Observation of Large Amounts of $^{18}O{=}C$ Exchange Concurrent with Acid-Catalyzed Hydrolysis of Toluamides Having Amine Portions of Reduced Basicity. The Involvement of Protonated Intermediates in the Acid-Catalyzed Hydrolysis of *N*-Toluoylpyrrole

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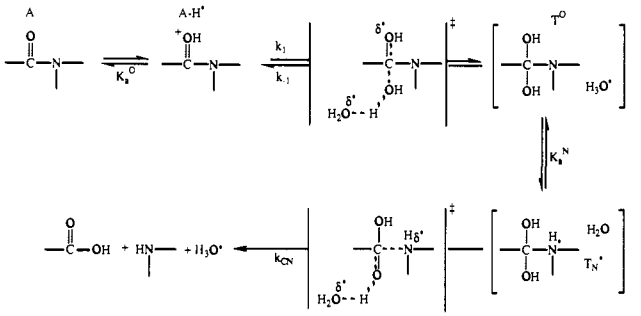
Abstract: *N*-Toluoylpyrrole (**2a**) and *N*-toluoyl-2,5-dimethylpyrrole (**2b**) have been prepared along with their ~50% ^{18}O-labeled analogues and the kinetics of hydrolysis and ^{18}O-exchange studied in H_3O^+ at 72 °C. *N*-Toluoylpyrrole shows a k_{ex}/k_{hyd} ratio of ~50 that is independent of $[H_3O^+]$ between pH 0 and 1. Both k_{ex} and k_{hyd} are first order in $[H_3O^+]$ in this range. The 2,5-dimethyl derivative (**2b**) exhibits an apparent reduction in k_{ex}/k_{hyd} of $\sim 10^4$ relative to **2a**. While the hydrolysis of **2a** is shown to proceed normally to produce pyrrole and toluic acid, hydrolysis of **2b** is abnormal in that the initial products are toluamide and 2,5-hexanedione. Solvent kinetic isotope studies with **2a** indicate a $(k_{ex})_{H/D}$ value of 0.81 ± 0.08 and $(k_{hyd})_{H/D}$ value of 0.91 ± 0.18. The large amount of ^{18}O-exchange observed for **2a** relative to that for benzamide, acetanilide, and *N*,2,4-trimethylacetanilide results from the low basicity of the pyrrole moiety which inhibits protonation and favors C–O cleavage. A generalized mechanism of acid-catalyzed hydrolysis for the above amides is presented.

Introduction

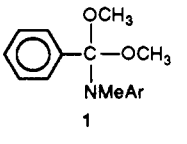
The generally accepted mechanism for H_3O^+-catalyzed amide hydrolysis involves the initial attack of H_2O on the O-protonated amide to produce a neutral tetrahedral intermediate (T^0), that rapidly undergoes N-protonation and breakdown to products.[1] At moderate $[H_3O^+]$ the rate-limiting step during the hydrolysis is considered to be the attack of H_2O on A–H^+ with general base assistance from another H_2O molecule. The observation a small but significant amount of carbonyl ^{18}O-exchange occurring during the hydrolysis of benzamide in 5.9% H_2SO_4 solution at 85 °C[2] demonstrates that the acid-catalyzed hydrolysis of amides is mechanistically similar to the hydrolysis of other carboxylic acid derivatives which are known to proceed through tetrahedral intermediates. Recently we reported that carbonyl ^{18}O-exchange occurred during the hydrolysis of acetanilide in aqueous HCl, and a significantly larger amount of exchange occurred for the sterically congested *N*,2,4-trimethylacetanilide.[3] The kinetics and observation of ^{18}O-exchange therefore suggest a similarity in mechanism for the hydrolysis of benzamides and acetanilides in acidic media. On the basis of deuterium solvent kinetic isotope effects and energetic calculations we proposed a detailed mechanism for acid-catalyzed hydrolysis of acetanilide shown in Scheme I.

Whether ^{18}O-exchange is observed during H_3O^+-catalyzed amide hydrolysis depends upon the C–N/C–O cleavage ratio and on the ability to place the requisite proton on N. Therefore, in an effort to increase the amount of exchange (slow down C–N cleavage with respect to reversal), we sought an amide with an amine moiety of reduced basicity which should disfavor formation of T_{N^+}. Some indication that such an approach might work comes from a study of anilide amide acetals (**1**) by McClelland and Patel[4] showing that the rate constant for C–N cleavage under acidic conditions dropped linearly when the pK_a of the anilinium ion of the leaving group was less than 4.5.

Scheme I



The hydrolysis of aroyl pyrroles (e.g. **2a,b**) in acidic media has not previously been reported; however, Cipiciani et al. have published data on the acid-catalyzed hydrolysis of *N*-(trifluoroacetyl)pyrrole, -indole, -tetrahydrocarbazole, and *N*-acetylindole.[5] On the basis of the observation of a hydrate (gem-diol) of *N*-(trifluoroacetyl)pyrrole (**3**), kinetic solvent isotope effects, and Bunnett type plots, the authors concluded that for the above amides the mechanism consisted of a rapid and reversible formation of T^0 followed by rate-limiting general acid-catalyzed breakdown of the gem-diol. From the study of these CF_3 and CH_3 derivatives, it was suggested[5] that the initial hydration of acyl pyrroles to yield T^0 was not acid-catalyzed. The main implication of this is that the rate constant for carbonyl ^{18}O exchange (k_{ex}) should be independent of acid concentration, although these studies were not reported.



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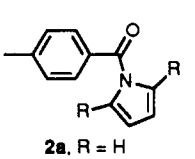
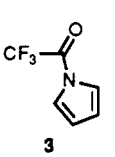


2a, R = H
2b, R = Me



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Herein we report that between pH 1 and 0, the rate constants for hydrolysis and ^{18}O exchange (k_{hyd}, k_{ex}) of toluoylpyrrole (**2a**) are both linearly dependent on acid concentration which requires that the transition states leading to exchange and hydrolysis both

(1) For leading references to generalized hydrolytic mechanisms see: (a) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill Inc.: New York, 1969; pp 523-527. (b) Lowry, T. H.; Richardson, K. S. In *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row Inc.: New York, 1987; pp 714-717. (c) O'Connor, C. J. *Q. Rev. Chem. Soc.* **1971**, *24*, 553. (d) Bender, M. L. *Chem. Rev.* **1960**, *60*, 53.

(2) McClelland, R. A. *J. Am. Chem. Soc.* **1975**, *94*, 8811.

(3) Bennet, A. J.; Ślebocka-Tilk, H.; Brown, R. S.; Guthrie, J. P.; Jodhan, A. *J. Am. Chem. Soc.* **1990**, *112*, 8497.

(4) McClelland, R. A.; Patel, G. *J. Am. Chem. Soc.* **1981**, *103*, 6908.

(5) Cipiciani, A.; Linda, P.; Savelli, G.; Bunton, C. A. *J. Am. Chem. Soc.* **1981**, *103*, 4874.

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Table I. Hydrolysis and Exchange Rate Constants for Toluamides **2a** and **2b** in Acidic Media, T = 72 °C, μ = 1.0 (KCl)

amide	$[L_3O^+]$, M	k_{hyd}, s^{-1}	k_{ex}, s^{-1}	k_{ex}/k_{hyd}
2a	1.00	$(1.80 \pm 0.05) \times 10^{-5}$		
	0.92		$(7.1 \pm 1.6) \times 10^{-4}$	43 ± 10^a
	0.116	$(2.2 \pm 0.4) \times 10^{-6}$	$(1.06 \pm 0.04) \times 10^{-4}$	48 ± 9
D_2O	0.115	$(2.4 \pm 0.2) \times 10^{-6}$	$(1.30 \pm 0.11) \times 10^{-4}$	55 ± 7
2b	1.00	$(5.59 \pm 0.07) \times 10^{-3}$		
	0.10		$(1.9 \pm 2.1) \times 10^{-6}$	$(3.4 \pm 3.8) \times 10^{-3}$ [a]

[a] Calculated from second-order rate constant for exchange and hydrolytic rate constant at $[H_3O^+]$ = 1.0 M.

have incorporated one proton. We also report product studies for the hydrolysis of **2a**, **2b**, and **3** in moderately concentrated acidic media.

Experimental Section

(a) Materials. Toluoylpyrroles **2a** and **2b** were prepared analogously to procedures reported for the preparation of substituted benzoylpyrroles.[6]

p-Toluoylpyrrole was purified by Kugelrohr distillation (80–100 °C, 0.1–0.4 mmHg) followed by three recrystallizations from MeOH (−35 °C) to yield white needles. Exact mass for $C_{12}H_{11}NO$ calcd 185.0841, found 185.0844. Anal. C, H, N. Mp = 28.5–29.0 °C (lit.[6] 30–32 °C).

p-Toluoyl-2,5-dimethylpyrrole was purifed by Kugelrohr distillation (100 °C, 0.1–0.3 mmHg) and recrystallization from MeOH (−35 °C) followed by vacuum sublimation to yield pale yellow crystals. Exact mass for $C_{14}H_{15}NO$: calcd 213.1154, found 213.1150. Anal. C, H, N. Mp = 41.5–42.5 °C.

Both **2a** and **2b** have been characterized by single-crystal X-ray diffraction and other spectroscopic techniques.[7]

N-(Trifluoroacetyl)pyrrole (**3**) was prepared and purified by the literature procedure except that THF was used as a solvent instead of ether.[5]

^{18}O-Labeled **2a** and **2b** were prepared as above except that ~50% ^{18}O-labeled toluoylchloride[8] was the source of the acyl portion.

(b) Kinetics. The rate of hydrolysis of amide **2a** was determined by high-performance liquid chromatography (HPLC) analysis. Solutions of acid in H_2O or D_2O (1.0, 0.12 M in H_3O^+ or D_3O^+) were prepared and titrated with a standardized NaOH solution (bromothymol blue indicator). The acid solution (25.0 mL) was placed in a water bath at 72 °C to equilibrate for 30 min, and then to this solution was added 0.25 mL of a solution of amide in DME such that the final concentration of amide was 2.06 mM. At various times, an aliquot of the solution (0.5 mL) was withdrawn and quenched by addition to a solution of methanol (0.75 mL) containing enough NaOAc to neutralize the acid. Twenty microliters of this solution was then subjected to HPLC analysis. HPLC conditions were as follows: flow rate = 1.4 mL/min; column, Waters 8 MB C18 10μ radial pak; solvent = MeOH:H_2O 60:40 (containing 0.1% HOAc); UV detection at 254 nm. The hydrolytic rate constants (k_{hyd}) were calculated using a nonlinear least-squares fit of the percentage amide (moles of amide/(moles of amide + moles of acid)) against time data to a standard exponential model. The absolute amounts of amide (retention time (r.t.) 19.7 min) and acid (r.t. 6.75 min) were calculated from standard calibrations obtained under identical conditions.

The hydrolysis of amide **2b** was monitored by observing the rate of decrease in absorbance at 260 nm of a 47 μM solution of the amide at 72 °C using a Cary 210 UV–vis spectrophotometer. A stock solution of amide **2b** in DME was prepared (4.7 mM) and the reaction initiated by injecting 30 μL of this solution into a 1-cm quartz cuvette containing 3.0 mL of 1.0 M HCl that had been equilibrated for 30 min at 72 °C in the cell holder. A clean isosbestic point at 244 nm was observed and a rate constant was obtained by nonlinear least-squares fitting of the absorbance vs time data.

(c) Product Studies. The products of the hydrolysis of amide **2a** were determined by ^1H NMR analysis using a Bruker WH-400 spectrometer. Amide **2a** (1.3 mg) was dissolved in a mixture of 1.0 M HCl (250 μL) and dioxane-d_8 (250 μL) and sealed in a 5-mm NMR tube. The ^1H NMR spectra were accumulated using a presaturation water suppression technique at t = 0 and after 3 and 18 h at 100 °C. The peaks attributable to the toluoyl portion of the starting amide (δ 7.55, 7.30, and 2.32) were slowly replaced by those of toluic acid (δ 7.78, 7.21, and 2.30). The peaks of the pyrrole moiety of the starting amide (δ 7.20 and 6.29) decreased in intensity and small peaks attributable to pyrrole (δ 6.68 and 5.98) appeared. Pyrrole undergoes an acid-catalyzed polymerization reaction, and thus is not stable to the acidic conditions used.[9] Consequently the amount of pyrrole observed in the ^1H NMR spectrum never equals the quantity of toluic acid observed.

The products of hydrolysis of amide **2b** were determined by ^1H NMR using a Bruker WP-80 spectrometer and by high-resolution mass spectrometry. A solution of amide (28.5 mg) in 1 mL of DME was added to 50 mL of 1.0 M HCl at 72 °C (equilibrated for 30 min). This solution was kept at 72 °C for 15 min and then cooled in an ice–water bath. This mixture was then extracted with CH_2Cl_2 (two 50 mL portions) and the combined organic layers were dried ($MgSO_4$) and the volatiles were removed under reduced pressure. The ^1H NMR spectrum of the residue showed two overlapping toluoyl groups in the aromatic region, peaks attributable to starting amide at δ 5.8, 2.4, and 2.1, and a second aromatic methyl group at δ 2.35. Also observed were two peaks at δ 2.7 and 2.2 in the ratio of 2:3. The residue was also submitted for high-resolution mass spectrometry and the following major peaks were identified: $C_{14}H_{15}NO$ calcd 213.1154, found 213.1153 (starting material); C_8H_9NO calcd 135.0684, found 135.0684; and $C_6H_{10}O_2$ calcd 114.0681, found 114.0679. The mass spectrum of pure amide shows neither of the peaks at 135 and 114. The data are consistent with the hydrolysis of amide **2b** in acid giving *p*-toluamide and 2,5-hexanedione.

The products of the hydrolysis of amide **3** were followed by ^1H NMR analysis using a Bruker WH-400 spectrometer. Amide **3** was dissolved in CD_3CN and the ^1H NMR (400 MHz) spectrum showed resonances at δ 7.38 and 6.46 attributable to the starting amide. The spectrum (accumulated using a presaturation water suppression technique), within 5 min of addition of a 0.5 M solution of HCl in H_2O (final ratio H_2O/CD_3CN = 30:70), showed four new peaks at δ 6.92 and 6.11 (gem-diol) and at δ 6.73 and 6.07 (pyrrole). The peaks at δ 7.38, 6.92, 6.46, and 6.11 were slowly replaced by the peaks at 6.73 and 6.07. The ratio of the amide to gem-diol was constant throughout the experiment, indicating that the hydration equilibrium was reached in less than 5 min. The dissociation constant (K_d) of the gem-diol was calculated to be 24 M (in 30% aqueous CD_3CN); this compares favorably with the literature value of 25 M (in 17% aqueous CH_3CN).[10]

(d) ^{18}O Exchange Kinetics with 2a. A typical exchange experiment was conducted as follows. A 50-mL solution of aqueous HCl/DCl (μ = 1.0 KCl) was equilibrated at 72 °C in a water bath for 40 min. The reaction was initiated by rapid injection of a solution of labeled amide (~2.7 mg) in DME (0.5 mL), allowed to proceed for a certain time, and then quenched by rapidly cooling the sample in an ice–water bath. The cooled aqueous layer was extracted immediately with three 10-mL portions of freshly distilled CH_2Cl_2, and the combined extracts were washed with saturated NaCl and water. The organic layer was dried ($MgSO_4$) and stripped of solvent to yield the residual amide which was subjected to analysis with an AE1 MS-12 low-resolution mass spectrometer. In all cases duplicate or triplicate isolation experiments were performed. For mass analysis, 21 scans of the ^{16}O and ^{18}O peaks were done for each sample and the ^{18}O content was evaluated as $\%\ ^{18}O = I_{(M+2)^+}/(I_{M^+} + I_{(M+2)^+}) \times 100$ where I = peak intensity and M and (M + 2) refer to the molecular peaks used in the analysis. The results of several such runs at different times were used to calculate the rate constant (k_{ex}) using a nonlinear least-squares fit to a standard exponential model. The peaks used in the analysis for the k_{ex} in H_2O were the molecular ion peaks at m/z 185 and 187. However, in D_2O because of the extensive deuteration of the pyrrole ring, the peaks of the acylium fragment ion (at m/z 119 and 121) were used. As a control, it was shown for the amide extracted from H_2O/HCl, that the ratio of the m/z 185/187 peaks was within experimental error identical to the m/z 119/121 ratio.

(e) Deuterium Exchange on the Pyrrole Ring. A solution of 5.3 mg of toluoylpyrrole in 0.7 mL of DME was added to a 0.25 M DCl/D_2O solution (35 mL, μ = 1.0 KCl) that had been equilibrated at 72 °C for 30 min. This solution was quenched after a reaction time of 121 min by immersion in an ice–water bath. The amide was extracted as above and

(6) Cipiciani, A.; Linda, P.; Savelli, G. *J. Heterocycl. Chem.* **1979**, *16*, 673.
(7) Bennet, A. J.; Somayaji, V.; Brown, R. S.; Santarsiero, B. D. *J. Am. Chem. Soc.*, in press.
(8) Ślebocka-Tilk, H.; Bennet, A. J.; Hogg, H. J.; Brown, R. S. *J. Am. Chem. Soc.* **1991**, *113*, 1288.
(9) Smith, G. F. *Adv. Heterocycl. Chem.* **1963**, *2*, 287.
(10) Cipiciani, A.; Linda, P.; Savelli, G. *J. Chem. Soc., Chem. Commun.* **1977**, 857.

Scheme II

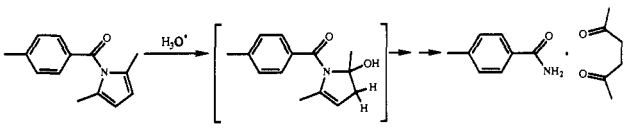


Table II. Rate Constants for Deuterium Incorporation into the Pyrrole Ring of Toluoylpyrrole, **2a**, T = 72 °C, μ = 1.0 (KCl)

$[D_3O^+]$, M	$k_{2,5}$,[a,b] s^{-1}	$k_{3,4}$,[a,c] s^{-1}
0.25	1.9×10^{-4}	5.9×10^{-5}

[a] Estimated errors ±10%. [b] Exchange at the 2,5-positions of the pyrrole ring. [c] Exchange at the 3,4-positions of the pyrrole ring.

submitted to low-resolution MS. Analysis of the ion cluster at 185–190 showed the following percentages of deuteration: d_0, 1%; d_1, 3%; d_2, 58%; d_3, 33%; d_4, 5%. This sample was also analyzed by ^{1}H NMR spectrometry and showed ~0.5 proton (δ 7.20) at the 2,5-positions and ~1.3 protons (δ 6.29) at the 3,4-positions per molecule of recovered amide.

Results and Discussion

(i) Toluoylpyrrole (2a) and Toluoyl-2,5-dimethylpyrrole (2b). Given in Table I are the k_{ex} and k_{hyd} values observed at 72 °C, μ = 1.0 (KCl) for both amides. The data for the exchange and hydrolysis processes for **2a** are within experimental error linearly dependent on $[H_3O^+]$ for the concentration range studied. The fact that the rate constant for the carbonyl ^{18}O-exchange (k_{ex}) is dependent on $[H_3O^+]$ shows that at least in the case of **2a** the hydration of the amide (A) to the gem-diol (T^0) is acid-catalyzed.

(ii) Unusual Reactivity of Toluoyl-2,5-dimethylpyrrole. From the data in Table I it can be seen that there is an apparent reduction in k_{ex}/k_{hyd} of about 10^4 on addition of the two methyl groups in **2b**. This large apparent change in the partitioning ratio of the intermediate(s) between starting materials and products cannot easily be explained in terms of steric interactions, which for the partitioning of intermediates formed during basic hydrolysis of secondary amides was shown to be negligible.[11] In the case of acetanilide and *N*,2,4-trimethylacetanilide, a variation in the k_{ex}/k_{hyd} ratio from 0.01 → 0.23 was observed and attributed to steric effects in the latter that destabilized T_{N^+}. However, such basicity changes are not expected for **2a,b**. The apparent increase in k_{hyd} for **2b** of over 300 when compared to **2a** is easily explained as the "hydrolysis" reaction for **2b** occurs by a completely different mechanism to yield products in which the nucleophilic attack has occurred on the pyrrole ring.[12] This reaction (depicted in Scheme II) is acid-catalyzed; however because of the anomalous reaction pathway, studies with this amide were discontinued.

(iii) Product Studies on 2a and 3. Cipiciani et al. reported that the hydrolysis of **3** when monitored by ^{1}H NMR in 17% H_2O–MeCN (v/v) under acidic conditions (pH 3.5) gives two sets of peaks attributable to the α-H of pyrrole in the amide and its gem-diol.[10] However, the same authors also showed for *N*-(trifluoroacetyl)indole that the reaction at pH 3.5 (aqueous solution) becomes first order with respect to hydroxide ion concentration.[13] Therefore, to ensure that the acid-catalyzed reaction proceeded to yield normal hydrolysis products, we repeated the product studies on **3** in a more acidic medium (30% 0.5 M HCl–CH_3CN (v/v)). In this medium, the same two sets of peaks identified by Cipiciani et al.[10] are observed, followed by the hydrolysis to form pyrrole. Thus both **2a** and **3** both hydrolyze in moderately concentrated acid solutions to give the expected products of C–N bond cleavage.

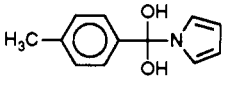
(iv) Ring Deuteration of Toluoylpyrrole. Shown in Table II are the rate constants for deuteration of the pyrrole ring in DCl/D_2O. Of note is that the rate constant for deuterium exchange at the 2-position is approximately 3-fold greater than that at the 3-position. This order of reactivity in the presence of a strongly electron withdrawing group is qualitatively similar to that found for benzoylpyrrole in trifluoroacetic acid[14] for which no tetrahedral intermediate comparable to T^0 can be formed. This similarity implies that H/D interchange in the ring of **2a** occurs at the stage of the amide although perhaps not exclusively so since it could also occur at a later stage from T^0 (vide infra). Whatever the case, the rate constants for deuterium incorporation at the 2- or 3-positions (when corrected for the $[D_3O^+]$ and number of exchange sites) are smaller by factors of 2.9 and 9.5, respectively, than the rate of carbonyl ^{18}O exchange. Thus, any mechanism for the oxygen exchange process in which H_2O attack occurs at the carbonyl center of a C-protonated pyrrole amide may be ruled out.

Table III. Solvent Kinetic Isotope Effect for the Acid-Catalyzed Hydrolysis of Toluoylpyrrole, **2a**, T = 72 °C, μ = 1.0 (KCl)[a]

$(k_{hyd})_{H/D}$	$(k_{ex})_{H/D}$	$(k_{ex}/k_{hyd})_{H/D}$
0.91 ± 0.18	0.81 ± 0.08	0.87 ± 0.20

[a] Calculated from data in Table I.

(v) Deductions from the Observed ^{18}O Exchange. For **2a**, exchange and hydrolysis are both acid-catalyzed with exchange being approximately 50 times faster than hydrolysis. Certain deductions can be made from these observations. First, there must be an intermediate that partitions back to starting materials faster (~100×) than forward to products. Second, this intermediate is not formed from a ring protonated amide since, as above, H/D exchange in the ring is slower than ^{18}O exchange in recovered starting material. The intermediate is reasonably assumed to be T^0, the geminal diol.



T^0

(vi) Deductions from the Deuterium Solvent Kinetic Isotope Effect. The experimental observations for **2a** are that the solvent kinetic isotope effect (SKIE) is indistinguishable from 1.0 for hydrolysis and slightly inverse for exchange. The isotope effects are summarized in Table III.

For the mechanism shown in Scheme I, with k_1 redefined to incorporate the protonation step, and k_2 redefined to absorb the $T^0 \rightleftharpoons T_{N^+}$ equilibrium and breakdown of T_{N^+} to products, the observable rate constants are given by

$$k_{hyd} = \frac{k_1 k_2}{k_{-1} + k_2}$$

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

$$\frac{k_{ex}}{k_{hyd}} = \frac{k_{-1}}{2k_2}$$

For toluoylpyrrole (**2a**), $k_{ex}/k_{hyd} \approx 50$ and thus $k_{-1} \gg k_2$ so $k_{ex} = (k_1)/2$ and $k_{hyd} = k_1 k_2 / k_{-1}$.

The rate-limiting transition state for the exchange mechanism is then the acid-catalyzed attack of water on the amide carbonyl group (k_1). We have previously ruled out attack on a C-protonated pyrrole as a viable pathway because the rate of deuterium incorporation into the pyrrole ring is too slow to account for the rate of oxygen exchange. The pathway involving nitrogen protonation is kinetically possible but probably unlikely as the pK_a of the conjugate acid of nitrogen in pyrrole itself is <-3.8[15] and in the presence of a strongly electron withdrawing carbonyl group this pK_a would be even lower. Thus the N-protonated species is

(11) Šlebocka-Tilk, H.; Bennet, A. J.; Keillor, J. W.; Brown, R. S.; Guthrie, J. P.; Jodhan, A. *J. Am. Chem. Soc.* **1990**, *112*, 8507.

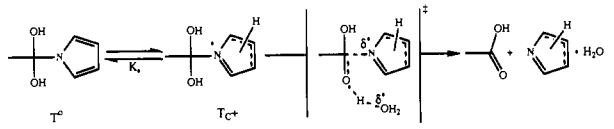
(12) This is the reverse of the reaction used in the synthesis of 2,5-dimethylpyrrole itself. Young, D. M.; Allen, C. F. H. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 219.

(13) Cipiciani, A.; Linda, P.; Savelli, G. *J. Heterocycl. Chem.* **1978**, *15*, 1541.

(14) Gilow, H. M.; Hong, Y. H.; Millirons, P. L.; Snyder, R. C.; Castell, W. J., Jr. *J. Heterocycl. Chem.* **1986**, *23*, 1475.

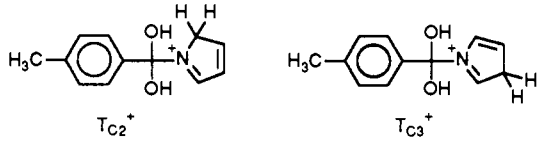
(15) Chiang, Y.; Whipple, E. B. *J. Am. Chem. Soc.* **1963**, *85*, 2763.

Scheme III



almost certainly a nonviable intermediate, which leaves O-protonated toluoylpyrrole as the likely first intermediate leading to T^0. The SKIE for exchange of $k_H/k_D = 0.81 \pm 0.08$ is in the range typical for a specific acid-catalyzed protonation followed by a rate-limiting attack of water (with general-base assistance by a second H_2O).[3] This SKIE certainly rules out a kinetically equivalent general acid catalyzed protonation of the C=O occurring simultaneously with a general base promoted delivery of H_2O since that process would involve at least two protons in flight and an anticipated k_H/k_D of >2.[16] The slightly inverse SKIE for the formation of T^0 from **2a** when compared to the value found[3] for *N*,2,4-trimethylacetanilide (1.0) is probably an indication of an earlier transition state for the former. In accordance with Hammond's postulate, this is caused by a destabilization of the starting amide relative to the transition state and results from removal of "amidic conjugation" by occupying the nitrogen lone pair in an aromatic sextet.

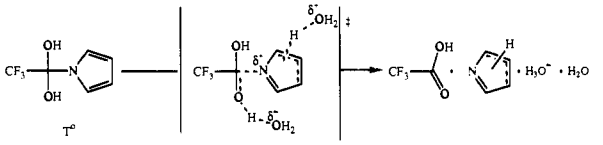
The SKIE's for breakdown of the tetrahedral intermediate(s) for both toluoylpyrrole $(k_{hyd})_{H/D} = 0.91 \pm 0.18$, and that for *N*,2,4-trimethylacetanilide[3] are, within experimental uncertainty, indistinguishable from unity. This implies a mechanistic similarity for these amides insofar as the number of protons in flight at the transition state for C–N cleavage. Furthermore, the observed SKIE of unity, when analyzed according to the mechanism given in Scheme I, suggests that the requisite proton is fully in place somewhere on the amine leaving group prior to product formation. The site of protonation, while uncertain, is probably at C_2 or C_3, although we cannot rule out the N. Cipiciani et al.[10] have argued on the basis of the ^1H NMR of **3** and its gem-diol that the $CF_3(C{=}O)$ group is more electron withdrawing than $CF_3C(OH)_2$; the same should be true for $Ar(C{=}O)$ relative to $ArC(OH)_2$ in the case of **2a**. This conclusion, when coupled with the observation that **2a** exchanges the protons at $C_{2,3}$ via a C-protonated intermediate, implies that T_{C2}^+ and T_{C3}^+ may also be reversibly formed from T^0 and therefore could be the protonated intermediates required for breakdown. The transition state for hydrolysis would



then involve a solvent-mediated general base-catalyzed breakdown of either the N protonated form, T_{C2}^+ or T_{C3}^+ to give toluic acid, hydronium ion, and for the latter two, a tautomer of pyrrole. This mechanism, shown in Scheme III, is consistent with the SKIE observed for hydrolysis of **2a** which arises from a normal isotope effect of a proton in flight superimposed upon an inverse equilibrium isotope effect.[3]

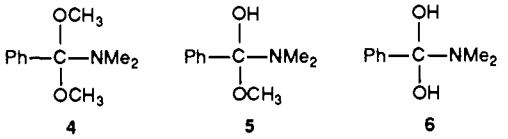
For **2a**, the SKIE suggests that the mechanism for breakdown of the intermediate is different than that operative for the trifluoroacetyl derivatives and *N*-acetylindole studied by Cipiciani et al.[5] in aqueous HCl or moderately concentrated sulfuric acid. There, the measured hydrolysis SKIE's were in the range of k_H/k_D = 1.5–3.5 (2.2–2.4 in aqueous solutions of comparable acidity to those used here). The difference in behavior between toluoylpyrrole (**2a**) and *N*-(trifluoroacetyl)pyrrole (**3**) is almost certainly due to the lower basicity of the trifluoroacetyl derivative which destabilizes any protonated species. In that case, the rate-limiting step for hydrolysis is probably a general acid-catalyzed protonation of the ring of T^0 occurring concurrently with a general base-catalyzed removal of a proton by water as depicted in Scheme IV. This mechanism, which is essentially the same as proposed by Cipiciani et al.,[5] is consistent with the SKIE observed for the hydrolysis of **3** and predicts that neither T_{C2}^+ nor T_{C3}^+ (for trifluoroacetyl derivatives) is stable enough to exist as discrete intermediates.

Scheme IV



(vii) Generalized Scheme for Acid-Catalyzed Amide Hydrolysis. The presently available ^{18}O exchange and SKIE data for the exchange and hydrolysis of amides such as benzamide, acetanilide, and **2a** in H_3O^+ are fully consistent with the mechanism given in Scheme I. Previously, McClelland for benzamide[2] and we for acetanilide[3] have shown that very small k_{ex}/k_{hyd} ratios (0.005–0.01) that are independent of $[H_3O^+]$ obtain. ^{18}O exchange accompanying acid hydrolysis of benzamide had not been observed in earlier studies[17] but this was undoubtedly due to the low intrinsic reversal and low levels of ^{18}O incorporation in the substrate. N-Methylation of benzamide apparently does not increase the amount of ^{18}O exchange, at least in a highly acidic medium of 80% H_2SO_4.[18] However, we have also reported[3] that *N*,2,4-trimethylacetanilide has a significantly increased k_{ex}/k_{hyd} ratio of ~0.23 which is attributable to a reduction in the pK_a of the N-protonated form imposed by steric crowding.[19] McClelland and Patel observed that anilide acetals (**1**) suffer a linear reduction in the acid-catalyzed C–N cleavage rate when the anilinium pK_a drops below 4.5. If such species can be taken as models for the tetrahedral intermediate T^0 produced during amide hydrolysis, then it might be predicted that amides having an amine portion of reduced basicity should show large amounts of ^{18}O exchange concurrent with hydrolysis. This is clearly the case for toluoylpyrrole **2a** for which the k_{ex}/k_{hyd} ratio is ~50. In retrospect, this is not surprising since in the limit where the amine portion of T^0 cannot become protonated, an amide should behave as an aldehyde or ketone which reversibly adds H_2O under acidic conditions. It is important to note that the large amount of exchange seen here for **2a** does not arise from a mechanistic change since the intermediates involved in C–N cleavage are fully protonated prior to that event. This is the same situation as was shown for acetanilide and *N*,2,4-trimethylacetanilide by SKIE studies,[3] but there, the requisite H^+ was on N and not the C as is probably the case for **2a**. There will be a mechanistic change from specific acid to general acid catalysis for the breakdown on further reduction of the pyrrole basicity since the protonated forms become too unstable to exist as discrete intermediates. This is the probable situation for **3**.[5]

As a final point, we consider the subtle differences in the partitioning of T^0 produced from the above amides, and other tetrahedral species (**4**, **5**) which are taken as models for T^0. Amide



4 **5** **6**

acetal **4** has been shown to exhibit an approximate 1:1 partitioning between C–O and C–N cleavage in acid.[20] That ratio must be

(16) The SKIE for such a process, analyzed by the fractionation factor analysis given in ref 3, is predicted to be 2.75–4.0 depending on whether the fractionation factor for the protons in flight is taken as 0.5 or 0.4.

(17) (a) Bunton, C. A.; O'Connor, C.; Turney, T. A. *Chem. Ind. (London)* **1967**, 1835. (b) Bender, M. L.; Ginger, R. D. *J. Am. Chem. Soc.* **1955**, *77*, 348.

(18) Smith, C. R.; Yates, K. *J. Am. Chem. Soc.* **1972**, *94*, 8811.

(19) The 2,6-dimethylanilinium ion is more acidic than anilinium ion by 0.73 pKa units: Jencks, W. P.; Regenstein, J. In *CRC Handbook of Biochemistry*, 1st ed.; Sober, H. A., Ed.; The Chemical Rubber Co.: Cleveland, Ohio, 1968; pp J150–J189.

(20) McClelland, R. A. *J. Am. Chem. Soc.* **1978**, *100*, 1844.

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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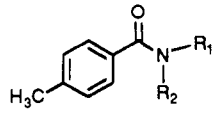
Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2, and Mass Spectrometry Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2. *Received August 16, 1991*

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

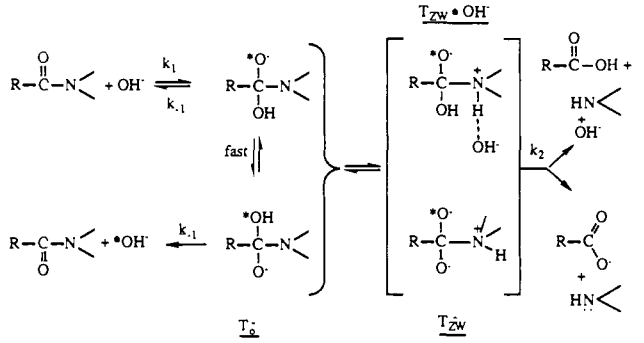
On the basis of carbonyl ^{18}O exchange studies and D_2O solvent kinetic isotope effects (SKIE), a common hydrolytic mechanism for the tertiary amides (I-III) in base was proposed.[1] For each



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^-,

† Department of Chemistry.
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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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