamides Containing Amine Portions of Reduced Basicity. *N*-Toluoyl-3,3,4,4-tetrafluoropyrrolidine and *N*-Toluoylpyrrole

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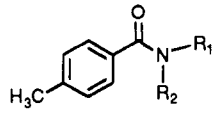
Abstract: Base-catalyzed hydrolysis and $^{18}O{=}C$ exchange kinetics for *N*-toluoyltetrafluoropyrrolidine (IV) and *N*-toluoylpyrrole (V) have been determined as a function of $[OH^-]$ at 73 and 25 °C respectively, μ = 1.0 (KCl). Both amides exhibit k_{hyd} vs $[OH^-]$ profiles that contain first-order and second-order domains in $[OH^-]$. For IV at low $[OH^-]$ where both the hydrolysis and exchange kinetics are first order in $[OH^-]$, k_{ex}/k_{hyd} = 9.0, and this value is progressively reduced as $[OH^-]$ increases. The solvent kinetic isotope effect for hydrolysis of IV at low $[OH^-]$ is slightly inverse $(k_{hyd})_{H/D}$ = 0.72, and at high $[OH^-]$ becomes 1.54, suggestive of a change in mechanism from one involving spontaneous expulsion of amide anion at low $[OH^-]$ to one involving a proton in flight concurrent with amide anion expulsion at high $[OH^-]$. For V, the k_{hyd} profile from pH 8.5 to 13.7 is approximately linear but shows a small inflection point at pH 10.8. At the same time, the k_{ex} vs $[OH^-]$ profile for V at low $[OH^-]$ is first order in $[OH^-]$ (k_{ex}/k_{hyd} = 0.24) but plateaus above pH 10.8 so that the k_{ex} and k_{hyd} profiles diverge. The hydrolytic and exchange processes for these amides are analyzed as involving a mechanism wherein the low $[OH^-]$ domain involves reversible attack of OH^- on the amide to form T_O^- followed by spontaneous C-N cleavage to expel the amide anion either without general acid assistance by solvent or with a small component of it. The difference in the k_{ex}/k_{hyd} ratios for the two amides is explicable since the pyrrolide anion is a better leaving group than the tetrafluoropyrrolidide anion. At higher $[OH^-]$, second-order terms in $[OH^-]$ come into play wherein OH^- deprotonates T_O^- concurrently with expulsion of the amide anion. This process effectively halts the reversal and $^{18}O{=}C$ exchange at high $[OH^-]$, since each time T_O^- is produced it immediately undergoes OH^- promoted breakdown to products. A unified picture of base promoted hydrolysis of toluamides containing amine portions of basicity varying over ~15 pK_a units is presented.

Introduction

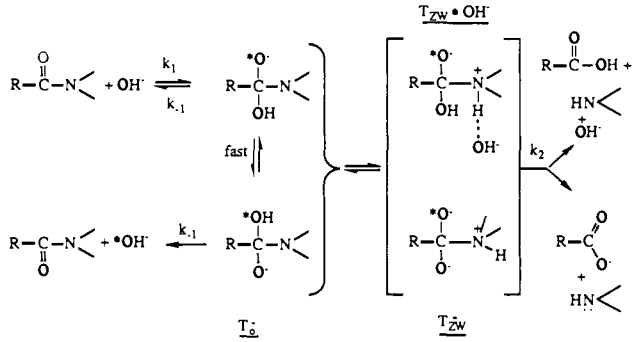
On the basis of carbonyl ^{18}O exchange studies and D_2O solvent kinetic isotope effects (SKIE), a common hydrolytic mechanism for the tertiary amides (I-III) in base was proposed.[1] For each



I: $R_1 = R_2 = CH_3$
II: $R_1 = R_2 = (CH_2)_4$
III: $R_1 = CH_2CF_3$; $R_2 = CH_2CH_3$

amide, the hydrolysis and exchange processes are first order in $[OH^-]$ throughout the concentration ranges studied. However, the k_{ex}/k_{hyd} ratio (defined as $k_{ex}/k_{hyd} = k_{-1}/2k_2$; Scheme I) varies within the series from 0.01-0.015 (I)[1c] to 0.013-0.02 (II)[1c] to 33.4 (III),[1d] all at T = 100 °C, μ = 1.0 (KCl). This can be understood within the mechanistic context of Scheme I since breakdown to product (via T_{ZW}^- or $T_{ZW\cdot OH}^-$) occurs from tetrahedral intermediates that have a protonated N in place prior to C-N cleavage. Thus, in III where the basicity of the amine portion is reduced (pK_a(conjugate acid) = 6.3[1d]) relative to dimethylamine or pyrrolidine (pK_a(conjugate acids) = 10.64 and 11.27[2]), protonation

Scheme I[a]



[a] *O = ^{18}O.

of the amine and subsequent C-N cleavage is inhibited so that more reversal and ^{18}O exchange is observed.

At some point, further reductions in amine basicity should so inhibit N-protonation that the amine cannot be expelled from T_O^-,

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(1) (a) Ślebocka-Tilk, H.; Brown. R. S. *J. Org. Chem.* **1988**, *53*, 1153. (b) Ślebocka-Tilk, H.; Brown, R. S. *J. Org. Chem.* **1987**, *52*, 805. (c) Ślebocka-Tilk, H.; Bennet, A. J.; Keillor, J. W.; Brown, R. S.; Guthrie, J. P.; Jodhan, A. *J. Am. Chem. Soc.* **1990**, *112*, 8507. (d) Ślebocka-Tilk, H.; Bennet, A. J.; Hogg, H. J.; Brown, R. S. *J. Am. Chem. Soc.* **1991**, *113*, 1288.
(2) *CRC Handbook of Chemistry and Physics*, 48th ed.; Weast, R. C., Ed.; CRC Press: Boca Raton, FL, 1967; pp D87-D89.

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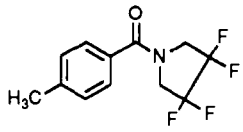
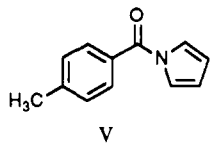
since T_{ZW}^- or $T_{ZW\cdot OH}^-$ are too high in energy to be viable intermediates. Therefore, new pathways for breakdown will be required. Indeed, it has been reported[3] that *N*-aroylpyrroles, which contain a very nonbasic N (pK_a conjugate acid = −3.8[4]), exhibit second-order terms in [OH^-] although detailed kinetic and isotopic exchange studies were not reported. Herein we report such studies with IV and V which demonstrate the above expected changes



IV



V

in the mechanism of hydrolysis. Moreover, for amides where the hydrolyses exhibit second-order terms in [OH^-], an opportunity exists to experimentally test the two critical but necessary assumptions in the use of the ^{18}O-exchange methodology, namely (1) that the tetrahedral intermediates that lead to exchange are on the hydrolysis reaction pathway and (2) that protonic equilibration of the ^{16}O and ^{18}O oxygens is established in T_O^-.

Experimental Sections

(a) Materials. *N*-Toluoyltetrafluoropyrrolidine (IV) was synthesized by a standard Schotten-Bauman reaction of *p*-toluoyl chloride (0.78 g, 5.05 mmol) that was slowly added to 0.72 g of tetrafluoropyrrolidine[5] (5.04 mmol) in 15 mL of 10% NaOH and 5 mL of CH_2Cl_2. Extraction of the mixture with CH_2Cl_2, followed by drying ($MgSO_4$) and removal of volatiles gave 1.3 g of white crystalline material. Two recrystallizations from EtOH/H_2O yielded 0.5 g (38%) of the pure amide: mp 83–84 °C; ^1H NMR ($CDCl_3$, 25 °C) δ 2.40 (s, 3 H), 4.05 (bs, 4 H), 7.35 (4 H, AA'BB'); ^{19}F NMR ($CFCl_3$, 25 °C) δ −123.77, −125.13; IR (KBr 1637.5 cm^{-1}); exact mass for $C_{12}H_{11}NOF_4$ calcd 261.07768, found 261.07771. Anal. Calcd for $C_{12}H_{11}NOF_4$: C, 55.18; H, 4.24; N, 5.36. Found: C, 55.16; H, 4.18; N, 5.22.

N-Toluoylpyrrole (described in the preceding paper,[5] and in ref 6) was prepared by the general procedure of Cipiciani et al.[3b]

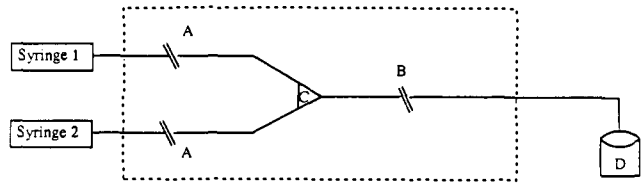
The 50% ^{18}O-labeled amides (IV and V) were prepared exactly as above with the exception that ~50% ^{18}O-labeled toluoyl chloride[1c] was used.

(b) Kinetics. (i) The rates of hydrolysis of IV in H_2O and D_2O were obtained by observing the rate of decrease in absorbance at 235 nm of 1×10^{-4} M aqueous solutions of IV (containing 4% of dimethoxyethane (DME) for solubility) using a Cary 210 UV–vis spectrophotometer. The temperature was maintained at 73 ± 0.2 °C using an external MGW Lauda RM20 water circulating bath. Solutions of various base concentrations (0.002–2.27 M; μ = 1.0 (KCl) except for [NaOH] > 1.0 M) were equilibrated in the cell holder for 20–30 min prior to the initiation of a run. Reactions were initiated by the injection of 30 μL of a 1×10^{-2} M stock solution of IV in DME into the cell. All aqueous solutions were CO_2-free (Osmonics Aries water purification system with two MR-1 mixed bed cartridges and one MROX-1 mixed bed, organic and oxygen removal cartridge). All manipulations were performed in an argon-filled drybox, or with syringes. Observed pseudo-first-order rate constants (k_{hyd}) were obtained by fitting the absorbance vs time curves to a standard exponential model. Values reported in Table 1S (supplementary material) are the averages of two to three determinations.

The hydrolysis of *N*-toluoylpyrrole (V) was conducted in a variety of ways over a pH range from 8.50 to 13.70 (μ = 1.0 (KCl)) at T = 25.0 °C. Following are representative descriptions of each of the five different apparatus setups, the results obtained through their use being presented in Table 2S (supplementary material).

(a) A solution of V (1.09×10^{-4} M) in 1.0 M KCl (containing 0.3% DME for solubility) was mixed with an equal volume of aqueous NaOH (μ = 1.0 KCl) in a Durrum 110 stopped-flow spectrophotometer. Solutions in each of the drive syringes were thermostated for 30 min at 25 °C prior to reaction. The rate of change in absorbance at 260 nm was followed. Base concentration was determined by titration of the effluent from the cell after mixing using standardized HCl and a bromothymol blue indicator (pH 12.35–13.70).

Scheme II. Fluid Flow System for Determining ^{18}O Exchange Where Hydrolysis Is Fast



A - teflon tubes to allow thermostating of unreacted components (5 meters each)

B - teflon tube of known volume (5.508 mL) in which reaction occurs

C - three way teflon mixing block

D - receiver to quench contents of flow from tube B

(b) A solution of amide (1.17×10^{-4} M) in 1.0 M KCl (2% DME for solubility) was mixed with an equal volume of NaOH, μ = 1.0 (KCl) using a Hi-Tech SFA-11 rapid mixing accessory with its cell in the thermostated sample compartment of a Hewlett-Packard 8451 A diode array spectrophotometer. The change in absorbance at 260 nm was monitored. Base concentrations were determined by titration of the initial base solution with standardized HCl, bromothymol blue, and dividing the so-determined concentration by 2 for mixing (pH 11.5–12.72).

(c) A solution of standardized NaOH solution (0.105 M, μ = 1.0 KCl) was diluted to 50 mL with 1.0 M KCl. To this was added a 30-μL aliquot of V in DME (5.05 mM) and the change in absorbance at 260 nm was monitored using the HP 8451 system, pH 11.32.

(d) To follow the hydrolysis using a pH–stat methodology, a UV–vis quartz cell was fused via a 10 cm tube to the bottom of a 100-mL flask which contained five necks with 14/20 joints. The five necks accommodated a Radiometer GK2321C combination electrode, a microaddition pipet for addition of titrant, a thermometer, an inlet for a long syringe needle through which Ar could pass for sparging the solution, and an Ar outlet tube. This assembly was placed in the thermostated cell holder of the HP8451 diode array spectrophotometer. The electrode and micropipet were connected to a Radiometer TTT 2 titrator with a PHA843B titrigraph module and ABU12 autoburet. The kinetics were monitored at 260 nm with pH controlled by the pH-stat assembly; (pH 9.7–10.5).

(e) Stock solutions of CHES (*N*-cyclohexylaminoethanesulfonic acid) (0.1 M; μ = 1.0 KCl) and CHES (0.1 M; μ = 1.0 KCl) containing 1.0 equiv of NaOH were mixed in varying ratios to give buffer solutions of pH 8.5–10.06, $[buffer]_t$ = 20, 40, 60, 80, and 100 mM. The hydrolysis of 5×10^{-5} M V in the various solutions was monitored at T = 25 °C, λ = 260 nm using a Cary 210 UV–vis spectrophotometer.

Reaction rates in D_2O were determined using protocol e, above, and CHES buffers, as well as using the stopped flow protocol a.

(ii) ^{18}O Exchange. The rate constants for carbonyl ^{18}O exchange (k_{ex}) were studied from 0.01 M ≤ [OH^-] ≤ 1.0 M (T = 73.0 °C, μ = 1.0 KCl) for IV, and at various pH values between 8.52 and 12.03 (T = 25 °C, μ = 1.0 KCl) for V. For slower reactions with IV, a protocol analogous to that reported before[1c,d] was used wherein a 200-mL 0.002 M, 4% (v/v) DME solution of the amide was divided into eight portions, each being placed in a 30-mL Teflon FEP tube sealed with a leakproof Nalgene cap having a Teflon liner. These were immersed into a 73 °C thermostated bath with two tubes being withdrawn after 15 min, cooled in an ice bath, and worked up[1c,d] to provide the ^{18}O content for IV at time zero. The remaining tubes were withdrawn in pairs at various times and worked up[1c,d] and their ^{18}O contents determined by low-resolution mass analysis using methodologies and instrumentation already described.[1c,d]

For faster reactions, a fluid flow system schematized in Scheme II was developed which consisted of two drive syringes, each connected to ~5 m of Teflon tubing (tube A) which in turn were connected via a three-way mixing block (C) to a single 10-ft Teflon tube (tube B) for which the volume was accurately determined in a previous set of determinations (v = 5.508 mL). The entire tubing assembly and three-way mixing block was immersed in a 73 °C bath. Into one 30-mL drive syringe was placed the base solution (μ = 1.0 KCl), while into the other was placed a 1.0 M KCl solution containing 8% DME (for solubility) and 1.5×10^{-2} M in IV. The syringes were then installed on a Sage Instruments Model 355 dual syringe pump, the speed of which could be adjusted as necessary. The syringe pump was started and the effluent from the mixing tube was collected. The first 10 mL of fluid was discarded and then 40 mL of fluid was drained into a 50-mL volumetric flask immersed in an ice bath and containing 10.0 mL of a 1:1 KH_2PO_4:Na_2HPO_4 buffer (pH

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(4) Chiang, Y.; Whipple, E. B. *J. Am. Chem. Soc.* **1963**, *85*, 2763.

(5) Bennet, A. J.; Slebocka-Tilk, H.; Brown, R. S. *J. Am. Chem. Soc.*, preceding paper in this issue.

(6) Bennet, A. J.; Somayaji, V.; Brown, R. S.; Santarsiero, B. D. *J. Am. Chem. Soc.*, in press.

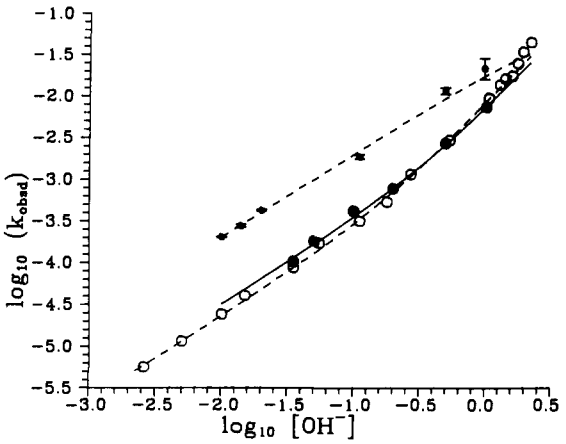


Figure 1. Plots of k_{hyd} (O) and k_{ex} (⧗) vs [OH^-] for base-promoted hydrolysis of amide IV, T = 73 °C, μ = 1.0 (KCl); k_{hyd} in D_2O (O). Lines through the data are calculated NLLSQ fits to eqs 2 and 3 according to methods given in text. k_{hyd} data in D_2O (●); for k_{ex} data, error bars are 2 × standard deviation.

6.5) to quench the reaction. The time necessary to collect 40 mL of effluent (t_1) was recorded and the average time of residence of the reaction mixture in the 73 °C bath (t_2) was calculated as

$$t_2 = \frac{\text{volume of 10-ft tube} \times t_1}{40\text{ mL}} = \frac{5.508t_1}{40}$$

The contents of the 50-mL volumetrics were worked up and mass analyzed as described.[1c,d] In a typical experiment, eight to nine individual points were used to calculate the k_{ex} values determined in this way. Control experiments with the flow system protocol established that at a [OH^-] where both standard extraction and flow methodologies were feasible, the k_{ex} values obtained by both methods were the same within 5%.

^{18}O exchange studies for 50%-^{18}O-labeled V were conducted using the above two protocols but at 25 °C. For the standard extraction method, the reaction was quenched by the rapid addition of an excess of 1 N HCl. For the flow methodology, the reaction was quenched by running the effluent from tube B into a 50-mL ice cold solution of 1 N HCl.

For V, ^{18}O exchange in some pH regions employed a pH-stat methodology where pH was monitored with a Radiometer GK2321C electrode and was controlled by a Radiometer TTT2 titrator and PHA843B titration module. After the attainment of a suitable pH, and thermal equilibration of the contents in a 25 °C bath, the reaction was initiated by injecting 600 μL of a 25 mM solution of labeled amide in DME. After a set time, the reaction mixture was extracted with 60 mL of purified CH_2Cl_2 and this was worked up and analyzed as described.[1c,d] For the slowest k_{ex} experiments, CHES buffers (as described above) were employed at 10 and 100 mM, μ = 1.0 KCl.

(c) Product Studies. These were done for IV by ^{19}F NMR monitoring of a 1 × 10^{-3} M solution of the amide in 4% DME, NaOH (0.01–1.0 M; μ = 1.0 KCl). A 25-mL portion of the solution was withdrawn from the hydrolysis bath (73 °C) after appropriate times (for 1 M NaOH, 10 $t_{1/2}$; for 0.3 M NaOH; t = 0, $t_{1/2}$; for 0.01 M NaOH, t = $t_{1/2}$) and extracted with 1 mL of $CDCl_3$. The chloroform phase was used directly for ^{19}F NMR. At t = 0, only amide peaks at δ −124.1, −125.4 were observed; at t = $t_{1/2}$, both amide and amine peaks at δ −121.39 (decoupled) were observed; at t = 5 or 10$t_{1/2}$, only the amine peak was observed. No other fluorine resonances were detected.

For the hydrolysis of V, a clean isosbestic point at 238 ± 1 nm was observed throughout the hydrolysis range. The products for base hydrolysis of V[3b] and *N*-benzoylpyrrole[3a] have previously been shown to be the acid and pyrrole.

Results

Given in Tables 1S ans 2S (supplementary material) are the exchange and hydrolysis rates for IV and V as a function of [OL^-]. The results are graphically illustrated in Figures 1 and 2. The upward curvature in the k_{hyd} plot of Figure 1 at increasing [OH^-] signifies the onset of a second order in [hydroxide] term in the hydrolysis of IV. Shown on that plot as the closed circles are the k_{hyd} data in OD^-: this plot crosses that for OH^- and indicates that there is a change in the solvent kinetic isotope effect (SKIE) from slightly inverse at low [OL^-] to normal at increased [OL^-]. Of note in Figure 2 is the apparent linearity in the k_{hyd} plot for

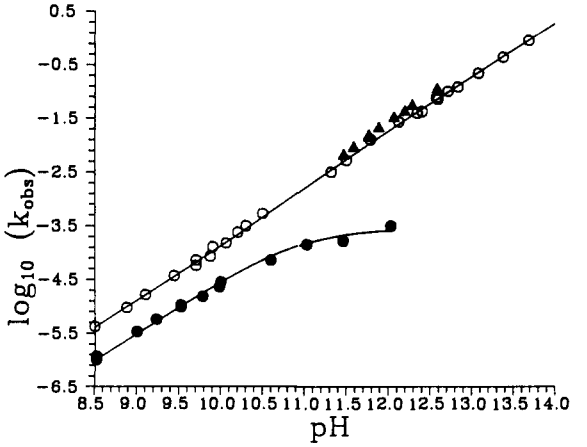


Figure 2. Plot of k_{hyd} (O) and k_{ex} (●) vs [OH^-] for base-promoted hydrolysis of amide V, T = 25 °C, μ = 1.0 (KCl); lines through the data are calculated NLLSQ fits to eqs 2 and 3 according to methods given in the text; ▲ data of Menger and Donohue[3a] for *N*-benzoylpyrrole.

V from pH 8.5 to 13.7 (slope 1.04 ± 0.001, all data) and curvature in the k_{ex} plot occurring between pH 10.5 and 11.5. In actuality there is a slight inflection in the k_{hyd} plot. The fact that a 158 500-fold increase in [OH^-] generates a 219 420-fold increase in k_{hyd} suggests some domain where terms higher than first order in [OH^-] come into play. Nevertheless, this would scarcely be convincing without the corroborating ^{18}O-exchange evidence.

Presented in Figure 2 as the closed triangles are the k_{hyd} data reported by Menger and Donohue[3a] for *N*-benzoylpyrrole. It is important to point out that the data reported for *N*-benzoylpyrrole[3a] cover only a 13-fold increase in [OH^-] and 17-fold increase in k_{hyd} under conditions where ionic strength was not controlled. When presented in the customary format of Figure 2, those data provide little convincing evidence for the proposed[3a] second order term in [OH^-] for the hydrolysis.[7]

A mechanism consistent with the hydrolysis and exchange data for both IV and V is presented in eq 1 from which can be derived the k_{hyd} and k_{ex} expressions given in eqs 2 and 3. In eq 3, the factor of 2 obtains from a necessary assumption that the two oxygens are protonically equilibrated and that only half of the reversal leads to ^{18}O loss.

$$\text{amide} + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} T_O^- \xrightarrow[k_3[OH^-]]{k_2} P \qquad (1)$$

$$k_{hyd} = \frac{k_1[OH^-](k_2' + k_3'[OH^-])}{1 + k_2' + k_3'[OH^-]} \qquad (2)$$

where $k_2' = k_2/k_{-1}$ and $k_3' = k_3/k_{-1}$

$$k_{ex} = \frac{k_1[OH^-]}{2\,(1. + k_2' + k_3'[OH^-])} \qquad (3)$$

Unfortunately none of the individual sets of data used to construct Figure 1 or 2 can be used to derive an unconstrained nonlinear least-squares (NLLSQ) fit to eq 2 or 3. This is because the attack rate constant (k_1) and the partitioning constants (k_2/k_{-1}; k_3/k_{-1}) are heavily correlated. However, these constants can be derived in the following way from the data at the extrema of the [OH^-]. For IV at low [OH^-], eq 3 can be recast as

$$k_{ex} = k_1[OH^-]/2(1 + k_2/k_{-1})$$

and

$$k_{hyd}/k_{ex} = 2k_2/k_{-1} = 0.118 \text{ at } [OH^-] = 0.01\text{ M}$$

(7) It is curious that in ref 3a, a plot of the log (k_{hyd}) vs pH data (from pH 9.02 to 10.11) for *N*-(*p*-nitrobenzoyl)pyrrole was claimed to have a slope of 1.1 ± 0.1 which was interpreted in terms of simple bimolecular amide hydrolysis. (Our analysis of the so-reported data has a slope of 1.12 ± 0.05.) A similarly constructed plot using the data reported for *N*-benzoylpyrrole[3a] by our analysis has a slope of 1.10 ± 0.01, apparently indistinguishable from that reported for *N*-(*p*-nitrobenzoyl)pyrrole.

Table I. Attack Rate Constants and Partitioning Ratios for OH^- Promoted Hydrolysis of IV and V[a]

amide	k_1, M^{-1} s^{-1}	k_2/k_{-1}	k_3/k_{-1}, M^{-1}	k_3/k_2, M^{-1}
IV	4.3×10^{-2} [b]	5.56×10^{-2} [c]	1.80×10^{-1} [c]	3.24
	(4.8×10^{-2})[d]	(6.95×10^{-2})[c,d]	(1.05×10^{-1})[c,d]	(1.51)[d]
V	1.81 ± 0.03[e]	2.11 ± 0.15[f]	3300 ± 360[g]	1.5×10^3

[a] At 73 °C and 25 °C for IV and V, respectively; μ = 1.0 (KCl). [b] k_1 from $k_{ex} = k_1[OH^-]/2(1 + k_2/k_{-1})$; at low $[OH^-]$, $k_{-1} \simeq 17k_2$. [c] NLLSQ fit to eq 2 using k_1 defined as in *b*; estimated error ±5%. [d] D_2O. [e] From unconstrained linear fits of five highest $[OH^-]$ (pH 12.6–13.7) to $k_{hyd} = k_1[OH^-]$. [f] k_{hyd}/k_{ex} at low $[OH^-] = 2k_2/k_{-1}$. [g] $k_{ex} = k_1k_{-1}/2k_3$ at high $[OH^-]$; k_1 = 1.81 M^{-1} s^{-1} as in footnote *e*.

Table II. k_{ex}/k_{hyd} Ratios for Various Toluamides[a] and pK_a Values for Corresponding Ammonium Ions

amide	k_{ex}/k_{hyd}	T, °C	pK_a $H^+N\lessdot$ (25 °C)
I[b]	0.01–0.015	100	10.64
II[b]	0.013–0.02	100	11.27
III[c]	33.4	100	6.3
IV[d]	9.0	73	4.05[e]
V[d]	0.24	25	<−3.8[f]

[a] Determined in the range of $[OH^-]$ where both k_{ex} and k_{hyd} are first order in $[OH^-]$. [b] Reference 1c. [c] Reference 1d. [d] This work. [e] Roberts, R. D.; Ferran, H. E., Jr.; Gula, M. J.; Spencer, T. A. *J. Am. Chem. Soc.* **1980**, *102*, 7054. [f] Reference 4, since the value of −3.8 refers to the thermodynamically preferred ring protonation, pK_a of the N protonated form should be even lower.

Using these two relationships, k_1 can be defined as 4.3×10^{-2} M^{-1} s^{-1} which in turn is fixed as input into the NLLSQ fit of eq 2 to the k_{hyd} data in order to generate k_2/k_{-1} and k_3/k_{-1}. The D_2O data for IV were fit in a similar way but $(k_1)_D$ was iteratively adjusted so that eq 3 yielded the experimental value of $k_{ex}^{D_2O}$ of $(2.26 \pm 0.02) \times 10^{-4}$ s^{-1} at $[OD^-]$ = 0.01 M. The k_1 rate and partitioning constants so-determined are presented in Table I: these values generate the lines through the data in Figure 1. The iterative procedure to produce $(k_1)_D$ generates an inverse isotope effect $(k_1)_{H/D} \simeq 0.89$ for the attack step which is consistent with other data for I–III[1c,d] and for the experimental value found for V below.

In the case of V at high $[OH^-]$, eq 2 can be recast as

$$k_{hyd} = k_1[OH^-]$$

and

$$k_{ex} = k_1k_{-1}/2k_3$$

while at low $[OH^-]$

$$k_{hyd}/k_{ex} = 2k_2/k_{-1}$$

The experimentally derived parameters are also given in Table I and can be used to generate the lines drawn in Figure 2 which can be seen to fit the data well.

Finally, given in Table II are the k_{ex}/k_{hyd} ratios for amides I–V determined in the $[OH^-]$ region where both terms are first order in $[OH^-]$ and refer principally to the $[OH^-]$ independent partitioning, $k_{-1}/2k_2$.

Discussion

The mechanism given in eq 1 and associated parameters in Table I invite comparison with previous interpretations for OH^--promoted hydrolysis of *N*-benzoylpyrrole[3a] or *N*-toluoylpyrrole (V).[3b] It was suggested[3] that neither compound exhibited a domain in which T_O^- spontaneously breaks down to product via k_2. The suggested mechanism requires the k_{hyd} kinetics to exhibit only two $[OH^-]$-dependent domains: second order at low $[OH^-]$ giving way to first order at high $[OH^-]$. In addition, that mechanism requires that the k_{hyd}/k_{ex} ratio $(=2k_3[OH^-]/k_{-1})$ is linearly dependent on $[OH^-]$ throughout its complete range. The fact that the k_{ex} and k_{hyd} plots for V in Figure 2 are parallel at low $[OH^-]$ and diverge at high $[OH^-]$ conclusively indicates that the proposed mechanism[3] must be modified to include a spontaneous pathway (k_2) by which T_O^- decomposes at low $[OH^-]$.

That V exhibits so much ^{18}O exchange accompanying its base hydrolysis has important implications for the increasingly discredited[8] stereoelectronic theory[9] insofar as it pertains to the cleavage of tetrahedral intermediates produced from base hydrolysis of amides. According to that theory,[9] such a tetrahedral intermediate can only expel the leaving group (X = OH or amine) whose C–X σ-bond is antiperiplanar to lone pairs of electrons on the two remaining groups. For amides, observable ^{18}O exchange in base would require that protonic equilibration of the ^{16}O and ^{18}O oxygens occur and that the remaining N lone pair would have to reorient itself (by C–N rotation or N-inversion) to be disposed antiperiplanar to the departing $^{18}OH^-$. We have shown that for I or II,[1c] $k_{ex}/k_{hyd} \simeq 0.01$–0.02 while the value for III is 33.4 at T = 100 °C, μ = 1.0 (KCl),[1d] so that conformational mobility at N is unimportant in determining whether a tertiary amide is capable of exhibiting ^{18}O exchange. In the low $[OH^-]$ range, the k_{ex}/k_{hyd} $(=k_{-1}/2k_2)$ value for V of 0.24 is much larger than that for II, but all arguments would indicate that the N lone pair of electrons in pyrrole is preoccupied in an aromatic sextet and therefore is far less available to assist in the departure of an OH^- from T_O^- than is the case for I or II. Following Perrin and Nuñez,[8a] we suggest that in such anionic tetrahedral intermediates, neither the orientation of a second lone pair nor even its presence is necessary in determining whether a given group will depart. Apparently O^- provides a sufficiently powerful driving force for leaving group departure that assistance from a second antiperiplanar set of electrons is not required.

(a) Validation of Assumptions Necessary for Use of $^{18}O{=}C$ Exchange Methodology. The two critical assumptions for the use of $^{18}O{=}C$ exchange methodologies to provide mechanistic information about the reversible formation of tetrahedral intermediates are (1) that the intermediates that lead to exchange are on the hydrolytic pathway and (2) that protonic equilibration of the ^{16}O and ^{18}O atoms is faster than reversal of T_O^-. Previously, based on solvent KIE's of 1.05 ± 0.04 and 0.90 ± 0.05 for the k_{hyd} and k_{ex} of **III**, we have proposed that both assumptions are valid.[1d] Thus, if protonic equilibration was in some way limiting k_{ex}, the solvent KIE should be large and normal. The same should obtain if the exchange intermediate is not on the hydrolytic pathway since the exchange must occur via a transition state having several proton transfers occurring at a rate that is fast relative to the lifetime of T_O^-.[1c] An alternative way of addressing the above two assumptions is available from k_{ex} and k_{hyd} studies of amides that exhibit domains of changing order in $[OH^-]$. The k_{ex} expression in eq 3 explicitly requires the assumption that only half of the reversal (by k_{-1}) leads to ^{18}O exchange. A plot of the reciprocal of k_{ex} vs $1/[OH^-]$, e.g.

$$\frac{1}{k_{ex}} = \frac{2(k_{-1} + k_2)}{k_1k_{-1}[OH^-]} + \frac{2k_3}{k_1k_{-1}}$$

gives a line of slope $2(k_{-1} + k_2)/k_1k_{-1} = 3.25 \pm 0.15$ M·s (errors from standard deviation of least-squares fit). The k_{hyd} expression of eq 2 also incorporates a reversal term (k_{-1}) but there is no explicit assumption that expulsion of either oxygen occurs with equal propensity (e.g., no requirement for protonic equilibration). From the hydrolysis kinetics, it can be computed (Appendix) that

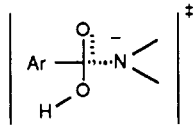
(8) (a) Perrin, C. L.; Nuñez, O. *J. Am. Chem. Soc.* **1986**, *108*, 5997 and references therein. (b) Sinnott, M. L. *Adv. Phys. Org. Chem.* **1988**, *24*, 113 and references therein. (c) Ratcliffe, A. J.; Mootoo, D. R.; Andrews, C. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 7661.

(9) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983; pp 108–118. (b) Deslongchamps, P.; Cheriyan, U. O.; Guida, A.; Taillefer, R. J. *Nouv. J. Chim.* **1977**, *1*, 235. (c) Deslongchamps, P.; Gerval, P.; Cheriyan, U. O.; Guida, A.; Taillefer, R. J. *Nouv. J. Chim.* **1978**, *2*, 631. (d) Deslongchamps, P.; Bartlett, R.; Taillefer, R. J. *Can. J. Chem.* **1980**, *58*, 2167.

$2(k_{-1} + k_2)/k_1k_{-1} = 3.87 \pm 0.56$ M·s. That the two independent kinetic analyses yield the same complex constant (within experimental error) for the partitioning of the intermediate requires (1) that the intermediates on the exchange and hydrolysis pathway are the same and (2) the intermediate is protonically equilibrated, at least in the case of T_O^- from V. We note that the hydrolysis and $^{18}O{=}C$ exchange of ethyl trifluorothiolacetate has been analyzed in the above way to determine that the exchange and hydrolysis intermediates are the same.[10]

(b) Mechanism for the Breakdown of T_O^- for Amides with an Amine Portion of Reduced Basicity. The purpose of our continuing studies of the base-promoted hydrolyses of toluamides[1] is to identify the mechanistic changes that occur as a function of diminished leaving ability of the amine. For amides I–III[1c,d] in which the exchange and hydrolysis transition states each have one incorporated OH^- (both processes are first order in $[OH^-]$), the k_{ex}/k_{hyd} ratio increases as the amine basicity decreases (Table II). This is understandable since the hydrolysis of I–III (Scheme I) proceeds via an intermediate where the N is protonated prior to C–N cleavage. For that mechanism, further reduction in amine basicity should increase the energy of any N-protonated form as well as any of the transition states proceeding through those intermediates. At some point, where the amine basicity is reduced to the point where T_{ZW}^- or $T_{ZW}{\cdot}OH^-$ cannot be viable intermediates, the hydrolytic mechanism must change to one in which the amine departs as an anion, possibly with general acid assistance of the solvent. At the same time, those factors that inhibit N protonation also acidify the remaining OH group of T_O^- so that a new pathway for hydrolysis involving a second OH^- may come into play.

Exactly the above predicted behavior occurs with IV and V. In the low $[OH^-]$ region where both the k_{ex} and k_{hyd} are first order in $[OH^-]$, their ratio refers to the partitioning of T_O^- through monoanionic transition states. However for these amides, the available evidence suggests that C–N cleavage occurs directly from T_O^- via transition state VI and not from T_{ZW}^- or $T_{ZW}{\cdot}OH^-$. First,



VI

k_{ex}/k_{hyd} for IV is lower than for III, and that for V is lower yet. If IV and V hydrolyzed by an N protonated intermediate analogous to those formed from III, one would anticipate even more exchange. Although one must be mindful of the differences in temperature involved in the comparisons,[11] this is unlikely to have such a substantial effect so as to dramatically alter the k_{ex}/k_{hyd} ratios. Second, for both III and IV, since $k_{ex} > k_{hyd}$, the rate-limiting step in each hydrolysis is k_2 and involves not OH^- attack but cleavage of the C–N bond. The attack step (k_1) of OH^- on IV at 73 °C is ~21 times faster than the attack on III[12a] at 100 °C (4.3×10^{-2} M^{-1} s^{-1} vs 2.0×10^{-3} M^{-1} s^{-1}). This is the expected result if the amine portion in IV is less electron donating to the C=O than the amine in III. However, k_{hyd} for IV at low $[OH^-]$ (where there is not a second order in $[OH^-]$ term) is 2.4×10^{-3} M^{-1} s^{-1} while the k_{hyd} for III at 73 °C[12b] is 430 times slower at

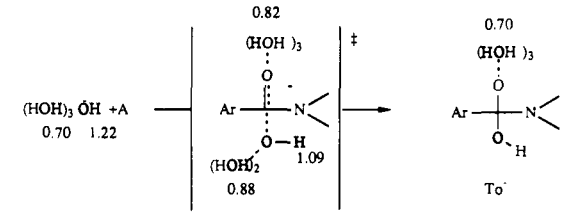


Figure 3. Proposed mechanism and fractionation factors for attack of OH^- on amide IV or V with a TS 0.6 along the reaction pathway. (Bold H's have indicated fractionation factors; all other H's are unity.)

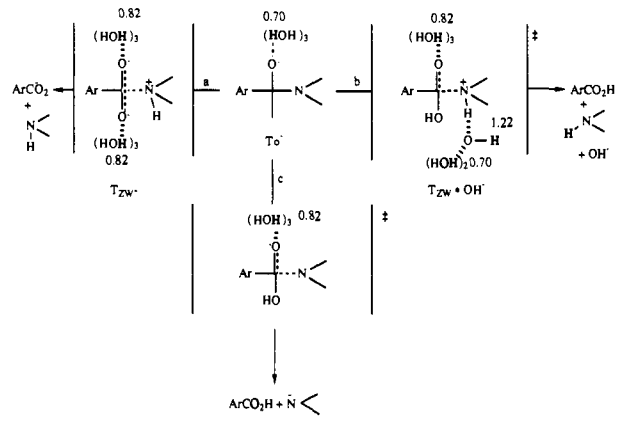


Figure 4. Possible pathways with associated fractionation factors for the spontaneous breakdown of T_O^- with TS positioned 0.4 along reaction pathway. (Bold H's have indicated fractionation factors; all other H's are unity.)

5.6×10^{-6} M^{-1} s^{-1}. Thus, the rate limiting TS involving C–N cleavage for IV is of lower energy than that for III and suggests a different mode of cleavage for the former that does not involve prior N protonation. A third piece of evidence in support of the above comes from the solvent KIE's presented in the following section.

(c) Solvent Kinetic Isotope Effects for IV and V. Previously[1c,d] we have analyzed the SKIE's for hydrolysis of I–III in terms of fractionation factors[13] according to $k_D/k_H = \Pi\phi^{TS}/\Pi\phi^{GS}$ where $\Pi\phi^{GS}$ is the product of the fractionation factors for the ground state ($HO^-(HOH)_3$), and $\Pi\phi^{TS}$ is the product of the fractionation factors for the attack (k_1) and breakdown (k_2) steps. The analyses for the attack of OH^- on I–III assumed the transition states were close to the tetrahedral intermediate, with their positions along the reaction coordinate being 0.7 for formation and 0.3 for breakdown of T_O^-.[1d] For the more reactive amides, IV and V, the TS for attack could be assumed to be earlier, and that for breakdown of the more stable T_O^- somewhat later. All other assumptions for the analysis here are the same as those given in ref 1c,d. For III, the experimental SKIE on $(k_1)_{H/D} = 0.90 \pm 0.08$. The values for IV and V (Table I) are 0.89 and 0.83 ± 0.08. (The former value has no error limits because k_1 was fixed for the NLLSQ fits, vide supra.) Shown in Figure 3 is the proposed mechanism and fractionation factors for attack of OH^- on these amides assuming a slightly earlier TS (0.6) for which is calculated a $(k_1)_{H/D}$ of 0.90 that fits the experimental data well. The assumed earlier TS thus seems justified since k_1 for IV and V is greater than those for I–III.

The observed $(k_{hyd})_{H/D}$ of 1.05 ± 0.04 for III provides information about k_2 since the rate-limiting step for this hydrolysis is the breakdown of the intermediate to product (see Scheme I). The breakdown of T_O^- from IV is also rate limiting (k_2) since $k_{ex} \sim 9k_{hyd}$. The experimental SKIE for IV at low $[OH^-]$ can be

(10) Bender, M. L.; Heck, H. d'A. *J. Am. Chem. Soc.* **1967**, *89*, 1211.

(11) The temperature induced change in the partitioning of T_O^- depends upon the enthalpy differences ($\Delta\Delta H^\ddagger$) between the transition states leading to product and starting material.

$$\ln\left\{\frac{(2k_{ex}/k_{hyd})_{T_1}}{(2k_{ex}/k_{hyd})_{T_2}}\right\} = \frac{\Delta\Delta H^\ddagger}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right)$$

A change in the k_{ex}/k_{hyd} by a factor of 2 for a 27° rise in temperature (73 → 100°) requires a $\Delta\Delta H$ of 6.3 kcal/mol, a factor of 4 requires 12 kcal/mol, and a factor of 10 requires 21 kcal/mol.

(12) (a) The value of 2.0×10^{-3} M^{-1} s^{-1} comes from the k_{ex} for III which is $k_1/2$ ($k_{ex} = 1.01 \times 10^{-3}$ M^{-1} s^{-1}, ref 1d). (b) k_{hyd} for III at 73 °C calculated from activation parameters $\Delta H^\ddagger = 16.4$ kcal/mol; $\Delta S^\ddagger = -35.5$ (cal/K) mol given in ref 1d.

(13) (a) Schowen, R. L. In *Isotope Effects on Enzyme Catalyzed Reactions*; Cleland, W. W., O'Leary, M. H., Northrup, D. B., Eds.; University Park Press: Baltimore, MD, 1977. (b) Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275. (c) Schowen, K. B. J. In *Transition States of Biochemical Processes*; Gandour, R. D., Schowen, R. L., Eds.; Plenum Press: New York, 1978.

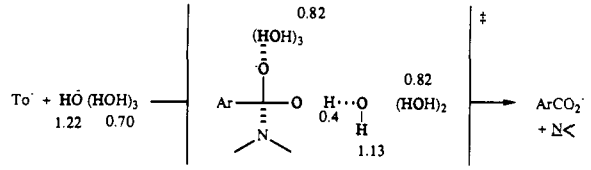


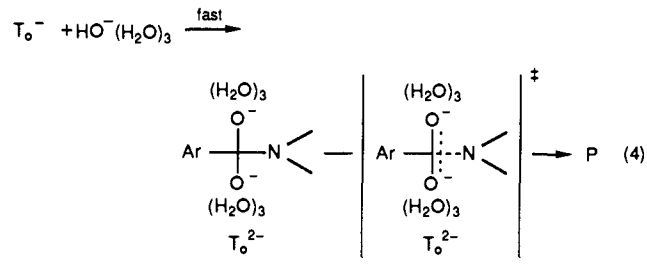
Figure 5. Proposed pathway for OH^- promoted breakdown of T_O^- and associated fractionation factors assuming TS is 0.4 along reaction pathway. (Bold H's have indicated fractionation factors; all other H's are unity.) This pathway proceeds from $T_O^- + HO^-(H_2O)_3$ which is itself referred to the ground state of A + $[HO^-(H_2O)_3]_2$.

calculated from the parameters given in Table I: $(k_{hyd})_{H/D} = (k_1k_2/k_{-1})_{H/D} = 0.72$ (probable error ±10%). That the SKIE for hydrolysis of IV is inverse, and different from that for III, suggests different degrees of association with solvent in the two breakdown TS's. Shown in Figure 4 are three different mechanisms for breakdown of T_O^- and associated fractionation factors assuming each monoanionic TS is 0.4 along the reaction pathway. For the two N protonated intermediates (T_{ZW}^- and $T_{ZW}{\cdot}OH^-$) the calculated SKIE's are 1.48 and 1.33, respectively, for cleavage by paths a and b. For the remaining TS proceeding via cleavage of the nonprotonated N (path c), the calculated SKIE is 0.74, which agrees nicely with the experimental value. It should be pointed out that in all cases, the SKIE arises not from protons in flight but from reordering of solvent molecules during the C–N cleavage. The data cannot rule out a weak association of the departing N with solvent in path c. However, for direct cleavage of T_O^-, an association of the departing N with solvent via a H bond increases the calculated SKIE to 0.86 (assuming the ϕ_{TS} for single H bond to N is 0.88). Furthermore, any general acid catalysis of the departure of N by solvent requires a proton in flight with an expected fractionation factor of 0.3–0.5[13a] and would increase the SKIE to 1.6–2.7, clearly greater than the observed value of 0.72. For V, the $(k_{hyd})_{H/D}$ value at low $[OH^-]$ is 0.66 (probable error ±10%), which is similar to that determined for IV, and thus suggests it also decomposes by the direct expulsion of amide anion from T_O^- (via k_2) without general acid catalysis by solvent. However, for V, because $k_{ex}/k_{hyd} \simeq 0.24$ in the low $[OH^-]$ region, the observed SKIE is not exclusively relegated to k_2 but refers to the virtual TS associated with k_2 and k_{-1}.

For the cleavage of T_O^- promoted by OH^-, the constants in Table I for IV indicate that $(k_1k_3/k_{-1})_{H/D} = 1.54$ (probable error ± 10%). That the SKIE changes from inverse for the spontaneous breakdown of T_O^- to normal in the case of the OH^- reaction suggests a significant contribution of a proton in flight for the latter. This is most likely due to the OH^- removing a proton from T_O^- concurrent with C–N cleavage. Fractionation factor analysis for this breakdown via the TS positioned 0.4 along the reaction given in Figure 5 provides a calculated SKIE of 1.05. The so-calculated value is lower than observed, but slight reductions in any of the values given in Figure 5 causes a significant increase in k_H/k_D. For example, if the TS is slightly earlier as might be expected for the strong base (OH^-) promoting the breakdown (e.g., TS is positioned 0.3 along the reaction) the k_H/k_D increases to 1.24. It is important to reiterate that any process proposed for the OH^- promoted breakdown must have a proton in flight, otherwise $k_H/k_D < 1.0$. Accordingly, we can rule out the specific base process in eq 4 where T_O^{2-} (VII) is generated prior to rate limiting C–N cleavage, for which the calculated SKIE is 0.72 if the TS is 0.3 along the reaction, and 0.58, if the TS is 0.4 along the reaction.

Conclusions

Amides IV and V which possess amine portions of reduced basicity are shown to hydrolyze in base by different mechanisms than those for I–III. For IV and V, nucleophilic attack of OH^- on the carbonyl group to form T_O^- is faster than for I–III. However, the reluctance of the amine portion to become protonated (pK_a of the corresponding ammonium ions 4.05 and <−3.8) raises the energy of any N-protonated intermediate and attendant TS for C–N cleavage involving it. The available evi-



VII

dence (k_{ex}/k_{hyd}, SKIE) supports a cleavage pathway of T_O^- (for IV and V) in which the amide anion is expelled. Those factors that preclude N-protonation also acidify the remaining OH group of T_O^- so that another pathway for hydrolysis involving a second OH^- becomes viable. For the toluamides, this mechanistic change for the base hydrolysis occurs when the pK_a of the corresponding ammonium group is between 6.3 and 4.05 (e.g., as in III and IV). Interestingly, the mechanistic change is not limited to toluamides since it has long been known that hydrolyses of acetanilides,[14a,b] formanilides,[14c] and trifluoroacetanilides[15] exhibit second-order terms in $[OH^-]$; here the pK_a for the corresponding ammonium ion lies in the range of 4–5 (pK_a NH^+ of aniline, 4.60; of *N,N*-dimethylaniline, 5.07).[2] The presently available evidence for toluamides I–V indicates that stereoelectronic factors as described by Deslongchamps[9] are of minimal importance (if at all) in determining the partitioning of the tetrahedral intermediates. The SKIE and kinetic evidence herein also indicate that oxygen protonic equilibration is achieved within the lifetime of the intermediates.

The most important factor in deciding whether a given amide will or will not exhibit ^{18}O exchange concurrent with its hydrolysis in base is the basicity of the amine leaving group and it is this factor that controls whether the amine leaves as its protonated form or as an anion. When the amide leaving group is relatively unstable as a departing anion (e.g., tetrafluoropyrrolidide), the k_{ex}/k_{hyd} ratio will be large since (from Table I) $k_2/k_{-1} = 5.5 \times 10^{-2}$. At the same time, the acidifying effect of that amine on T_O^- is not large so the second order in $[OH^-]$ hydrolysis domain comes into play only at high $[OH^-]$. Some measure of the relative viability of the OH^- promoted and spontaneous breakdown pathways for T_O^- is given by the k_3/k_2 ratio for IV of 3.24 M^{-1} given in Table I. The inverse of this number represents the $[OH^-]$ at which half of the breakdown proceeds by each pathway. As the ability of the N to depart as an anion becomes better as in the case of pyrrole,[16] the k_2/k_{-1} ratio will increase dramatically (to 2.1 for V, Table I), and k_{ex}/k_{hyd} is predicted to drop as observed. Correspondingly this same effect will further acidify T_O^- so that the k_3 term comes into play at a lower $[OH^-]$. For V, $k_3/k_2 = 1.5 \times 10^3$ M^{-1}, so that half of the breakdown of T_O^- proceeds through k_3 at $[OH^-] = 6.7 \times 10^{-4}$ M or pH = 10.8 which is where the inflection point in Figure 2 occurs. In the limit, further reductions in the amine pK_a can be expected to lead to a situation where the hydrolysis kinetics are only first order in $[OH^-]$; attack becomes rate limiting, $k_{ex}/k_{hyd} \rightarrow 0$ and k_3/k_2 becomes sufficiently large that T_O^- always progresses to T_O^{2-} faster than it breaks down spontaneously.

Acknowledgment. We gratefully acknowledge the Natural Sciences and Engineering Research Council of Canada, the

(14) (a) Bender, M. L.; Thomas, R. J. *J. Am. Chem. Soc.* **1961**, *83*, 4183. (b) Gani, V.; Viout, P. *Tetrahedron* **1976**, *32*, 1669. (c) DeWolfe, R. H.; Newcomb, R. C. *J. Org. Chem.* **1971**, *36*, 3870.

(15) (a) Young, J. K.; Pazhanisamy, S.; Schowen, R. L. *J. Org. Chem.* **1984**, *49*, 4148, and references therein. (b) Ericksson, S. O. *Acta Chem. Scand.* **1968**, *22*, 892, and references therein. (c) Pollack, R. M.; Dumsha, T. C. *J. Am. Chem. Soc.* **1973**, *95*, 4463. (d) Beichler, S.; Taft, R. W. *J. Am. Chem. Soc.* **1957**, *79*, 4927.

(16) (a) The pK_a of the HN of pyrrole is ~5 units higher than that for cyclopentadiene in DMSO, the pK_{HA}^{DMSO} values being 23 and 18: Bordwell, F. G.; Drucker, G. E.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 632. (b) In H_2O, pyrrole itself is predicted to have a pK_a of 17; see Barlin, G. B.; Perrin, D. D. *Q. Rev. Chem. Soc.* **1966**, *20*, 75.

University of Alberta, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Appendix

Determination of Partitioning Ratios for IV For exchange

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

and

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

Least-squares fit of $1/k_{ex}$ vs $1/[OH^-]$ gives

$$\frac{2(k_{-1} + k_2)}{k_1 k_{-1}} = 3.25 \pm 0.15 \text{ M·s}$$

and

$$2k_3/k_1 k_{-1} = (3.6 \pm 0.4) \times 10^3 \text{ s}$$

For hydrolysis

$$k_{hyd} = \frac{k_1[OH^-](k_2 + k_3[OH^-])}{k_{-1} + k_2 + k_3[OH^-]}$$

At low $[OH^-]$ where $(k_{-1} + k_2) \gg k_3[OH^-]$

$$\frac{k_{hyd}}{[OH^-]} = \frac{k_1 k_2}{k_{-1} + k_2}$$

At high $[OH^-]$ where $k_3[OH^-] \gg (k_{-1} + k_2)$

$$k_{hyd}/[OH^-] = k_1$$

An unconstrained linear fit of the log (k_{hyd}) vs pH data between pH 8.50 and 9.44 gives an extrapolated[17] log ($k_{hyd}/[OH^-]$) = 0.114 ± 0.024 (gradient = 1.003 ± 0.022). Similarly, an unconstrained linear fit of the log (k_{hyd}) vs pH data between pH 12.60 and 13.70 gave an extrapolated[18]

$$\log\left(\frac{k_{hyd}}{[OH^-]}\right) = 0.258 \pm 0.007 \text{ (gradient} = 1.012 \pm 0.007)$$

Thus

$$k_1 = 10^{0.258} \pm (10^{0.258} (\ln 10)\, 0.0068)^{19}$$
$$= 1.81 \pm 0.03 \text{ M}^{-1} \text{ s}^{-1}$$

and

$$\frac{k_1 k_2}{k_{-1} + k_2} = 10^{0.114} \pm (10^{0.114} (\ln 10)\, 0.024)^{19}$$
$$= 1.30 \pm 0.07 \text{ M}^{-1} \text{ s}^{-1}$$

Therefore

$$\frac{k_2}{k_{-1} + k_2} = 0.72 \pm 0.04$$

and

$$\frac{k_2}{k_{-1}} = \frac{k_2}{k_{-1} + k_2} \Big/ \left(1 - \frac{k_2}{k_{-1} + k_2}\right) = \frac{0.72}{(1 - 0.72)} \pm \frac{0.04}{(1 - 0.72)^2}^{19} = 2.53 \pm 0.51$$

To calculate

$$\frac{2(k_{-1} + k_2)}{k_1 k_{-1}} = 2\frac{(1 + k_2/k_{-1})}{k_1}$$

from hydrolysis kinetics only

$$\frac{2(1 + k_2/k_{-1})}{k_1} = \frac{2(1 + 2.5)}{1.81} \pm \left(\left(\frac{0.5}{3.5}\right)^2 + \left(\frac{0.03}{1.81}\right)^2\right)^{1/2} \frac{2(1 + 2.5)}{1.81}$$

so

$$\frac{2k_{-1} + k_2)}{k_{-1} k_2} = 3.87 \pm 0.56 \text{ M·s}$$

Within experimental error this value is the same as that obtained from the exchange data.

Registry No. IV, 139527-55-2; V, 70971-70-9; D_2, 7782-39-0; O_2, 7782-44-7.

Supplementary Material Available: Tables of rate and exchange constant data as a function of $[OL^-]$ for IV and V (Tables S1 and S2) (3 pages). Ordering information is given on any current masthead page.

(17) Extrapolated to pH = 10.0 to get calculated second-order rate constant.

(18) Extrapolated to pH = 14.0 to get calculated second-order rate constant.

(19) Standard deviation calculated according to Taylor, J. R. *An Introduction to Error Analysis*; University Science Books: Mill Walley, CA, 1982; p 63. If $q(x)$ is a function of one variable, x, then $\delta q = |dq/dx|\, \delta x$.