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^{18}O Exchange Accompanying the Basic Hydrolysis of Primary, Secondary, and Tertiary Toluamides. 2. The Importance of Amine Leaving Abilities from the Anionic Tetrahedral Intermediates

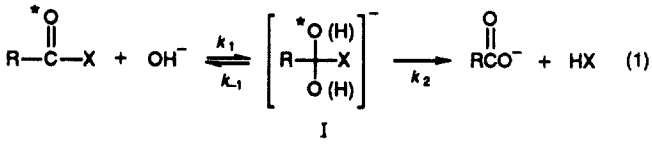
H. Slebocka-Tilk,[†] A. J. Bennet,[†] J. W. Keillor,[†] R. S. Brown,*[,†] J. Peter Guthrie,*[,‡] and A. Jodhan[§]

Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2, Department of Chemistry, University of Western Ontario, London, Ontario, Canada N6A 5B7, and Mass Spectrometry Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2. *Received February 22, 1990*

Abstract: A series of primary, secondary, and tertiary toluamides ($CH_3(C_6H_4)C{=}ONR_1R_2$) was studied with respect to their hydrolysis and C=O, ^{18}O exchange rate constants in basic media at 100 °C. For the primary amides ($R_1 = R_2 = H$) the k_{ex}/k_{hyd} ratio is 3.7 ± 0.2 and is independent of [OH^-]. For the secondary toluamides $R_1 = H$, R_2 = Et, *i*Pr, or *t*Bu, the k_{ex}/k_{hyd} ratio is constant at 0.4–0.75, despite the fact that k_{hyd} drops from 1.0 to 0.22 to 0.02 in passing through the series. The tertiary toluamides $R_1 = R_2 = CH_3$, R_1, $R_2 = (CH_2)_4$ have k_{ex}/k_{hyd} = 0.01–0.02 in H_2O, and that ratio increases somewhat in D_2O. Analysis of the energetics of the various possible intermediates, and their barriers for interconversion and breakdown, produces a mechanism consistent with presently known experimental data. The reaction proceeds stepwise via the addition of OH^- to produce an anionic intermediate (T^-). Breakdown of T^- to product involves a water-mediated proton switch to give an anionic zwitterion followed by rate-limiting C–N cleavage. By study of the partitioning of unsymmetrical amidines in base at 100 °C, an order of leaving ability from an anionic intermediate is established where R_2NH (130–180) > RNH_2 (15–20) > NH_3 (1.0). These data account for the observed k_{ex}/k_{hyd} ratios for the corresponding amides and indicate that amine leaving ability determines whether a given amide will exhibit significant ^{18}O exchange.

Introduction

The question of carbonyl ^{18}O exchange accompanying the base-promoted hydrolysis of carboxylic esters and amides has been extensively investigated in order to ascertain the importance of reversibly formed intermediates.[1-6] With respect to amides, the minimum scheme that accounts for the observed ^{18}O exchange is given in eq 1, and requires a reversibly formed intermediate

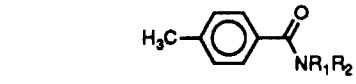


I

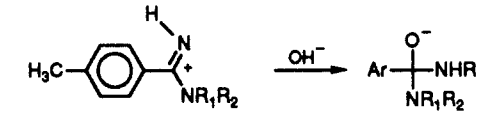
(I) which is symmetrical or two degenerate species in rapid equilibrium (or near equilibrium) which lead to an overall symmetric system. The order of ^{18}O exchange for benzamides[1,2] and toluamides[6a] is primary > secondary ≫ tertiary.

Recently, Deslongchamps and co-workers[4,5] have reinterpreted the original observations[2a,b] of negligible ^{18}O exchange concurrent with OH^- promoted hydrolysis of *N,N*-dimethylbenzamide in terms of the principle of stereoelectronic control.[5] In that interpretation, the lifetime of the anionic tetrahedral intermediate (I, X = $N(CH_3)_2$) is too short to allow conformational changes at nitrogen (either by bond rotation or N inversion) which would be required to assist in ejecting $^{18}OH^-$. It was suggested[5] (with some experimental support[4]) that in a given case, there may or may not be ^{18}O exchange and that would depend "upon the relative energy barriers for conformational change, and fragmentation".

We have recently reported the partitioning ratios (k_{-1}/k_2 in eq 1) observed during OH^- hydrolysis of toluamides (II).[6a] Those results confirmed that at 100 °C (μ = 1.0 KCl) the k_{ex}/k_{hyd} ratio (defined as $k_{ex}/k_{hyd} = k_{-1}/2k_2$) for IIa ($R_1 = R_2 = H$) is ~3.7 ± 0.2 and is independent of [OH^-]. That reported[6a] for IIb ($R_1 = R_2 = CH_3$) was 0.11 ± 0.007 which in this study is shown to be too large by a factor of 10 (vide infra); nevertheless, IIb does exchange. Despite reasonable explanations,[2a,4,5] the reasons why primary amides exhibit large amounts of exchange, while tertiary amides do not, remain obscure. We have therefore undertaken a systematic study to address this question with respect to (1) altering steric demands that might affect the partitioning of I formed from substituted secondary amides IIc–e, (2) altering the conformational mobility at N in I produced from tertiary amides IIb, f, (3) determining the relative leaving group ability of different amides produced from the anionic intermediate (IV) generated from OH^- attack on amidines III. The results reported herein



IIa $R_1 = R_2 = H$ b $R_1 = R_2 = CH_3$
c $R_1 = H$; R_2 = Et d $R_1 = H$; R_2 = *i*Pr
e $R_1 = H$; R_2 = *t*Bu f $R_1 = R_2 = (CH_2)_4$



IIIa R = Et, $R_1 = R_2 = H$
b R = *t*Bu, $R_1 = R_2 = H$
c R = Et, $R_1 = R_2 = CH_3$
d R = Et, R_1, $R_2 = (CH_2)_4$

IV

[†] University of Alberta.
[‡] University of Western Ontario.
[§] Mass Spectrometry Laboratory.

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indicate (1) passing from IIc–e does not influence the partitioning of the tetrahedral intermediate even though there is a 44-fold reduction in hydrolysis rate for IIe relative to IIc, (2) the expected conformational mobility differences in IIf are not reflected in its k_{ex}/k_{hyd} ratio relative to IIb, (3) leaving group abilities from IV are secondary amine > primary amine > NH_3 and of magnitudes that are sufficient to completely account for the observed differences in ^{18}O exchange accompanying the hydrolysis of the corresponding amides.

Experimental Section

(a) Materials. (i) Amides. Amides IIc–f were prepared by the addition of *p*-toluyl chloride to a solution of excess amine in CH_2Cl_2. Each amide was recrystallized from aqueous ethanol. Purity was checked by comparison of the melting points with those reported;[7] all amides had IR, NMR, and MS data consistent with the structures. Amide IIb was prepared as described.[6a]

^{18}O-Enriched amides were prepared in an analogous procedure starting with 40–55% ^{18}O-enriched[6a] *p*-toluoyl chloride.

1-Formylpyrrolidine (V) was prepared by the procedure of Deslongchamps et al.[4b] ^{18}O-Enriched 1-formylpyrrolidine (45%) was prepared by an analogous procedure with the exception that instead of 0.4 mL of H_2O, a mixture of 0.2 mL of H_2 ^{16}O and 0.2 mL of H_2 ^{18}O was used for the hydrolysis of 2.335 g of triethyl orthoformate.

(ii) Amidines. The toluamidines (IIIa,b) were prepared via the O–Me imidate.[8] From an ice-cooled solution of 31.5 g of *p*-toluonitrile and 13.5 mL of MeOH through which was passed dry HCl until no more gas was absorbed was obtained 25 g (71%) of methyltoluimidate hydrochloride as white crystals.

***N*-Ethyltoluamidine·HCl (IIIa).** Methyltoluimidate hydrochloride (5 g) was dissolved in dry MeOH and 2 equiv of $H_2NCH_2CH_3$ were added. The mixture was allowed to stand at room temperature and was periodically monitored by ^1H NMR. After 20 h no starting materials were present. Methanol was then removed by rotary evaporation and the crystalline residue treated with $CHCl_3$. The undissolved crystalline HCl salt of the unreacted amine was removed by filtration, and the filtrate was stripped of volatiles. The residue was recrystallized from MeOH/ether. After two recrystallizations, 2 g of the HCl salt of IIIa were obtained (38%): mp 212 °C; ^1H NMR (400 MHz, 0.1 N OD^-/D_2O) δ 1.23 (t, 3 H, J = 8 Hz), 2.37 (s, 3 H), 3.29 (q, 2 H, J = 8 Hz), 7.30, 7.50 (AA'BB', 4 H, J = 5 Hz). Exact mass calcd. for the free base $C_{10}H_{14}N_2$, 162.1157. Found, 162.1151.

***N*-*tert*-Butyltoluamidine·HCl (IIIb).** This was prepared in the same way as IIIa, except that the reaction with 2 equiv *tert*-butylamine was lengthened to 72 h and further purification was required to separate IIIb from residual *tert*-butylamine·HCl. The crystalline product (1 g) was dissolved in 20 mL of pH 11 (0.3 M CAPS) buffer. The solution was extracted with ether to remove *tert*-butylamine and then basified to pH 13. A second extraction with ether followed by drying of the extract with Na_2SO_4, filtering and removal of the volatiles yielded ~500 mg of IIIb which was judged to be >98% pure by 400-MHz ^1H NMR.

The residue was taken up in CH_2Cl_2 and dry HCl gas passed through the solution to induce precipitation. The HCl salt of IIIb was filtered and then recrystallized from MeOH/ether to give pure material: mp 261 °C; ^1H NMR (400 MHz, 0.1 N OD^-/D_2O) δ 1.42 (s, 9 H), 2.35 (s, 3 H), 7.27, 7.44 (AA'BB', 4 H, J = 4 Hz). Exact mass calcd. for the free base $C_{12}H_{18}N_2$, 190.1470. Found, 190.1471.

IIIc,d. *N,N*-Dimethyl-*N'*-ethyltoluamidine (IIIc) and pyrrolidinyl-*N*-ethyltoluamidine (IIId) were prepared according to the following route. A solution of 4.7 g (0.025 mol) of freshly prepared triethyloxonium tetrafluoroborate[8b] in 20 mL of CH_2Cl_2 (distilled from CaH_2), was added at room temperature to a solution of 4 g (0.025 mol) of *N*-ethyltoluamide (IIc) in 20 mL of dry CH_2Cl_2. The mixture was stirred in the absence of air overnight at room temperature, after which time no amide was detected by ^1H NMR analysis. The solution was reduced in volume by rotary evaporation to ~20 mL and then 100 mL of ether was added to it. This solution was then evaporated to yield a thick transparent oil which was dissolved in 25 mL of dry MeOH. The resulting mixture was divided into two equal portions. To the first was added 1.7 g (0.024 mol) of freshly distilled pyrrolidine, and to the second, 2 g (0.044 mol) of $(CH_3)_2NH$ dissolved in 10 mL of dry CH_3OH. Both mixtures were allowed to stand at room temperature for 4 days after which they were separately evaporated to dryness and treated with a small amount of cold H_2O. They were then made strongly basic with cold concentrated KOH and extracted twice with ether. The ether extracts were dried ($MgSO_4$) and then evaporated to yield a viscous oil. ^1H NMR analysis of the oil revealed the presence of the desired amidine along with ~20% *N*-ethyltoluamide. The amidines were then converted to their HCl salts (HCl gas, ether) and washed with H_2O. The H_2O layer was then basified and reextracted with ether to yield ~30% of the desired amidine as an oil contaminated with 5–7% of *N*-ethyltoluamide. Repeated treatments as above diminished the yields but failed to remove 5–7% amide (based on ^1H NMR) since it is produced by hydrolysis of the amidine. These materials were then used directly for ^1H NMR analysis of the partitioning in OD^-/D_2O, correcting the integrated intensities for the 5–7% of *N*-ethyltoluamide present at the start of the reaction.

IIIc: ^1H NMR (0.25 N DCl/D_2O) δ 1.04 (t, 3 H, J = 7.5 Hz), 2.42 (s, 3 H), 2.91 (s, 3 H), 3.09 (q, 2 H, J = 7.5 Hz), 3.24 (s, 3 H), 7.34 (d, 2 H, J = 8.5 Hz), 7.46 (d, 2 H, J = 8.5 Hz).

IIId: ^1H-NMR (0.25 N DCl/D_2O) δ 1.01 (t, 3 H, J = 7 Hz), 1.82 (m, 2 H), 2.06 (m, 2 H), 2.37 (s, 3 H), 3.07 (m, 2 H), 3.20 (t, 3 H, J = 7 Hz), 3.52 (t, 2 H, J = 7 Hz), 7.33 (d, 2 H, J = 8 Hz), 7.42 (d, 2 H, J = 8 Hz).

(b) Kinetics. (i) Amides IIb–f. The rates of hydrolysis of amides IIb–f were determined by ^1H NMR analysis with use of a Bruker WH-400 spectrometer. Solutions of base in H_2O or D_2O (1.0, 0.5, 0.27, 0.16 or 0.10 N in NaOH or NaOD) were prepared under CO_2-free conditions in an argon-filled dry box and were stored under Ar. A series of 1.0-mL samples containing 0.05 or 0.02 M of the amide (μ = 1.0 (KCl)) and 4% (by volume) DME for solubility was placed in each of ten, 10-mL Teflon FEP centrifuge tubes which were then sealed with leakproof Nalgene caps with Teflon linings. All operations were done in an Ar filled dry box. The tubes were then thermostated at 100 °C (in boiling water vapor) and were removed at various times, cooled, and subjected to ^1H NMR analysis. Immediately prior to the analysis, 40 μL of D_2O or dioxane-d_8 was added to 0.5 mL of the contents of the tube as a lock.

^1H NMR analysis on the H_2O samples was performed by using a presaturation water suppression technique. For the various amides, integration of signals, given in Table I as a function of time, allowed assessment of the reaction rate. For all amides except IIe, both the aromatic signals and *N*-alkyl signals of starting material and product were well-resolved and independently integrated to give two determinations of the rate from a single set of experiments. For IIe, only the *tert*-butyl signals of starting material and product were used. It is important to note that the chemical-shift values reported in Table I are internally consistent within a given experiment, but are not corrected for small chemical shift differences attributable to changes in the medium composition between separate experiments.

Hydrolysis rate constants (k_{hyd}) were calculated from the slope of the plot of ln {(I amide)/[(I amide) + (I product)]} versus time, where I = integrated intensity of the appropriate peak(s). Reactions were followed to two or more halftimes ($t_{1/2}$) except for the slowest (IId,e) which were followed to one $t_{1/2}$ hydrolysis. In all cases, 10 samples were used to determine the plots. Given in Table II are the k_{hyd} values for the amides IIb–f determined as above. The error limits quoted are the standard deviations (from linear least squares analysis) of the ln I versus t plots.

(ii) Amidines IIIa–d. The hydrolysis rates and final product compositions of the amidines were evaluated by ^1H NMR analysis of the reactions in D_2O solutions, T = 100 °C, μ = 1.0 (KCl). For the ethyl amidine IIIa, 12 mg were dissolved in 5 mL of 0.1 or 1.0 N NaOD in D_2O (μ = 1.0 (KCl)); for the less soluble *tert*-butylamidine (IIIb), a saturated solution in 0.1 N NaOD was used; for IIIc and IIId, 30 mg of the amidine was dissolved in 10 mL of 0.1 N OD^-/D_2O. Portions of the above solutions (0.8 mL) were placed in six 10-mL Teflon FEP vials which were then sealed under Ar with Nalgene caps having Teflon linings. The tubes were thermostated at 100 °C and withdrawn at various times (10, 20, and 60 min and then at about 10 and 20 $t_{1/2}$ of hydrolysis) to determine the solution composition.

Table I. ^1H NMR Signals in Starting Amide (IIb–f) and Products Used for Hydrolysis Kinetics in Basic Media[a]

amide	starting material (δ)	product (δ)
IIb	*N,N*-dimethyl (2.8, 2.9)	dimethylamine (2.1)
	aromatic ring (7.15)	toluic acid (7.6, 7.1)[b]
IIc	*N*-ethyl (CH_3) (1.30)	ethylamine (CH_3) (1.10)
	aromatic ring (7.70, 7.45)	toluic acid (7.85, 7.35)[b]
IId	*N*-isopropyl (CH_3) (1.15)	isopropylamine (CH_3) (0.95)
	aromatic ring (7.55)	toluic acid (7.70)[b]
IIe	*N*-*tert*-butyl (1.35)	*tert*-butylamine (1.05)
IIf	pyrrolidine (1.75, 1.9)	pyrrolidine (1.55, 2.65)
	aromatic ring (7.35)	toluic acid (7.70)[b]

[a] H_2O, 100 °C, μ = 1.0 (KCl). [b] Peak positions referenced to H_2O/OH^- and shift slightly depending upon medium's composition.

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Table II. Hydrolysis and Exchange Rate Constants for Toluamides IIa–f in Basic Media, T = 100 °C, μ = 1.0 (KCl)

amide	[OL^-], M	k_{hyd}, s^{-1}	[OL^-], M	k_{ex}, s^{-1}	k_{ex}/k_{hyd}
IIc	0.926	$(1.07 \pm 0.02) \times 10^{-4}$	0.933	$(5.24 \pm 0.15) \times 10^{-5}$	0.49 ± 0.03^a
	0.13	$(1.46 \pm 0.02) \times 10^{-5}$	0.086	$(4.85 \pm 0.10) \times 10^{-6}$	0.50 ± 0.02^a
IId	0.976	$(2.40 \pm 0.12) \times 10^{-5}$	0.976	$(1.55 \pm 0.06) \times 10^{-5}$	0.58 ± 0.05
	0.16	$(3.7 \pm 0.1) \times 10^{-6}$	0.16	$(2.6 \pm 0.1) \times 10^{-6}$	0.70 ± 0.05
IIe	1.01	$(2.50 \pm 0.05) \times 10^{-6}$	1.01	$(1.10 \pm 0.08) \times 10^{-6}$	0.44 ± 0.04
	0.273	$(7.0 \pm 0.3) \times 10^{-7}$	0.273	$(3.00 \pm 0.17) \times 10^{-7}$	0.43 ± 0.04
IIb	1.01	$(1.16 \pm 0.04) \times 10^{-3}$	1.01	$(1.12 \pm 0.11) \times 10^{-5}$	0.010 ± 0.002
	0.02[b]	$(1.91 \pm 0.1) \times 10^{-5}$	0.02	$(2.9 \pm 0.3) \times 10^{-7}$	0.015 ± 0.002
D_2O	1.0	$(1.28 \pm 0.2) \times 10^{-3}$	1.0	$(1.82 \pm 0.19) \times 10^{-5}$	0.014 ± 0.004
IIf	0.926	$(3.29 \pm 0.10) \times 10^{-4}$	1.0	$(4.60 \pm 0.40) \times 10^{-6}$	0.013 ± 0.002^a
	0.50	$(1.73 \pm 0.03) \times 10^{-4}$	0.0216	$(1.00 \pm 0.04) \times 10^{-7}$	0.013 ± 0.001^a
	0.16	$(5.60 \pm 0.18) \times 10^{-5}$	0.16	$(1.1 \pm 0.1) \times 10^{-6}$	0.020 ± 0.002
D_2O	1.0	$(3.85 \pm 0.07) \times 10^{-4}$	1.0	$(1.53 \pm 0.06) \times 10^{-5}$	0.040 ± 0.002

[a] Where [OL^-] is different for a given hydrolysis and exchange experiment, pseudo-first-order rate constants converted to second-order rate constants for comparison purposes. [b] k_{hyd} data extrapolated from ref 6a.

Two ^1H NMR signals were analyzed for each compound to determine the product ratio, namely the amide and amine. The identity of these products was determined by adding the authentic products to the reaction mixture which enhanced the expected signals' intensity.

The hydrolysis kinetics for the amidines were determined by observing the rate of production of the product amines, the ^1H NMR signals of which are well separated from those of the starting amidine or amide product. Unfortunately the signals corresponding to the latter two species are nearly coincident at 400 MHz and appear as two closely spaced but inseparable patterns. Thus the integrated intensities of the amine products were corrected for the (roughly) 5–7% (vide infra) of the reaction product that is attributable to amides IIc,e formed from the partitioning of the respective amidine.

IIIa. *N*-Ethyl signal of the amidine was gone after 8–10 $t_{1/2}$ and replaced with those of *N*-ethyl-*p*-toluamide (IIe, δ 1.20) and ethyl amine (δ 1.00). The ratio of amide/amine signals after 60 min (~12 $t_{1/2}$) was 6.3/100; after 120 min (~24 $t_{1/2}$) 5.5/100. The rate constant for hydrolysis was $(2.9 \pm 0.2) \times 10^{-3}$ s^{-1}, T = 100 °C, 0.1 N NaOD/D_2O.

IIIb. The ratio of *N-tert*-butyl signals of *N-tert*-butyl-*p*-toluamide (δ 1.45) and *tert*-butylamine (δ 1.10) after 150 min (~10 $t_{1/2}$) was 7.0/100 and after 300 min (~20 $t_{1/2}$) was 6.5/100. The corresponding rate constant for hydrolysis of IIIb was $(7.7 \pm 0.3) \times 10^{-4}$ s^{-1} at T = 100 °C, 0.1 N NaOD/D_2O. From Table II, the hydrolysis rate constants for the product amides IIc,e under comparable conditions, but in H_2O, are 300-fold and 3000-fold (respectively) slower than the amidine hydrolysis.

IIIc,d. The amidine was completely hydrolyzed after 1 h at 100 °C, 0.1 N OD^- as judged by the appearance of the NCH_2CH_3 signals attributable to ethylamine (δ 1.05, t) and *N*-ethyltoluamide (δ 1.25, t). After 1 h, for IIIc, the ratio of amine to amide was 12/100 while after 2 h it was 13/100. In the case of the pyrrolidine derivative IIId, $EtND_2$/N-ethyltoluamide ratio was 10/100 after 1 h and 11/100 after 2 h.

(iii) ^{18}O Exchange Kinetics. All solutions were CO_2 free and manipulations were performed in an Ar-filled dry box. A typical exchange experiment was conducted as followed. A 200-mL solution of amide ((0.01–0.05 M), μ = 1.0 (KCl), 40–55% ^{18}O-enriched) in base (0.1–1.0 M NaOH) was divided into eight portions, each being placed into a 30-mL Teflon FEP tube which was sealed with a leak-proof Nalgene cap having a Teflon liner. The tubes were thermostated for the required time at 100 °C (20 °C for 1-formylpyrrolidine). Two tubes were withdrawn and cooled (ice bath) after 15 min of equilibration, and the remaining pairs withdrawn after times corresponding to $^1/_2$, 1, and 1 $^1/_2$ or 2 $t_{1/2}$ for hydrolysis. The tubes were opened, and the contents was separately extracted with 2 × 20 mL of purified CH_2Cl_2, and the combined extracts were washed with saturated NaCl. The organic layer was dried ($MgSO_4$) and stripped of solvent to yield the residual amide which was subjected to mass analysis using an AEI MS-12 low-resolution mass spectrometer. The ^{18}O content of the reisolated material was calculated as % $^{18}O = (I_{M^+ + 2})/(I_{M^+} + I_{M^+ + 2})$ where I refers to the intensity of the parent and enriched parent ions. Scans (18–21) of these ions were recorded and the average ^{18}O content (supplementary material) and standard deviations calculated accordingly. As a check for the presence of extracted co-contaminants that would artifically alter the I_{M^+} or $I_{M^+ + 2}$ peaks, the samples (after low-resolution mass analysis) were subjected to exact mass analysis (KRATOS AEI MS-50). With the larger concentrations of amide used in this study, high-resolution mass analysis (HRMA) detected no extraneous peaks close to the M^+ and $M^+ + 2$ ions. However, if the amide concentrations used were substantially less which allows recovery of smaller amounts of material, significant co-contamination with some amides was identified by HRMA.[9] In any experiments where co-contaminants were identified, the results were discarded and the experiment was repeated with use of slightly larger concentrations.

Results and Discussions

(a) Amide Hydrolysis and ^{18}O Exchange. Given in Table II are the hydrolysis and exchange rate constants for amides IIb–f in basic media at 100 °C. In each case, the hydrolysis and exchange pseudo-first-order rate constants were determined in at least two base concentrations in order to determine that there was a first order dependence in [OH^-]. The errors quoted in the pseudo-first-order rate constants are calculated as the standard deviations of the ln I vs time plots, where I = NMR peak intensity or ^{18}O content for hydrolysis and exchange processes, respectively. In column 6 of Table II are the k_{ex}/k_{hyd} ratios. The quoted error limits are based upon the cumulative % uncertainties in each of K_{ex} and k_{hyd}. In the cases where different [OH^-] were used to measure the pseudo-first-order k_{hyd} and k_{ex} values, these rate constants were converted to second-order ones in order to make the comparisons.

The k_{ex} and k_{hyd} values were reinvestigated by using a different protocol than in the original work,[6a] and lower values than originally reported were found for k_{ex} of IIb. The source of the error lies in the previously reported k_{ex} values and was found to reside in the presence of co-contaminants having m/z = 163[9] that coincide with the M^+ of IIb under low-resolution mass analysis. To overcome this difficulty in the present study, larger volumes (30 mL vs 10 mL) of solutions containing higher amide concentrations (0.01–0.05 vs 0.0005–0.005 M previously) were employed which allowed the reisolation of more material so that the importance of cocontamination is diminished. At the same time, each amide sample that was recovered and mass analyzed at low resolution was subsequently analyzed at high resolution to determine that no co-contaminant peaks were close to the M^+ and $M^+ + 2$ peaks. For each of the series of MS data used in determining the k_{ex} values in Table II, this was found to be the case.

(b) Steric Effects in II. Perhaps part of the reason that the k_{ex}/k_{hyd} ratios for a primary toluamide exceeds that for the tertiary toluamides by a factor of 200–300 is attributable to steric compression in I formed from the tertiary amide that lowers the barrier for C–N cleavage more than that for C–O cleavage. A similar, but less pronounced effect[11] might be anticipated for a series of

(9) For example, when HR mass analysis was conducted on small amounts of recovered *N,N*-dimethyltoluamide, (m/z = 163.0997), a co-contaminant having m/z = 163.0395 was routinely encountered (probably from dimethylphthalate).[10] Under low-resolution analysis, these peaks would not be separable and would lead to an artificial enhancement of I_{M^+} giving anomalously high exchange. This is the probably source of the too high exchange reported earlier[6a] for IIb.

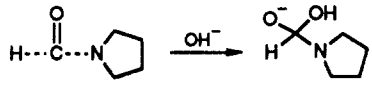
(10) Hites, R. A. *CRC Handbook of Mass Spectra of Environmental Contaminants*, CRC Press, Boca Raton, FL, 1985.

(11) Less pronounced because in the secondary amides, (whose dominant configuration has the *n*-alkyl *syn* to the C=O[12]) and subsequently produced I, the *N*-alkyl group can adopt an orientation anti to the aryl group. Thus, the effect of increasing the *N*-alkyl steric bulk introduces compression into I only insofar as there is enhanced buttressing between the adjacent oxygens and N–R.

secondary amides (IIc–e) in which the steric bulk of the amine could influence the C–N/C–O cleavage ratio.

From Table II, it can be seen that for the secondary amides IIc–e, the k_{ex}/k_{hyd} ratios lie in the range of 0.4–0.75, despite the fact that the k_{hyd} values diminish 4.5- and 44-fold in passing from IIc–e. This indicates that increased steric bulk in the secondary amide retards the attack of OH^-, but unexpectedly, steric effects do not markedly influence the partitioning of the tetrahedral intermediate (I) formed from those secondary amides.

On the other hand, steric compression could be more prevalent in the anionic intermediates produced from tertiary amides since in no rotomer of I can the N avoid placing at least one of its alkyl residues gauche to the aryl group. One possible probe to test the importance of this might be to compare the k_{ex}/k_{hyd} ratio for IIf (0.013–0.020, Table II) with that for a less encumbered tertiary amide, *N*-formylpyrrolidine (V). The anionic tetrahedral intermediate (Va) produced from [OH^-] attack on V has a reduced steric bulk at the C portion of the C–N bond and, if that is important in controlling the C–N/C–O cleavage ratio, should lead to more exchange in V relative to IIf. Since V hydrolyzes much

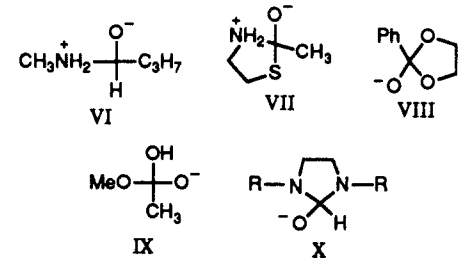


V Va

more rapidly than IIf, its K_{hyd} values were determined at 20 and 50 °C C, the pseudo-first-order values being $(1.95 \pm 0.01) \times 10^{-4}$ s^{-1} (20 °C, 1.0 N NaOH), $(1.95 \pm 0.05) \times 10^{-5}$ s^{-1} (20 °C, 0.1 N NaOH), and $(2.25 \pm 0.03) \times 10^{-4}$ s^{-1} (50 °C, 0.1 N NaOH). Correspondingly, mass analysis of the M^+ and $M^+ + 2$ peaks of ~45% ^{18}O-labeled V recovered from the hydrolytic medium (1.01 N NaOH, T = 20 °C) at times 0, 60, and 120 min (corresponding to 0, $t^{1/2}$, 2 $t_{1/2}$ hydrolysis) indicated the % ^{18}O to be 45.43 ± 0.17, 45.51 ± 0.24 (0), and 45.59 ± 0.07, 45.75 ± 0.07, 45.81 ± 0.06 ($t_{1/2}$), and 45.75 ± 0.11, 45.58 ± 0.13 (2 $t_{1/2}$). Hence there is no evidence for significant ^{18}O exchange such as might be expected if the above-mentioned steric compression effects in the *N*-formylanionic intermediate (Va) were reduced relative to those in the intermediate produced from IIf. Admittedly, entropic factors might be expected to increase the importance of exchange at higher temperatures,[4b,c] but it is unlikely that it will go from nonimportance at 20 °C to being competitive at 100 °C.[13]

(c) Tertiary Amides IIb,f. From Table II, the new k_{ex}/k_{hyd} values for IIb and those for IIf at 100 °C, μ = 1.0 (KCl) are seen to be from 0.010 ± 0.002 to 0.015 ± 0.002 and 0.013 ± 0.002 to 0.020 ± 0.002, respectively, in H_2O. Amide IIf was chosen for comparison with dimethyltoluamide (IIb) under the expectation that the pyrrolidine ring in the former should have a different conformational mobility (greater with respect to ring inversion[14] and C–N rotation and smaller with respect to N inversion[15]) than the dimethylamino group. If conformational interconversions at N in some way limit the stereoelectronic assistance in ^{18}O exchange, as suggested by Deslongchamps,[4] then there is an anticipated difference in exchange between IIb and IIf although it is not easy to predict which should exchange more. The data for IIb,f, within experimental uncertainty, show no difference in k_{ex}/k_{hyd}, which could indicate fortuitous cancellation of the conformational differences, or that conformational effects are unimportant in controlling exchange.

Any analysis of ^{18}O exchange must consider the lifetimes of the anionic intermediates and the rates for the various proton switches[16] required to equilibrate the oxygens and provide the $-NR_2$:···HOH H-bond or protonated N necessary for amine departure. In the case of intermediates I, the lifetimes are not experimentally known, but it has generally been considered in ^{18}O exchange studies[1-6] (with some reservations[1d,2a,c,17]) that the proton switches are fast relative to breakdown. In a variety of analogous processes such as the hydrolysis of phenyl imidates[16a] and breakdown of VI,[18] VII,[19] VIII,[20] IX,[21] and X,[14b] the associated rate constants vary from 5×10^6 s^{-1} to $> 4 \times 10^9$ s^{-1} with the zwitterionic forms (VI, VII) decomposing fastest. Since the



VI VII VIII

IX X

proton switches through water bridges have rate constants on the order of 5×10^8 s^{-1},[16] they may well lag behind or in fact limit the rate of the decomposition of the intermediates.

Guthrie, by thermodynamic analysis of the attack of OH^- on $CH_3C(O)NMe_2$, has concluded that the barrier to reversion back to starting materials is 5 ± 2 kcal/mol.[22] In that analysis, since tertiary amides do not exhibit ^{18}O exchange (or only a small amount, depending on the amide, as shown here and by Deslongchamps[4]), the barrier for C–N cleavage was unspecified, but considered to be ~2 kcal/mol lower than that for C–OH cleavage. The absence, or near absence, of ^{18}O exchange in tertiary amides does not necessarily indicate the C–N cleavage has a lower barrier than C–OH cleavage, but only that the former barrier is lower than any of the steps required for $^{16}OH \rightleftharpoons {}^{18}OH$ interconversion and C–^{18}OH cleavage. Deslongchamps[4c,5] has considered the proton transfer steps to be fast, and that the lack of ^{18}O exchange is a manifestation of the retarded reorientation of the N lone pair to assist in C–^{18}OH departure. From the above, the proton transfer rates may be similar to or slower than C–N cleavage, although it seems clear that the C–N bond rotation and N inversion barriers of 6–10 kcal/mol in tertiary amines[15] are at least as high or higher than those for C–N cleavage. The question, as far as the Deslongchamps' analysis is concerned, boils down to whether N configuration changes are required to assist the C–^{18}OH ejection although most certainly $H^{16}O \rightleftharpoons H^{18}O$ equilibration is required. In any event, the transition state for C–OH cleavage must be very early so that putative orientational requirements are diminished.

(d) D_2O Effects with IIb,f. The experimental observations, in Table II, are that the solvent kinetic isotope effect is about 0.90 for the overall hydrolysis and rather more inverse for exchange reactions (0.62 for IIb and 0.30 for IIf). The most easily interpreted quantity is $(k_{ex}/k_{hyd})_{H/D}$ which compares the two transition states directly. Since the rate of exchange is never more than a

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(13) For *N*-methyl-*N*-benzylpropionamide, Deslongchamps and co-workers[4c] have observed that k_{ex} increases ~15-fold from 60–90 °C while k_{hyd} increases ~6-fold. For the corresponding *N*-formyl derivatives, increasing the temperature from 10–45 °C increases k_{hyd} and k_{ex} by 13- and 23-fold, respectively.

(14) (a) Perrin, C. L.; Nuñex, O. *J. Am. Chem. Soc.* **1987**, *109*, 522. (b) *Ibid.* **1986**, *108*, 5997.

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(16) (a) Jencks, W. P.; Satterthwait, A. C. *J. Am. Chem. Soc.* **1974**, *106*, 7018. (b) Grunwald, E.; Jumper, C. F.; Meiboom, S. *Ibid.* **1963**, *85*, 522. (c) Grunwald, E.; Meiboom, S. *Ibid.* **1963**, *85*, 1882. (d) Luz, Z.; Meiboom, S. *Ibid.* **1963**, *85*, 3923. (e) Eley, D. D.; Fawcett, A. S.; Hey, M. J. *J. Chem. Soc., Faraday Trans.* **1973**, *1*, 399.

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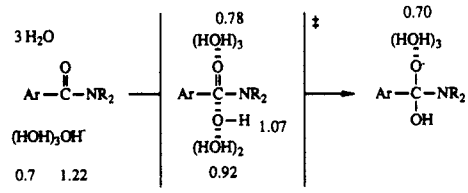

Figure 1. Fractionation factors for the addition of hydroxide to toluamides.

small fraction of the rate of hydrolysis, the observed values of the rate constants are given by

$$k_{hyd} = k_1k_2/(k_{-1} + k_2) \approx k_1$$

$$k_{ex} = k_1k_{-1}/2(k_{-1} + k_2) \approx k_1k_{-1}/2k_2$$

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

Thus given the approximation $k_2 \gg k_{-1}$ it is possible to get simple expressions for all of the isotope effects.

We had hoped that the solvent deuterium kinetic isotope effect data would permit the elimination of some of the imaginable mechanisms. As it turned out the four plausible mechanisms we can write for the product formation step are all consistent with the experimental results. The problem is that the small extent of exchange accompanying hydrolysis limits the precision of the isotope effect measurements and thus limits our ability to draw mechanistic conclusions. However, the energetics calculations given later allow us to select one mechanism as most likely. We analyze the situation by calculating the isotope effect expected for a mechanism by using the procedures outlined by Schowen[23,24] and Schowen,[25] modified by the use of Gold's[26] fractionation factors for hydroxide and its solvating waters, and by making the same assumptions as for the KIE analysis in the accompanying paper.[27]

The KIE for hydrolysis is determined by the k_1 step. If conformational isomerization is rate determining for exchange, the KIE on k_{ex}/k_{hyd} is determined by the partitioning between the isomerization and C–N cleavage pathways and we cannot analyze this effect further. However, we can state the expected value for the KIE for exchange. Conformational isomerization is expected to have an isotope effect similar to that for diffusion, because it involves a similar displacement of solvent molecules with attendant rearrangements of the hydrogen-bond network; it is in fact a kind of constrained two-dimensional diffusion. Following Ridd[28] we estimate from the viscosity[29,30] that diffusion would have a KIE of 1.16 at 100 °C. The observation that there is no major difference in exchange behavior between IIb and IIf despite expected differences in the ease of conformational isomerization leads us to conclude that any conformational changes required for exchange are fast relative to bond forming or breaking.

For $(k_{ex}/k_{hyd})_{H/D}$, we find values of 0.71 ± 0.25 for IIb, and 0.33 ± 0.05 for IIf. (This calculation uses only data at approximately 1 M OL^-, because k_{ex} was only measured at this concentration.) These values differ by more than the sum of the standard deviations and less than twice this sum. Thus at the 95% confidence level we cannot say that they are different. We now examine the expected values for reasonable models of the rate-determining steps.

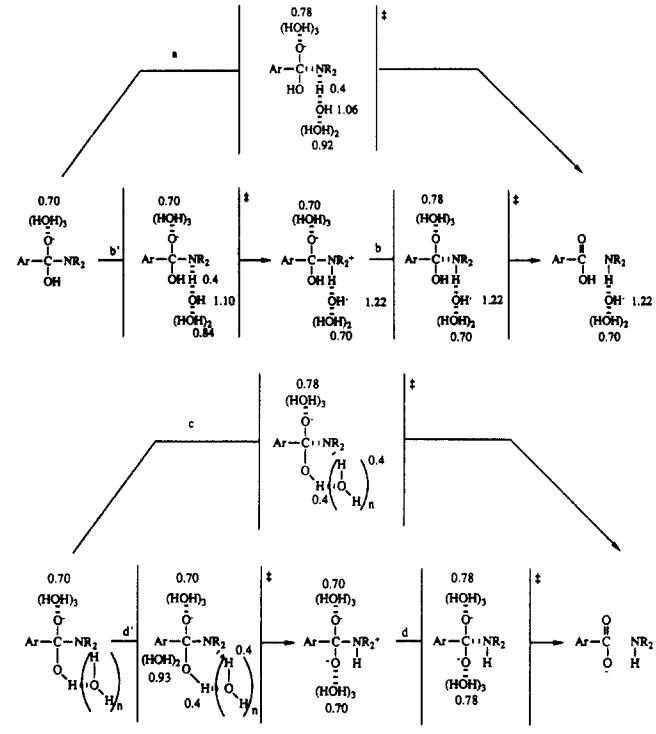

Figure 2. Fractionation factors for the alternative paths for the expulsion of amine from the anionic tetrahedral intermediate.

The magnitude of the SIE for hydroxide addition, which is at variance with the simple Schowen method,[23-25,31] is nicely explained by using Gold's suggestion for hydroxide;[26] hydroxide ion has a fractionation factor of 1.22 rather than 0.5, while the hydrogens involved in three hydrogen bonds to hydroxide have fractionation factors of 0.70. If one then assumes three developing hydrogen bonds to the amide oxygen which becomes an O^- similar to hydroxide in its solvation requirements, and assumes loss of one solvating water to allow hydroxide to attack the carbonyl, one obtains the situation in Figure 1, for which the calculated KIE is 0.97. (In Figures 1–3, the nonunity fractionation factors are shown beside the appropriate H; unit fractionation factors are omitted for clarity.)

For the product-forming step, the alternatives are (a) a concerted path, where expulsion of amide ion occurs with simultaneous transfer of a proton from water, (b) a stepwise path where preequilibrium proton transfer from water occurs, (b) the same path with rate-limiting proton transfer, (c) a cyclic concerted path involving simultaneous C–N bond cleavage and water-mediated proton shift from hydroxyl to nitrogen, (d) a process in which there is a preequilibrium intramolecular proton transfer, leading to an anionic zwitterion followed by rate-limiting C–N cleavage, and (d′) the same path with rate-limiting proton transfer. We should also examine the proton-transfer processes alone, because these will be needed in the discussion of energetics which follows. These assumed paths lead to the transition states and associated fractionation factors shown in Figure 2.

Path a leads to $(k_{ex}/k_{hyd})_{H/D} = 0.39$, but plausible variations in the fractionation factors give values from 0.29 to 0.49, within experimental errors of the values for IIb and IIf. We conclude that the concerted path for IIf is consistent with the experimental KIE data.

Assumption of path b, with preequilibrium proton transfer leads to $(k_{ex}/k_{hyd})_{H/D} = 0.65$. This process is consistent with experiments for IIb, but seems too high for IIf. Path b′ gives $(k_{ex}/k_{hyd})_{H/D} = 0.24$. This cannot be ruled out.

Path c, with two bridging water molecules, leads to $(k_{ex}/k_{hyd})_{H/D} = 0.07$. This is quite inconsistent with the experimental facts. If (which seems unlikely but perhaps cannot be ruled out) there

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were only one bridging water and the fractionation factor for the proton in flight were 0.5, then $(k_{ex}/k_{hyd})_{H/D} = 0.27$, which is quite close to the observed value for IIf. Although this mechanism looks improbable it cannot be ruled out.

Path d, assuming that C–N bond breaking is rate limiting, leads to $(k_{ex}/k_{hyd})_{H/D} = 0.52$. This is within the uncertainty limits of the value for IIb, and with plausible variations in values of the fractionation factors gives $(k_{ex}/k_{hyd})_{H/D} = 0.30$. We conclude that this mechanism is also consistent with the data. The water-mediated proton switch, path d′ would, if it were rate limiting, lead to $(k_{ex}/k_{hyd})_{H/D} = 0.11$, even with only one bridging water molecule. This cannot be the rate-limiting process. Thus path d is possible if C–N cleavage is rate limiting.

(e) Deductions from the Energies of the Intermediates. We can specify somewhat more closely the rates of these various processes by estimating the free-energy levels of the tetrahedral intermediates. These calculations, which are based on Marcus theory,[32-34] follow the pattern outlined[27,35] and are described in Appendix 2 (supplementary material), lead to the free energies in Table III.

As previously described,[27,35] we can examine the possibility of concerted reactions by use of eq 2

$$G = \alpha x + \beta x^2 + \gamma y + \delta y^2 + \epsilon xy \qquad (2)$$

where $\alpha = \Delta G°_x + 4\tilde{G}_x$, $\beta = -4\tilde{G}_x$, $\gamma = \Delta G°_y + 4\tilde{G}_y$, $\delta = -4\tilde{G}_y$, and $\epsilon = \Delta G_{reaction} - \Delta G_x - \Delta G_y$, and where ΔG_x and ΔG_y are the free energies of the "corner" intermediates, $\tilde{G}_x$ and $\tilde{G}_y$ are the intrinsic barriers for the "edge" reactions, and $\Delta G_{reaction}$ is the overall free energy change from starting material to immediate product of the (potentially) concerted reaction.

In order to apply the procedure in a truly predictive fashion, the intrinsic barriers for the possible "edge" reactions must be known. We have some confidence that the intrinsic barriers for proton transfers between oxygen and oxygen or oxygen and nitrogen should be small, i.e., 1 kcal/mol,[33] and that the barrier for addition of hydroxide should be 12.2 kcal/mol.[36] Cleavage of a C–N bond, is expected to have a barrier less than 14 and more than 4 kcal/mol.[27] For the breakdown of a zwitterionic tetrahedral intermediate with expulsion of an amine, data in the literature allow us to calculate the intrinsic barrier. Hine and Kokesh reported rate and equilibrium constants for the breakdown of formocholine chloride[38] which lead to an intrinsic barrier of 10.1 kcal/mol. Guthrie,[39] using estimates based on studies by Blackburn and Jencks,[40,41] gave rate and equilibrium constants for the reaction of dimethylamine and methyl formate which lead to an intrinsic barrier of 10.9 kcal/mol. Satterthwait and Jencks[42] report rate and equilibrium constants for the addition of dimethylamine to *p*-tolylacetate which lead to an intrinsic barrier of 10.4 kcal/mol. The average of these three is 10.5 kcal/mol. We have used intrinsic barriers derived from work at 25 °C. Examination of the expected temperature dependence suggests that these barriers, expressed in terms of free energies, will be quite insensitive to temperature in the range of interest here, particularly in the light of the other uncertainties in the values used.

The mechanisms considered above in discussing the isotope effects fall into two families in terms of three-dimensional reaction surfaces. In one (a, b, and b′) the reaction leads to toluic acid, dimethylamine, and hydroxide ion; in the other (c, d, and d′) reaction leads to toluate anion and dimethylamine.

Consideration of the first family leads to the conclusion that if the reaction leads to a state where the hydroxide is directly hydrogen bonded to dimethylamine, then the reaction will be stepwise, with the rate-limiting transition state being cleavage of the C–N bond after proton transfer from water to nitrogen. No reasonable values of the energies consistent with the constraints in Table III allow a concerted mechanism (path a). Rate-determining proton transfer (path b′) requires a relatively high intrinsic barrier for proton transfer (4–6 kcal/mol) accompanied by a low barrier for C–N cleavage (3–5 kcal/mol) which seems unreasonable. A stepwise reaction with C–N bond cleavage as the rate-determining step demands a rather low intrinsic barrier, of ca. 6 kcal/mol. This seems too small compared to the relatively high values found for hydroxide addition[36] and zwitterionic cleavage, vide infra. A contour diagram summarizing these calculations is shown in Figure 3.

Consideration of the second family of mechanisms (c, d, and d′) leads to the conclusion that the reactions will be stepwise, but that depending on the energetics the rate-determining step could be proton transfer (a water-mediated proton switch) or C–N bond

Table III. Calculated Free Energies of Formation for Various Intermediates and Transition States in Aqueous Solution at 100 °C Relative to *N,N*-Dimethyltoluamide, with $[OH^-] = 1.0$[a]

compound	$\Delta G°_f$ (aq) calculated	$\Delta G°_f$ (aq) by fitting
TolC(OH)(OH)(NMe_2)	22.7 ± 3[b]	19.7
TolC(OH)(O^-)(NMe_2)	21.7 ± 5[c]	16.7
TolC(OH)(O^-)(NMe_2H^+)	28.1 ± 6[c]	22.7
TolC(O^-)(O^-)(NMe_2H^+)	27.6 ± 8[c]	19.6
TolC(OH)(O^-)-NMe_2H^+, OH^-	29.6 ± 8[d]	
CO ts	27.03[e]	
CN ts	24.10[f]	
TolCOOH, Me_2N^-	57.4 ± 12[g]	48.4
TolCOOH, Me_2NH, OH^-	25.8 ± 9[h]	
$TolCOO^-$, Me_2NH	1.0 ± 7[i]	6.7

[a] Calculated values were obtained as described in Appendix 2 (supplementary material); values by fitting were obtained by varying within the uncertainty limits to obtain transition states and free energies of activation consistent with the kinetic isotope effects and the observed rates. [b] Estimated from the rates of alkaline hydrolysis at 25 °C as described in Appendix 2 (supplementary material). [c] Based on the estimated pK_a values in Table A2 (supplementary material). The estimated uncertainties are ±3 for the tetrahedral intermediate energy, ±2 for the pK_a estimation, and ±3 for zwitterion content. [d] Estimated by using: the pK_a for N protonation of the anionic tetrahedral intermediate; and hydrogen-bond formation between this N^+H and hydroxide, estimated after Stahl and Jencks[49] as 1.48 kcal/mol. The estimated uncertainties are ±3 for the tetrahedral intermediate energy, ±3 for the estimation of zwitterion content, and ±2 for hydrogen bond formation. The total uncertainty is ±8 kcal/mol. [e] Free energy of activation for the hydrolysis reaction; calculated from the apparent second-order rate constant at 1 M OH^-. [f] Free energy of activation for the C–N cleavage process calculated from the free energy of activation for the hydrolysis process and the free energy difference derived from $k_2/k_{-1} = k_{hyd}/2k_{ex}$. k_{ex} was calculated from the apparent second-order rate constant at 1 M OH^-. [g] Estimated by using: the free energy of amide hydrolysis; the free energy for proton transfer from dimethylamine to *p*-toluate anion; the free energy of desolvation of dimethylamide ion, for loss of one hydrogen-bonding water, estimated by using an equation based on the difference in pK_a of anions on transfer from water to DMSO[50] as 10.90 kcal/mol; and the free energy of encounter complex formation, estimated after Hine.[37] The estimated uncertainties are ±3 for amide hydrolysis, ±5 for proton transfer, and ±4 for desolvation–encounter complex formation, for a total uncertainty of ±12 kcal/mol. [h] Estimated by using: the free energy of amide hydrolysis; the free energy of encounter complex formation between toluic acid and dimethyl amine, estimated as described in Appendix 2 (supplementary material); and the free energy of hydrogen-bond formation for hydroxide and complexed dimethylamine. The estimated uncertainties are ±3 for amide hydrolysis, ±3 for amine–carboxylic acid complex formation, ±3 for hydrogen-bond formation. The total uncertainty is ±9 kcal/mol. [i] Estimated by using: the free energy of amide hydrolysis; and the free energy of encounter complex formation between toluate anion and dimethyl amine, estimated as described in Appendix 2 (supplementary material). The estimated uncertainties are ±3 for amide hydrolysis and ±4 for amine–carboxylic acid complex formation. The total uncertainty is ±7 kcal/mol.

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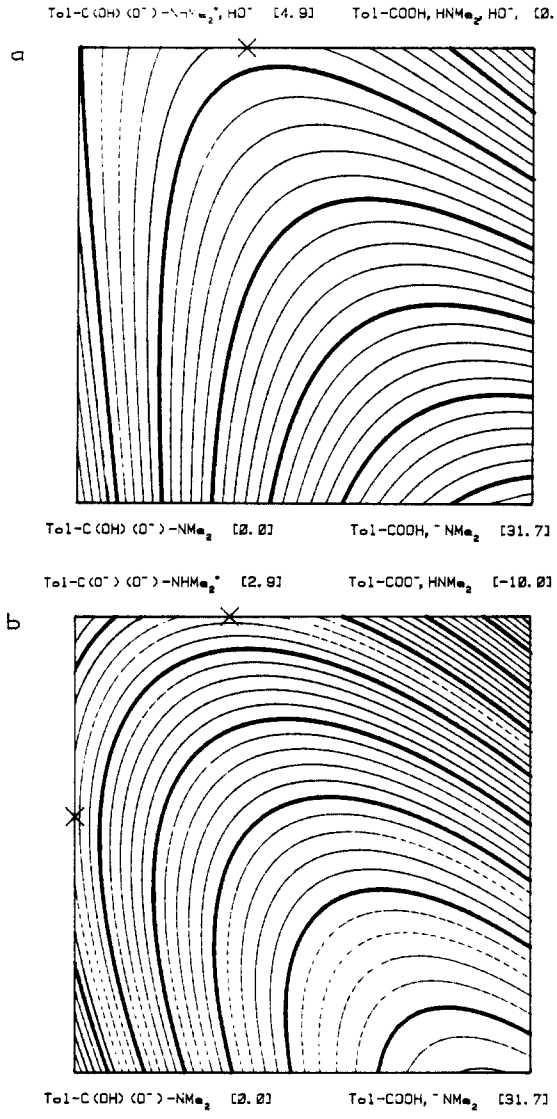

Figure 3. Contour diagrams for the expulsion of amine, calculated by using eq 2 of ref 27. The position of the transition state is indicated. Contours are drawn every kcal/mol, with heavier lines every 5 kcal/mol: (a) process leading to acid, amine, and hydroxide, calculated by using the lowest values for free energies of intermediates from Table III and intrinsic barriers of 1 kcal/mol for proton transfer and 4.6 kcal/mol for C–N bond cleavage, (b) process leading to anion and amine, calculated by using the adjusted values for free energies of intermediates from Table III, and intrinsic barriers of 6 kcal/mol for water-mediated proton switch and 10 kcal/mol for C–N bond cleavage.

cleavage. Neither of the two edge reactions has a small intrinsic barrier, so it is to be expected that the concerted path, i.e., c, will be energetically prohibited. The solvent kinetic isotope effect rules out rate-determining proton transfer, path d′. For path d, exploration of the effects of variations of the energies within the constraints in Table III showed that a free energy of activation consistent with experimental results was possible but only for a relative free energy of formation of the tetrahedral intermediate which was near the lower bound, and a high intrinsic barrier for C–N cleavage. An additional constraint can be imposed from the experimental requirement that exchange and hydrolysis are both first order in hydroxide. The intrinsic barrier for cleavage of the neutral zwitterion is known, and we have estimated the relative energy levels of the neutral and anionic zwitterions. The free energy of activation for breakdown of the neutral zwitterion can be estimated for each possible value of the free-energy change upon C–N bond cleavage, and for consistency with the kinetics data this must be greater than the observed free energy of activation for the k_2 process. This constraint can be satisfied if the free energy of the immediate product is at the high end of the

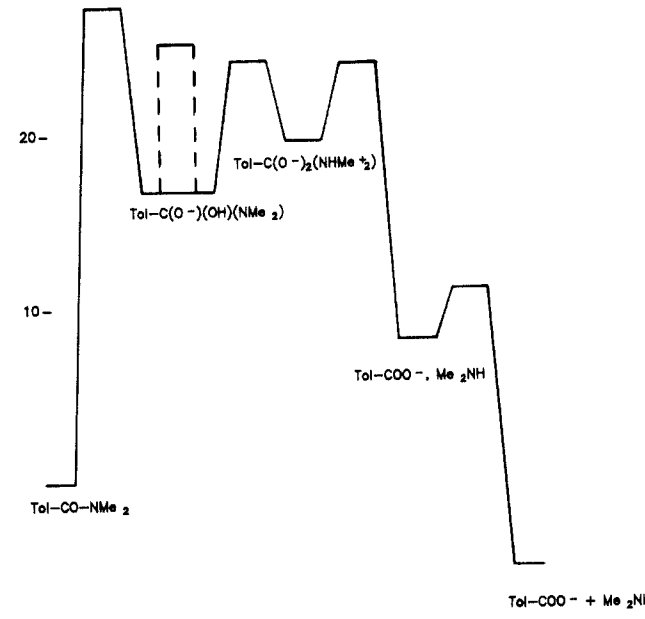

Figure 4. Two-dimensional projection of the reaction coordinate diagram for *N*,*N*-dimethyl-*p*-toluamide hydrolysis at 100 °C, using energies for the intermediates consistent with all the known constraints. This set of values assumes intrinsic barriers of 1 kcal/mol for simple proton transfer, 6 kcal/mol for water-mediated proton shift, and 10 kcal/mol for C–N bond cleavage. Activation energies for bond rotation (with an assumed rate constant of 10^8 s^{-1}) (dotted lines) are shown for the anionic intermediates.

allowed range, and path d can be at least partly rate limiting if the intrinsic barrier for breakdown of the anionic zwitterion is also around 10 kcal/mol. This seems reasonable for a process involving complicated adjustments in solvation as two strongly hydrogen-bonded oxo/anions become less strongly solvated. With an intrinsic barrier of only 10 kcal/mol for path d, the free energies of activation for paths d and d′ are very similar, so that neither step is rate limiting. The solvent deuterium KIE is consistent with this sort of "virtual transition state".[31] A contour diagram for this mechanism is included in Figure 3.

Of the mechanisms considered for the breakdown of the tetrahedral intermediate to products, the one which seems most probable, because it is energetically consistent, fits the kinetic isotope effect data, and requires realistic appearing intrinsic barriers, is water mediated proton switch to give an zwitterion followed by rate limiting C–B bond cleavage. Breakdown of an anionic zwitterion ("dipolar ion") was proposed by Bender and Thomas.[43]

Figure 4 shows the free energies for a two-dimensional projection of the reaction coordinate diagrams which are consistent with all of the facts presently known.

A necessary consequence of the mechanism which we have proposed is that in the reverse direction, amide formation under basic conditions should proceed by uncatalyzed attack of an amine on a carboxylate. Kinetically this is the pattern which was observed by Morawetz and Otaki,[44] but since the rate-determining step is presumably expulsion of HO^-, the kinetics say nothing about the rate law for the addition step. Attack of amine on carboxylate is kinetically indistinguishable from hydroxide-catalyzed attack of amine on the carboxylic acid. This alternative may be ruled out by comparison with ester aminolysis, where Jencks[41] has argued that the observed hydroxyde catalysis refers to trapping of the zwitterion, and not to concerted proton abstraction while C–N bond formation is taking place. For a reaction involving intramolecular attack of an amine on a carboxylate Kirby et al.

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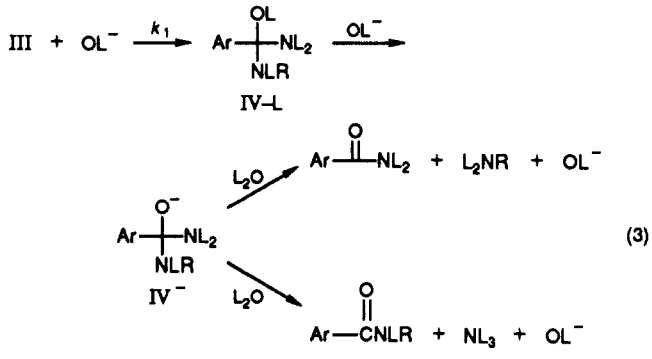
concluded that a concerted mechanism was operative.[45]

The analysis presented above leads to the prediction that there would be a shift to uncatalyzed breakdown via the neutral zwitterionic intermediate at lower hydroxide concentration. Since exchange would continue to involve an anionic transition state, the fraction of exchange is predicted to decrease at lower hydroxide. This prediction will be difficult to confirm experimentally, because the fraction of exchange is already very low, and the rates will become very slow at low hydroxide.

(f). Amidines IIIa–d. As far as we are aware, nowhere in the literature concerning ^{18}O exchange accompanying OH^- hydrolysis of amides is there included due consideration of leaving group abilities of amines from I which would have bearing on the different k_{ex}/k_{hyd} values observed for primary, secondary, and tertiary amides. As a probe for testing the relative leaving-group ability of ammonia, primary and secondary amines from a common anionic intermediate we investigated the partitioning of IV^- produced from OD^- attack on III in D_2O at 100 °C. In this system, the rate-limiting step is OL^- attack on the amidinium ion[14,46] and subsequent deprotonation of IV–L and C–N cleavage of IV^- are faster processes than the reejection of OL^- (eq 3). In



(3)

eq 3, the partitioning of IV^- can be evaluated by comparing the integrated ^1H NMR intensities of the amine and amide products. In the case of IIIa (R = Et) and b (R = *t*Bu), the amide (ArC(O)NLR)/amine (L_2NR) ratio was found to be 5.5–6.3/100 and 6.5–7.0/100, respectively. These results indicate that ethylamine and *tert*-butyl amine have similar leaving group abilities from IV^- of ~15–20-fold greater than that of NH_3. Steric effects of the amine do not markedly influence the partitioning, which coincides with the lack of steric effects on the ^{18}O-exchange process for IIIc–e. Finally, by comparison of the amine partitioning from IIIc,d, $(CH_3)_2NL$ and pyrrolidine depart ~8 and 10-fold better from IV^- than does $EtNL_2$. Taken together, the order of amine partitioning from IV^- is R_2NL (130–180) > RNL_2 (15–20) > NL_3 (1) at 100 °C. Perrin has also concluded a primary amine departs from acetamidines under basic hydrolysis (25 °C) about 10-fold faster, and that secondary amines about 50-fold faster than NH_3.[14a] In that system there is also no large steric effect on the leaving-group ability although there may be some small but nonspecific influence of amine basicity. On the other hand, basicity alone cannot account for our observations since the pK_a of the conjugate acids of $EtNH_2$, $tBuNH_2$, $(CH_3)_2NH$, and pyrrolidine are 10.8, 10.83, 10.7, and 11.27, respectively.[47]

For our purposes, there is a formal similarity of the partitioning of amine from IV^- and the ^{18}O exchange since both processes create amide and OH^-, the latter being generated with an amine in a circuitous route from IV^-. The partitioning results have a strong bearing on the ^{18}O-exchange data in Table II which indicates a 7–10-fold reduction in k_{ex}/k_{hyd} in passing from IIa to IIc–e, and 195–300 fold reduction in passing from IIa to IIb,f. Thus, the similarity in these values to those obtained for the amine partitioning from IV^- suggests that the amine leaving group ability[48] from the anionic tetrahedral intermediate (I) is essentially completely responsible for controlling the k_{ex}/k_{hyd} ratio.

Conclusions

(1) Base promoted hydrolysis of toluamide, secondary toluamides (NHEt, NH*i*Pr, NH*t*Bu), and tertiary toluamides ($N(CH_3)_2$, pyrrolidine) at 100 °C exhibit k_{ex}/k_{hyd} ratios of 3.7, 0.4–0.7, and 0.01–0.02, respectively, in H_2O. In each case, the k_{ex}/k_{hyd} ratio is independent of $[OH^-]$, and both processes are first order in $[OH^-]$.

(2) In the case of the secondary toluamides, although the k_{hyd} values diminish by 4.5- and 44-fold in passing from NHEt → NH*i*Pr → NH*t*Bu due to hindrance of attack of OH^-, once the anionic tetrahedral intermediate is formed the C–O/C–N partitioning is independent of steric effects.

(3) In D_2O solution at 100 °C the amount of exchange for the tertiary toluamides ($N(CH_3)_2$ and pyrrolidine) increases, the $k_{ex}^{H_2O}/k_{ex}^{D_2O}$ values being 0.61 ± 0.12 and 0.32 ± 0.05, respectively. The k_{hyd} values in D_2O are k_{OH^-}/k_{OD^-} = 0.90 ± 0.17 and 0.92 ± 0.05 for IIb and IIf, respectively. The fact that there is more exchange in D_2O than in H_2O suggests that the $H^{16}O \rightleftharpoons H^{18}O$ equilibrium in the intermediate is complete or nearly so, since if this were not the case less ^{18}O exchange would be observed in D_2O.

(4) The order of amine leaving group ability from the base-catalyzed hydrolysis of the various toluamidines in D_2O at 100 °C is NH_3 (1) ≤ RNH_2 (15–20 for R = Et, *t*Bu) < R_2NH (130–180 for $N(CH_3)_2$, pyrrolidine). Taken together with the ^{18}O-exchange data, these findings indicate that the diminishing amount of exchange in passing from toluamide to secondary to tertiary toluamides is a consequence of an enhanced leaving-group ability of the more highly substituted amine from the anionic tetrahedral intermediates. Without assessing what factors influence leaving-group ability,[48] the results suggest that there is no need to postulate that stereoelectronic effects are responsible for the observed minimal ^{18}O exchange accompanying the hydrolysis of tertiary amides.

(5) In Figure 4 we have presented an internally consistent picture of the detailed mechanism of the reaction which is in accord with all the available data. The product-forming step involves preequilibrium formation of an anionic zwitterion which then breaks down to give carboxylate anion and neutral amine.

(6) The tetrahedral species involved in this hydrolysis have very short lifetimes, both because they are interconverted by proton transfers which are inherently fast and because the breakdown processes with either C–O or C–N cleavage are very rapid from the appropriate intermediate. The lifetimes so calculated for the mechanism shown in Figure 4 are: T^-, 2×10^{-9} s; T^-_{zw}, 3×10^{-11} s. For T^-, the thermodynamically preferred form of the tetrahedral intermediate, one can also calculate a lifetime based on the rate to starting material or products: this lifetime is 2×10^{-8} s. Thus the intermediate has a long enough lifetime for rotational isomerization, though just barely.

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Supplementary Material Available: Tables of mass spectrometric M^+, $M^+ + 2$ intensities (Tables 1S–5S) used in determining the k_{ex} values for amides IIb–f and Appendices 1 and 2 showing the energetics calculations for the species shown in Table III, along with pertinent references (71 pages). Ordering information is given on any current masthead page.

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