solvent and excess substrate were evaporated in vacuo, and the products were separated by thin-layer chromatography on silica gel with pentane eluent. The products obtained in the presence of $EtMe_2SiH$ (93% conversion of starting material) were Ad_2SiH_2 (22%), $PhSiMe_2SiAd_2H$ (27%), $(EtMe_2Si)_2$ (9%), and $HSiAd_2SiEtMe_2$ (1%). In the presence of 2,3-dimethylbutadiene, the products were Ad_2SiH_2 (24%), $PhSiMe_2SiAd_2H$ (23%), and $PhSiMe_2SiAd_2CH_2CHMeCMe{=}CH_2$ (6%).

$PhSiMe_2SiAd_2H$: ^1H NMR (C_6D_6) δ 0.57 (s, 6 H, SiMe), 1.71 (m, 12 H, Ad), 1.79 (m, 6 H, Ad), 1.96 (m, 12 H, Ad), 3.48 (s, 1 H, SiH), 7.22 (m, 3 H, Ph), 7.62 (m, 2 H, Ph).

$(EtSiMe_2)_2$: ^1H NMR (C_6D_6) δ 0.01 (s, 12 H, SiMe), 0.58 (q, 4 H, J = 7.8 Hz. Et CH_2), 0.99 (t, 6 H, J = 7.8 Hz, Et CH_3).

$PhSiMe_2SiAd_2CH_2CHMeCMe{=}CH_2$: ^1H NMR (C_6D_6) δ 0.20–0.45 (m, 8 H, $SiCH_2$, SiMe), 0.9 (m, 3 H, Me), 1.35 (s, 3 H, Me), 1.79 (m, 12 H, Ad). 1.85 (m, 6 H, Ad), 1.95 (s, 12 H, Ad), 5.00 (m, 2 H, $=CH_2$), 7.2–7.5 (m, 5 H, Ph).

Photolysis and Thermolysis of 1,1-Diadamantylsiliranes. Photolysis. The reaction mixture was loaded into a quartz sample tube (6 mm (o.d.) × 4 mm (i.d.) × 20 cm) connected via a stainless steel sleeve to a Teflon high-vacuum stopcock. After being degassed to 0.02 Torr by freeze–pump–thaw cycles on a vacuum line, the reaction mixture was irradiated with an array of low-pressure mercury lamps in a Rayonet photochemical reactor. After irradiation, the reaction mixture was unloaded in a drybox, and solvent and excess volatile substrates were evaporated under reduced pressure.

Thermolysis. The reaction mixture was placed in a Pyrex tube (6 mm (o.d.) × 4 mm (i.d.) × 20 cm) with a preformed constriction, attached via a stainless steel adapter to a Teflon high-vacuum stopcock. After being degassed on a vacuum line by freeze–pump–thaw cycles to 0.02 Torr, the sample tube was sealed and then placed in a preheated oil bath. After thermolysis, the sealed tube was opened in a drybox, and solvent and excess volatile substrates were evaporated in vacuo.

The results from both photolysis and pyrolysis experiments, including quantities of reagents, reaction times and temperatures, conversions, product yields, and the isomeric composition of recovered starting and product siliranes are given in Schemes III–V and for competition experiments in Scheme VII.

Acknowledgment. We are grateful to the United States National Science Foundation for encouragement and support of this research under Grant No. CHE-88-02677. Professor Maitland Jones, Jr., provided the original stimulus for this project. We thank Professor Robert T. Conlin for helpful discussions and exchange of unpublished results. We are grateful to Dr. Andrew Tyler, Ms. Janet Braddock Wilking, and Mr. Dallas New for recording mass spectra, which were obtained at the Washington University Mass Spectrometry Resource, which is supported by National Institutes of Health Grant No. RR00954. The Washington University X-ray Crystallography Facility has received support from the NSF Chemical Instrumentation Program, Grant No. CHE-88-11456.

Supplementary Material Available: Crystal structure drawing, diagram of unit cell, structure determination summary and tables of atomic coordinates, bond lengths, bond angles, anisotropic displacement coefficients, and H atom coordinates (11 pages); observed and calculated structure factors (18 pages). Ordering information is given on any current masthead page.

Predominant ^{18}O Exchange Accompanying Base Hydrolysis of a Tertiary Toluamide: *N*-Ethyl-*N*-(trifluoroethyl)toluamide. Assessment of the Factors That Influence Partitioning of Anionic Tetrahedral Intermediates

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Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2. *Received May 31, 1990*

Abstract: The hydrolysis of *N*-ethyl-*N*-(trifluoroethyl)toluamide (III) in basic media at 100 °C (μ = 1.0 (KCl)) is reported. ^{18}O exchange in III recovered from the hydrolytic medium is observed; k_{ex}/k_{hyd} = 33.4 ± 1.6 and is independent of $[OH^-]$. The low basicity of the amine in III ($pK_a(H_2{}^+N(Et)CH_2CF_3)$ = 6.3) leads to 2300–3500-fold more exchange in III relative to *N,N*-dimethyltoluamide (I) or *N*-toluoylpyrrolidine (II). These findings indicate that amine leaving ability controls whether a tertiary amide will exhibit ^{18}O exchange and that restriction of conformational mobility in the manner required by the Deslongchamps' stereoelectronic theory is of little importance in the exchange process. Solvent deuterium kinetic isotope data for III indicate that $(k_{ex})_{H/D}$ = 0.90 ± 0.08 and $(k_{hyd})_{H/D}$ = 1.05 ± 0.04. These respective solvent kinetic isotope effects (SKIE) refer essentially to isolated kinetic processes k_1 (the attack of OH^- to form $T_0{}^-$) and k_2 (the breakdown of the anionic intermediate to product). The small observed SKIE on exchange and hydrolysis is analyzed in terms of the fractionation factors for species involved in the transition states leading to the anionic tetrahedral intermediate $T_0{}^-$ and away from it, respectively. The mechanism consistent for the SKIE on k_{hyd} is suggested to involve rate-limiting breakdown of one or both of two anionic forms having a protonated N, an anionic zwitterion $T_{ZW}{}^-$ or a neutral zwitterion with an encounter complex associated OH^-. On the basis of SKIE, ^{18}O exchange, and hydrolysis data for a series of tertiary toluamides having an amine portion varying in basicity by ~14 p*K* units, a unified mechanism for base-promoted hydrolysis is presented.

Introduction

Carbonyl ^{18}O exchange has been extensively used to determine the partitioning of anionic intermediates produced during the hydrolysis of amides in base.[1-6] The current scheme that accounts for the observed ^{18}O exchange is given in eq 1 and involves one or more reversibly formed intermediates (e.g., $T_0{}^-$) in which the ^{16}O and ^{18}O atoms are in protonic equilibrium (or near equilibrium).

The order of ^{18}O exchange for previously investigated benzamides[1,2] and toluamides[6,7] is primary > secondary ≫ tertiary,

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[†] Undergraduate research participant.

(1) (a) Bender, M. L. *J. Am. Chem. Soc.* **1951**, *73*, 1626. (b) Bender, M. L.; Ginger, R. D.; Kemp, K. C. *Ibid.* **1954**, *76*, 5350. (c) Bender, M. L.; Ginger, R. D. *Ibid.* **1955**, *77*, 348. (d) Bender, M. L.; Ginger, R. D.; Unik, J. P. *Ibid.* **1958**, *80*, 1044. (e) Bender, M. L.; Thomas, R. J. *Ibid.* **1961**, *83*, 4183.

(2) (a) Bunton, C. A.; Nayak, B.; O'Connor, C. J. *J. Org. Chem.* **1968**, *33*, 572. (b) Bunton, C. A.; Lewis, T. A.; Llewellyn, D. R. *Chem. Ind.* (*London*) **1954**, 1154. (c) Bunton, C. A.; Spatcher, D. N. *J. Chem. Soc.* **1971**, *36*, 3870.

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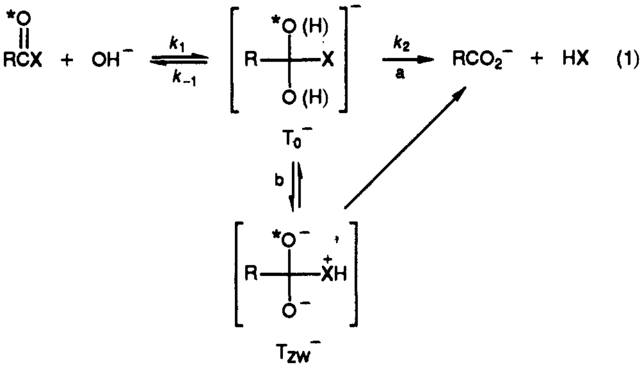
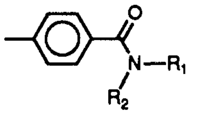


and we have recently shown this to be attributable to the relative amine leaving ability (LA) from the anionic tetrahedral intermediate.[7] From D_2O solvent kinetic isotope effect studies on the k_{ex}/k_{hyd} ratios (defined as $k_{ex}/k_{hyd} = k_{-1}/2k_2$) for two tertiary toluamides (*N*,*N*-dimethyltoluamide (I) and *N*-toluoylpyrrolidine (II)), we have proposed that the breakdown of T_0^- to products involves the rapid formation of an anionic zwitterion T_{ZW}^- followed by a slower C–N cleavage.[7]



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

Two definitive conclusions arise from our previous study.[7] First, since amine LA determines whether ^{18}O exchange will be observed during OH^--promoted amide hydrolysis, it is unnecessary to postulate that lack of exchange in tertiary benzamides or toluamides is attributable either to stereoelectronic effects[4] or to inability to achieve protonic equilibration of the ^{16}O and ^{18}O atoms.[2a] Second, since the k_{ex}/k_{hyd} ratios for I and II are 0.01–0.015 and 0.013–0.02, respectively, ($T = 100$ °C, $\mu = 1.0$) and are independent of $[OH^-]$, the rate-limiting step for both hydrolysis and exchange is k_1. Thus, for the tertiary benz- and toluamides heretofore investigated it is difficult to obtain good mechanistic information about the product-forming transition state (k_2 in eq 1). This is because the low observed ^{18}O exchange is subject to unavoidably large experimental uncertainties that complicate the comparison of k_{ex}/k_{hyd} in H_2O and D_2O, which have bearing on the mechanistic evaluation.

In order to address the above problem, we have sought a tertiary toluamide that possesses an amine with a diminished LA, which would raise the k_2 barrier above that of k_{-1}. Herein we report our findings with the *N*-ethyl-*N*-trifluoroethyl derivative III, which shows a surprisingly large k_{ex}/k_{hyd} ratio of 33.4 ± 1.6 in NaOH ($T = 100$ °C). As well, we present kinetic solvent isotope exchange and hydrolysis data for III and IV along with activation parameters for the hydrolysis of I–III and some other tertiary toluamides. These data allow a detailed mechanistic analysis to be made for a series of toluamides in which the rate-limiting steps vary from OH^- attack (k_1 for I and II) to breakdown of the anionic intermediates (k_2 for III).

Experimental Section

(a) Materials. *N*-Ethyltoluamide (IV) was prepared as previously described,[7] as were I[6a] and II.[7]

N-Ethyl-*N*-(trifluoroethyl)amine was prepared by a modification of a reported procedure[8] as follows. To an ice-cooled solution containing 30.26 mL of trifluoroacetic anhydride in 175 mL of dry ether was added dropwise a solution of 34 mL of ethylamine in 75 mL of ether. After the addition was complete, the mixture was stirred for an additional 15 min and then filtered. The filtrate was concentrated and the residue distilled (water aspirator, 55 °C) to give 17.2 g of *N*-ethyltrifluoroacetamide (57%).

Reduction was accomplished by addition of a solution of 10 g (71 mmol) of *N*-ethyltrifluoroacetamide in 500 mL of dry ether to a stirred mixture of 4.1 g of $LiAlH_4$ in 150 mL of ether at such a rate as to induce gentle reflux. The resulting mixture was heated at reflux for 72 h after which it was cooled and quenched by the dropwise addition of 10 mL of H_2O, followed by 10 mL of 15% aqueous NaOH and then a further 30 mL of H_2O. The resulting mixture was stirred for 20 min and then filtered. The solid was washed with 3 × 20 mL of ether, the combined filtrate and ethereal washings were then extracted with 3 × 40 mL of H_2O, and the solid was dried ($MgSO_4$). After filtration, the ether solution was flushed with HCl gas until no further precipitation was observed and then filtered to yield 8.7 g (75%) of the HCl salt of *N*-ethyl-*N*-(trifluoroethyl)amine: ^1H NMR (D_2O) δ 1.34 (t, 3 H, $J = 7$ Hz), 3.29 (q, 2 H, $J = 7$ Hz), 3.98 (q, 2 H, $J = 9$ Hz); IR (KBr disk) 3400–2600 (br), 2557, 2441, 2394, 1598, 1480, 1424, 1353, 1270, 1207, 1186, 1110, 1047 cm^{-1}; exact mass for $C_4H_8NF_3$, calcd 127.0609, found 127.0613.

N-Ethyl-*N*-(trifluoroethyl)toluamide (III) was prepared by the addition of 1.72 g (11 mmol) of *p*-toluoyl chloride to a solution consisting of 2.0 g (12 mmol) of the above amine hydrochloride salt, 2.0 mL of H_2O, and 5 mL of triethylamine. The mixture was allowed to stand for 30 min after which it was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with 10 mL of 0.01 N HCl, then dried ($MgSO_4$), and stripped of solvent. The residue was distilled at 100 °C/0.5 Torr to yield 2.3 g (82%) of the desired amide: ^1H NMR (50 °C, $CDCl_3$) δ 1.15 (t, 3 H, $J = 6$ Hz), 2.39 (s, 3 H), 3.53 (q, 2 H, $J = 6$ Hz), 4.10 (br q, 2 H, $J = 7.2$ Hz), 7.26 (4 H, AA′BB′); IR (film) 1659 cm^{-1}; exact mass for $C_{12}H_{14}NOF_3$; calcd 245.1027, found 245.1026. Anal. Calcd for $C_{12}H_{14}NOF_3$: C, 58.77; H, 5.75; N, 5.71. Found: C, 59.06; H, 5.80; N, 5.61.

The 50% ^{18}O-labeled amide III was prepared exactly as above with the exception that ~50% ^{18}O-labeled toluoyl chloride[7] was used.

(b) Kinetics. (i) The rates of hydrolysis of III and IV studied were determined by ^1H NMR analyses (Bruker WH-400 spectrometer) with methodologies previously described.[7] The low solubility of III in H_2O or D_2O necessitated a slightly modified procedure. A series of 10 30-mL samples of NaOH (~1.0 or 0.1 N, $\mu = 1.0$ (KCl)) containing 4% (by volume) of DME for solubility and 3 mg (0.4 mmol) of III were placed in 30-mL Teflon FEP centrifuge tubes, which were sealed with Nalgene leak-proof caps having Teflon liners. Solutions of base in either H_2O or D_2O were prepared under CO_2-free conditions in an Ar-filled drybox and stored under Ar. All subsequent operations with these solutions were performed in the Ar-filled drybox. OD^-/D_2O solutions were prepared by dissolving the appropriate amount of Na metal in D_2O. Base concentrations were determined by titration with standardized 1.0 or 0.1 N HCl, phenolphthalein indicator. The charged, sealed, FEP tubes were then thermostated at 100 °C (boiling H_2O vapor) and removed at various times. The tube corresponding to time zero (t_0) was removed after a 15-min equilibration period. After removal of the tubes, they were cooled and the contents transferred to a 50-mL separatory funnel containing 1.0 mL of CD_2Cl_2 NMR solvent. The contents were shaken and the phases allowed to separate after which the CD_2Cl_2 layer was carefully pipetted out, dried ($MgSO_4$), and subjected to ^1H NMR analysis. The residual H in CD_2Cl_2 provided an internal reference that was integrated and compared with the intensity of the signal at δ 7.25 attributable to the aromatic protons of the recovered unreacted amide. A control second extraction experiment was conducted with use of 1.0 mL of fresh CD_2Cl_2 to reextract the solution. No amide was observed in the second CD_2Cl_2 extract, which confirmed that all the amide was removed by the first 1.0 mL of CD_2Cl_2.

The hydrolysis kinetics were unable to be monitored by UV techniques since the absorbance vs time plots showed marked deviation from first-order behavior. This was found to be due to a subsequent reaction of the *N*-ethyl-*N*-(trifluoroethyl)amine produced from hydrolysis of the amide. Thus, an aqueous solution containing base and 10^{-4} M each of the au-

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(3) DeWolfe, R. H.; Newcomb, R. C. *J. Org. Chem.* **1971**, *36*, 3870.

(4) (a) Deslongchamps, P.; Cheriyan, U. O.; Guida, A.; Taillefer, R. J. *Nouv. J. Chim.* **1977**, *1*, 235. (b) Deslongchamps, P.; Gerval, P.; Cheriyan, U. O.; Guida, A.; Taillefer, R. J. *Nouv. J. Chim.* **1978**, *2*, 631. (c) Deslongchamps, P.; Bartlett, R.; Taillefer, R. J. *Can. J. Chem.* **1980**, *58*, 2167.

(5) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983. (b) For discussion of this point, see ref 5a, pp 108–118.

(6) (a) Šlebocka-Tilk, H.; Brown, R. S. *J. Org. Chem.* **1988**, *53*, 1153. (b) Šlebocka-Tilk, H.; Brown, R. S. *Ibid.* **1987**, *52*, 805.

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Table I. Hydrolysis and Exchange Rate Constants for Toluamides III and IV in Basic Media[a]

amide	$[OL^-]$ (M)	k_{hyd} (s^{-1})	$[OL^-]$ (M)	k_{ex} (s^{-1})	k_{ex}/k_{hyd}
III (H_2O)	1.08	$(3.38 \pm 0.09) \times 10^{-5}$	1.08	$(1.09 \pm 0.02) \times 10^{-3}$	32.2 ± 1.6
	0.205	$(6.26 \pm 0.11) \times 10^{-6}$	0.095	$(1.00 \pm 0.01) \times 10^{-4}$	34.5 ± 1.0
III (D_2O)	1.03	$(3.06 \pm 0.03) \times 10^{-5}$	1.03	$(1.09 \pm 0.03) \times 10^{-3}$	35.6 ± 1.4
IV (H_2O)[b]	0.926	$(1.07 \pm 0.02) \times 10^{-4}$	0.933	$(5.24 \pm 0.15) \times 10^{-5}$	0.49 ± 0.03[c]
	0.13	$(1.46 \pm 0.02) \times 10^{-5}$	0.086	$(4.85 \pm 0.10) \times 10^{-6}$	0.50 ± 0.02[c]
IV (D_2O)	1.03	$(1.10 \pm 0.02) \times 10^{-4}$	1.06	$(5.87 \pm 0.27) \times 10^{-5}$	0.53 ± 0.04[c]

[a] $T = 100$ °C, $\mu = 1.0$ (KCl). [b] Data from ref 7. [c] Where $[OL^-]$ is different for a given hydrolysis and exchange experiment, pseudo-first-order rate constants were converted to second-order rate constants for determining k_{ex}/k_{hyd} ratios.

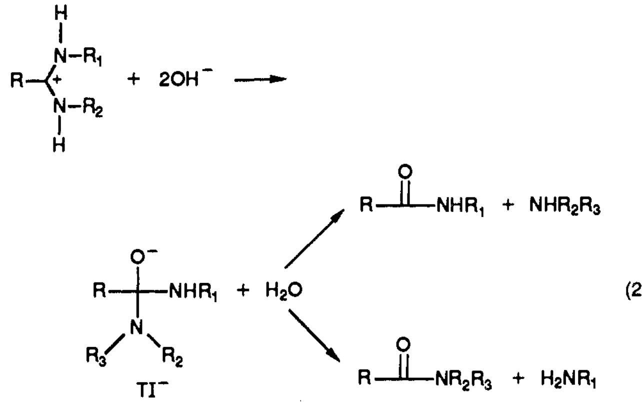
thentic toluic acid and amine products was shown to exhibit a changing UV spectrum when heated at 70 °C. The final UV spectrum of this solution matched an infinity spectrum for the hydrolysis of 10^{-4} M III under the same conditions at 70 °C.

The hydrolysis rate constants (k_{hyd}) were evaluated from the slopes of the plots of ln (I(amide)/I(reference) vs time plots, where I refers to the integrated intensity of the residual amide aromatic and reference $CDHCl_2$ peaks. Each reaction was followed to 2 or more half-lives and the quoted error limits are those of the standard deviations obtained from linear least-squares treatment of the ln I vs time plots.

(ii) The rates of ^{18}O exchange were assessed with methodologies and mass spectrometric instrumentation previously described.[6,7] Exchange rate constants (k_{ex}) were evaluated from the slopes of the plots of ln $[I_{M^++2}/(I_{M^+} + I_{M^++2})]$ vs time where I represents the intensity of the parent and parent + 2 mass ions. Eight points up to at least 2 half-lives were taken for each plot, and the errors in the quoted k_{ex} values were determined as the standard deviation of the linear regression lines.

Results and Discussion

Our search for a tertiary toluamide that exhibits large amounts of ^{18}O exchange accompanying its base hydrolysis was guided by earlier work on amine LA from the intermediates TI^- produced from base hydrolysis of amidines[7,9] (eq 2). It is generally believed[9] that TI^- produced from an unsymmetrical amidine partitions with the expulsion of the more basic amine. The preference is not absolute, however, since exceptions exist wherein a more sterically demanding, but less basic, amine is the better leaving group.[9a] We have also shown that amine partitioning from unsymmetrical toluamidines hydrolyzed in base at 100 °C parallels the ordering of ^{18}O exchange for the corresponding amide so that the LA of the amine from T_0^- or TI^- is $R_2NH > RNH_2 > NH_3$.[7] We must point out that basicity arguments alone cannot explain why $HN(CH_3)_2$ ($pK_a(H_2N^+(CH_3)_2) = 10.64$) departs at 10–50-fold better from T_0^- or TI^- than does H_2NCH_3 ($pK_a(H_3N^+CH_3) = 10.62$); here solvation or steric effects could affect the relative LA.

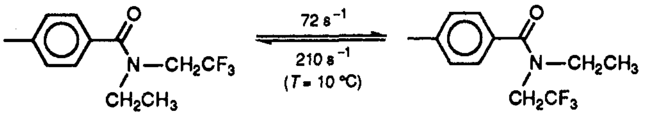


(2)

Finally, it must be mentioned that the trends suggested for amine departure from TI^- could be different from those in neutral or postively charged tetrahedral intermediates. Indeed, Page, Webster, and Ghosez[9c] have reported that neutral tetrahedral intermediates produced from OH^- attack on azetidin-2-ylidenammonium salts preferentially expel the amine containing an electron-withdrawing substituent.

With the above reservations in mind, a likely choice for comparison with I or II would require a secondary amine with steric requirements similar to $HN(CH_3)_2$ or pyrrolidine, but a vastly lower basicity. Thus, $HN(CH_2CH_3)(CH_2CF_3)$ (pK_a(conjugate acid) = 6.3, $\mu = 1.0$ (KCl), $T = 25$ °C) appeared an appropriate choice.

In $CDCl_3$ solution, III exists as an equilibrium 3/1 mixture of two conformers tentatively assigned as IIIa,b;[10] line shape analysis of the CH_2CH_3 quartets at δ 3.67 (minor) and 3.46 (major) gives $\Delta G^\ddagger_{10^\circ C}$(major $\rightarrow$ minor) = 14.1 kcal/mol and $\Delta G^\ddagger_{10^\circ C}$(minor $\rightarrow$ major) = 13.5 kcal/mol as the barriers to rotation about the amidic bond. These values are only slightly lower than those found for a variety of R-substituted N,N-dimethylbenzamides in $CDCl_3$ (14.5–16 kcal/mol).[11]



major IIIa minor IIIb

Given in Table I are k_{hyd} and k_{ex} data for III and IV in H_2O and D_2O ($T = 100$ °C, $\mu = 1.0$ (KCl)). In H_2O, the rate constants were determined at two $[OH^-]$ in order to determine that each of k_{ex} and k_{hyd} was linearly dependent on [base]. For all amides investigated, this was found to be the case in the range of concentrations used. The most striking aspect of the data for III is the large amount of exchange ($k_{ex}/k_{hyd} = 33.4 \pm 1.6$), which indicates that the intermediate(s) formed must partition back to starting amide at least 65–70 times faster than proceeding to products. By comparison of the k_{ex}/k_{hyd} ratio for III and I or II,[7] it is apparent that the structural change of incorporating CF_3 into the amine unit leads to a 2300–3500-fold diminished leaving ability from T_0^- relative to $HN(CH_3)_2$ or pyrrolidine.

The data in Table I allow several definitive conclusions to be made. First, that both k_{ex} and k_{hyd} for the amides in Table I and for I and II[7] are first-order in $[OH^-]$ requires that the transition states leading to exchange and hydrolysis each have one OH^- incorporated. Second, that tertiary amide III exhibits so much exchange reinforces our earlier conclusions[6,7] that stereoelectronic factors (as proposed by Deslongchamps et al.[4]) are unimportant in determining whether a tertiary amide will or will not exchange. In that analysis,[4] the reluctance of N,N-dimethylbenzamide[2a] or N,N-dimethyltoluamide[6a] to exchange is necessarily attributed to an inability of their respective T_0^- to attain conformational equilibration at N that would be required to assist in ejecting $^{18}OH^-$. In the case of the hydrolysis of III, the steric bulk of the amine is expected to be similar to or greater than that in the case of the latter two amides. Thus, if anything, conformational equilibration at N in T_0^- is expected to be slower in the case of III than in I or II so that less exchange should be observed for the former. That this is not the case strongly suggests conformational mobility at N either is unimportant or is completely attained for I–III. In either event, the data would indicate that stereoelectronic effects[4] are of minimal importance in explaining the exchange and that LA of the amine dominates.

(a) **D₂O Effects with III and IV.** In the case of III if the kinetics are interpreted within the context of the mechanism in eq 1, then

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[9] (a) Perrin, C. L.; Nuñez, O. *J. Am. Chem. Soc.* **1987**, *109*, 522; **1986**, *108*, 5997 and references therein. (b) Burdick, B. A.; Benkovic, P. A.; Benkovic, S. J. *Ibid.* **1977**, *99*, 5716. (c) For a discussion of amine basicity influences on LA from neutral tetrahedral intermediates, see: Page, M. I.; Webster, P. S.; Ghosez, L. *J. Chem. Soc., Perkin Trans. 2* **1990**, 813.

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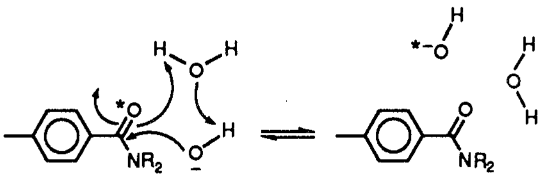
[11] Fong, C. W.; Lincoln, S. F.; Williams, E. H. *Aust. J. Chem.* **1978**, *31*, 2615.

the rate-limiting step for hydrolysis must be k_2, the breakdown of the intermediate. Thus, the anionic tetrahedral intermediate must be produced in a preequilibrium since k_{ex}/k_{hyd} is ~33. The D_2O results for k_{ex} in III then have a strong bearing on the two critical assumptions that are necessary for the use of ^{18}O exchange to probe reversible formation of intermediates.[1-7] These assumptions require the following: (1) the intermediates that lead to exchange are on the hydrolytic pathway and (2) protonic equilibration of the ^{16}O and ^{18}O atoms is faster than reversal of T_0^-. The first assumption as discussed by Jencks[12] seems eminently reasonable (but as yet unproven) unless one envisions a concerted mechanism leading to exchange, which involves several proton transfers (as in V) occurring in a side reaction at a rate that is fast relative to the lifetime of T_0^-. A process such as that in V is anticipated to exhibit a large, normal solvent kinetic isotope effect (SKIE).[13] The $(k_{ex})_{H/D}$ ratio for III of 0.90 ± 0.08 shows no such large solvent isotope effect, which attests to the validity of assumption 1, at least in the hydrolysis of III. Also if proton transfer via intervening L_2O molecules were in some way limiting the equilibrium of $^{16}O/^{18}O$ atoms, that process would be retarded in D_2O and k_{ex} should decrease. Since the SKIE is about unity, protonic equilibration of the ^{16}O and ^{18}O atoms cannot be substantially slower than breakdown, so the second assumption also appears valid.



V

The experimental observations are that the SKIE is 0.91 ± 0.18 (I),[7] 0.92 ± 0.05 (II),[7] and 1.05 ± 0.04 (III) for the k_{hyd} of three tertiary amides and that the SKIE for k_{ex} ranges from 0.61 ± 0.12 (I)[7] to 0.30 ± 0.05 (II)[7] and 0.90 ± 0.05 (III). (These calculations for III use data at ~1.0 N OL^- since the isotope effects were only determined at this concentration.) For I and II, which exhibit low amounts of exchange, the $(k_{ex})_{H/D}$ values differ by more than the sum of their standard deviations but less than twice this sum so that, at the 95% confidence level, we cannot say that they are different. The problem lies in the accuracy with which low amounts of ^{18}O exchange can be determined,[7] but in the case of III, which shows large amounts of ^{18}O exchange, $(k_{ex})_{H/D}$ is reliably given as 0.90 ± 0.05.

For I and II since exchange is small relative to hydrolysis, the observed values of the rate constants are the following:

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

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

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

For III where hydrolysis is small relative to exchange, the observed rate constants are the following:

$$k_{hyd} \simeq k_1k_2/k_{-1} \qquad k_{ex} \simeq k_1/2 \qquad k_{ex}/k_{hyd} = k_{-1}/2k_2$$

Thus, in both limiting cases, it is possible to obtain simple expressions for all of the isotope effects. From the above, the SKIE on k_{ex} for III and on k_{hyd} for I and II are expected (and found) to be similar since each of these is essentially dictated by k_1, the attack of OH^- on the amide.

We analyze the expected SIE on k_{ex} and k_{hyd} in terms of the anticipated fractionation factors[13] according to $k_D/k_H = \Pi\phi^{TS}/\Pi\phi^{GS}$ where $\Pi\phi^{GS}$ is the product of the fractionation factors for the ground state $(OH^-(H_2O)_3)$ and $\Pi\phi^{TS}$ are the products of the fractionation factors in the TS for the attack (k_1) step and breakdown (k_2) steps. We assume that the transition states are close to tetrahedral species, with the position of the TS along the reaction being 0.7 for formation and 0.3 for breakdown.[7] Also, the primary KIE for a proton in flight between oxygens or oxygen and nitrogen is based on a TS fractionation factor of 0.4 (with values of 0.3–0.5 used as limits).[13a] In analyzing the SIE on the k_1 step for III, we follow Gold's suggestion for OH^-:[14] Hydroxide ion has a fractionation factor of 1.22 rather than 0.5[13] while the three hydrogens involved in H bonding to OH^- have fractionation factors of 0.70. One then assumes three developing H bonds to the amide oxygen, which becomes an O^- similar to OH^- in its solvation requirements, and assumes loss of one solvating H_2O to allow OH^- to attack the carbonyl. Finally, one assumes the fractionation factor for the internal hydrogen of the attacking OH^- will be reduced toward that of an OH in a hemiacetal (1.0[15]), with attendant loosening of its waters of solvation. Given in Figure 1 are the fractionation factors used: Bold-type H's have the indicated factors, while nonbold H's have unit fractionation factors. For attack (Figure 1), the calculated KIE is 0.99, which agrees nicely with the observed KIE on III ($(k_{ex})_{H/D}$ = 0.90 ± 0.08) and the observed effects on $(k_{hyd})_{H/D}$ for I and II.[7]

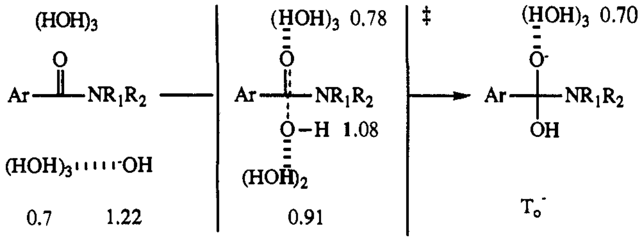


Figure 1. Proposed mechanism and fractionation factors for attack of OH^- on tertiary amide III.

The observed $(k_{hyd})_{H/D}$ of 1.05 ± 0.04 for III provides information about k_2 since the rate-limiting step for hydrolysis is the breakdown of the intermediate to product. Within the mechanistic context of eq 1, the alternatives for breakdown are the following: (a) a concerted path where expulsion of amide ion occurs with simultaneous proton transfer from H_2O, (b) a stepwise path where a preequilibrium proton transfer from H_2O occurs, (b′) the same pathway with rate-limiting proton transfer, (c) a cyclic concerted path involving simultaneous C–N cleavage and a water-mediated proton shift from hydroxyl to N, (d) a process with a preequilibrium intramolecular proton transfer leading to an anionic zwitterion (T_{ZW}^-), and (d′) the same path with a rate-limiting proton transfer. These pathways with the associated fractionation factors are given in Figures 2 and 3. Pathways a, b, and b′ (Figure 2) lead to a product set consisting of carboxylic acid, amine, and OH^-, while paths c, d, and d′ (Figure 3) lead to carboxylate and amine. For formation of both product sets, those processes that involve protons in flight as part of the rate-limiting step (pathways a, b′, c, and d′) are expected to show large normal isotope effects,[13] these being proportional to the number of OL bonds being broken. Only paths b and d are expected to show small isotope effects, since all the associated proton switches occur prior to the rate-limiting $C-^+NHR_1R_2$ cleavage. For paths b and d with use of the fractionation factors in Figures 2 and 3, the calculated KIE values are ~1.47 and 1.86, respectively, and arises not from protons in flight but from reordering of several solvent molecules in the C–N cleavage TS. These calculated SKIE values could be further reduced toward the observed value of 1.05 by slight increases in any of the associated fractionation factors. Although for the analyses presented in Figures 1–3 we have used a fractionation factor for the alkoxy oxygen in the tetrahedral intermediates similar to that of OH^- (0.70[13]), an alternative appropriate choice could be that for CH_3O^- (0.74[13]). With use of the latter value and the assumed position of the breakdown TS as 0.30, the

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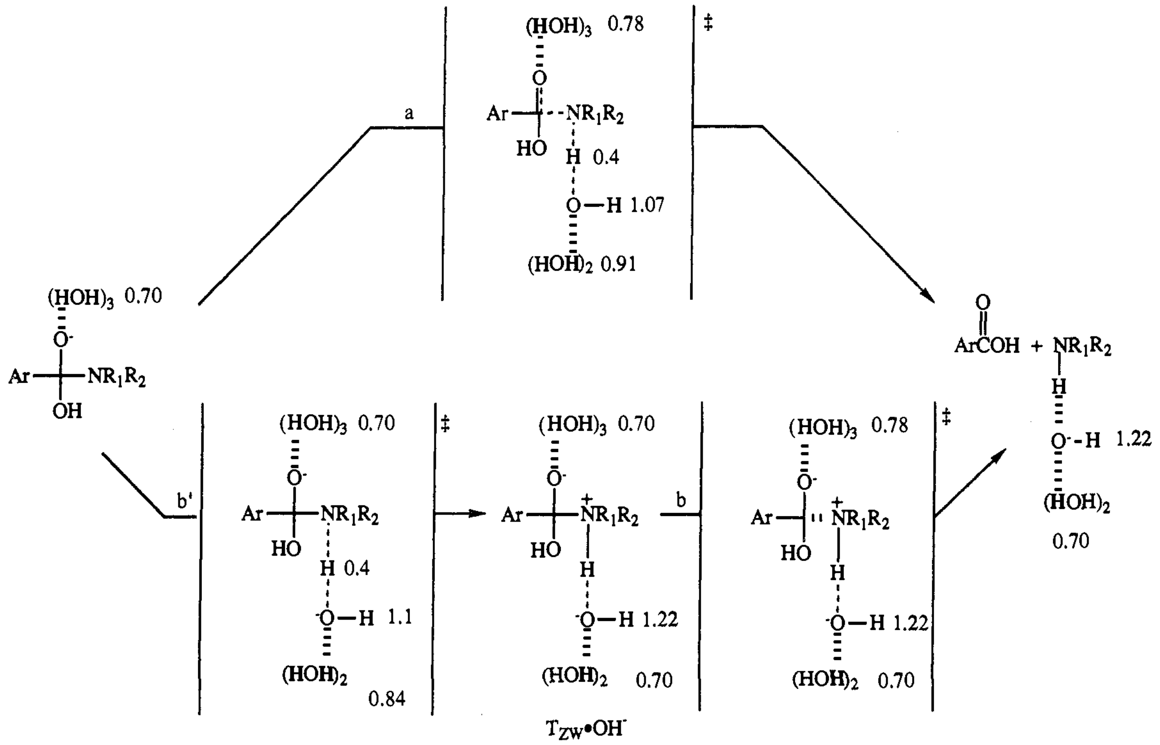

Figure 2. Possible pathways for breakdown of T_0^- to carboxylic acid and $R_1R_2NH{:}OH^-$ encounter complex with associated fractionation factors.

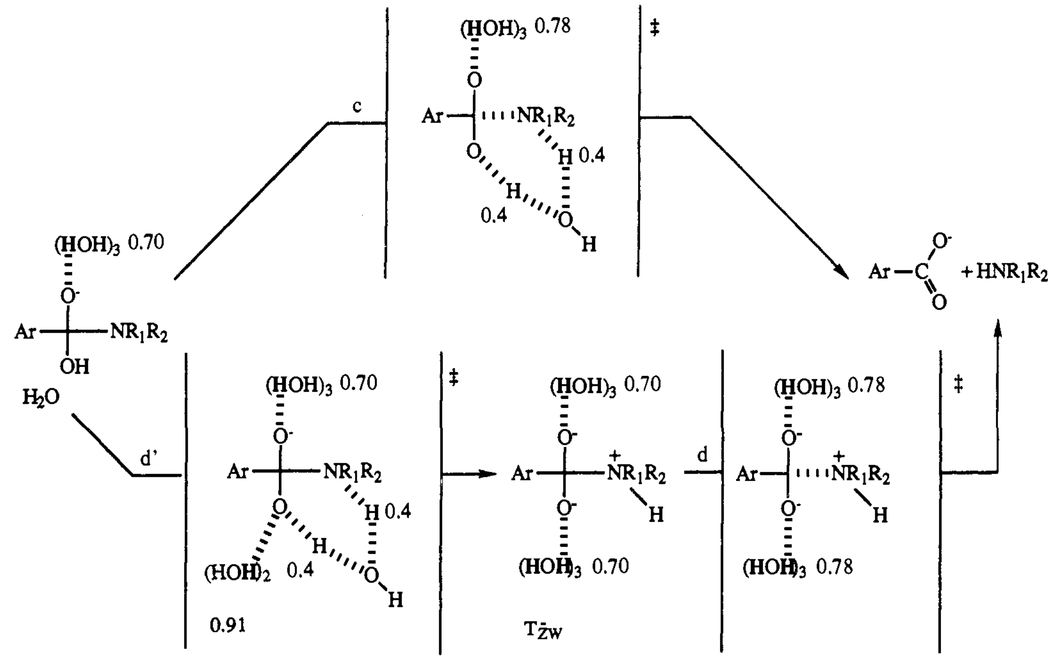

Figure 3. Possible pathways for breakdown of T_0^- to amine and carboxylate products with associated fractionation factors.

calculated SKIE for path b is 1.27 and for d is 1.39.

The observed SKIE on k_{hyd} for III is consistent with either of paths b and d but does not allow a distinction to be made between them. Previously, on the basis of energetics calculations,[7] path d was considered as most likely for I and II since it was consistent with the H_2O/D_2O SKIE data and required realistic appearing intrinsic barriers for C–N cleavage from T_{ZW}^-. Breakdown of an anionic zwitterion has also been proposed by Bender and Thomas for the OH^- hydrolysis of anilides.[16] A necessary consequence of the two product-forming pathways b and d is that, in the reverse direction, amide formation under basic conditions should proceed by uncatalyzed attack of the amine on carboxylate (d) or its kinetic equivalent, attack on a carboxylic acid by an amine that is hydrogen bonded to OH^- in a preassociation complex (b).[16] In the latter case, proton removal from the amine occurs after the C–N bond-forming reaction so that the hydroxide catalysis refers to trapping of T_{ZW} and not to concerted proton abstraction while C–N bond formation is taking place. An analogous process has been suggested for ester aminolysis, but in this case the catalysis by OH^- was suggested to arise from diffusion-limited trapping of the zwitterion.[17] In the present case, the latter mechanism also requires that the proton back-transfer required to interconvert $T_{ZW}{\cdot}OH^- \rightleftharpoons T_0^-$ must be faster than diffusional separation of OH^- from T_{ZW} and that breakdown of $T_{ZW}{\cdot}OH^-$ to product must also be faster than diffusional separation.

In the case of secondary amide IV where the k_{ex}/k_{hyd} ratio in H_2O is 0.49 ± 0.03, the intermediates partition between reversal

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Table II. Activation Parameters for the Base-Catalyzed Hydrolysis of I–III, V, and VI[a]

amide	$\Delta H^‡$ (kcal mol^{-1})	$\Delta S^‡$ (cal K^{-1} mol^{-1})	$\Delta G^‡_{100\ °C}$ (kcal mol^{-1})
p-toluylaziridine (V)[b]	9.1 (0.2)	−29.5 (0.6)	20.1 ± 0.4
p-toluylazetidine (VI)[c]	14.6 (0.2)	−29.6 (0.6)	25.6 ± 0.4
I[d]	14.8 (0.6)	−32.9 (1.7)	27.1 ± 1.2
II[e]	18.2 (0.9)	−26.4 (2.5)	28.0 ± 1.8
III[f]	16.4 (0.6)	−35.5 (1.5)	29.6 ± 1.2

[a] μ = 1.0 (KCl). [b] Temperatures used: 5.7, 13.0, 20.5, 27.4, 34.3, 41.5, 48.1 °C. [c] Temperatures used: 25, 37.1, 49.5, 58.3, 70.6 °C. [d] Temperatures used: 49.8, 62, 74.4, 100 °C. [e] Temperatures used: 56, 65, 80, 100 °C. [f] Temperatures used: 72, 84.5, 100 °C.

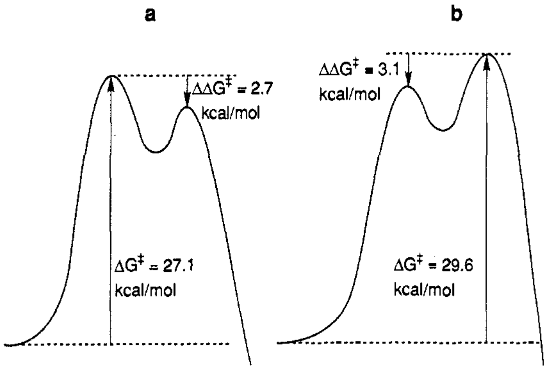
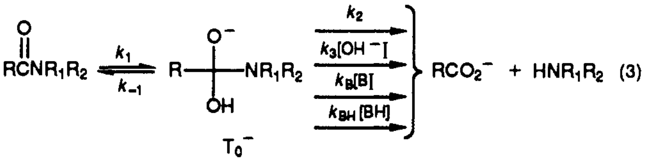


Figure 4. Free energy diagram for base-promoted hydrolysis of II (a) and III (b) from k_{ex} and k_{hyd} data (T = 100 °C, μ = 1.0 (KCl)). $\Delta G^‡ = \Delta H^‡ - T\Delta S^‡$; $\Delta\Delta G^‡ = -RT \ln (2k_{ex}/k_{hyd})$.

and product formation with nearly equal propensity. In this case, $(k_{ex}/k_{hyd})_{H/D}$ compares the SKIE on the two transition states directly, the value being 0.92 ± 0.09. This value is consistent with the $(k_{ex}/k_{hyd})_{H/D}$ value of 0.86 ± 0.07 for III in which the forward and reverse transition states differ markedly in energy so that IV and III apparently hydrolyze by similar mechanisms.

(b) Activation Energies for Tertiary Toluamides. Given in Table II are the activation energies for base hydrolysis of I–III as well as the aziridine (V) and azetidine (VI) derivatives in aqueous solution (μ = 1.0). It is of note that, for all amides, the entropies of activation are large and negative and at 100°C contribute between 43 and 55% to the free energy of activation. In the case of I, II,[7] and V,[6b] which show little or no exchange accompanying hydrolysis, the activation parameters refer essentially to k_1. This is probably true also for VI, although we have not conducted the pertinent ^{18}O-exchange measurements. In the case of III, the activation parameters pertain to k_2, the breakdown of T_0^- via T_{ZW}^- or $T_{ZW}\cdot OH^-$. In either limiting case in accordance with the SKIE data for I, II,[7] and III, the large $-\Delta S^‡$ values are consistent with restriction of water of solvation in the transition states leading to or away from T_0^-. Shown in Figure 4 are two-dimensional reaction coordinate diagrams for I and III based on the data in Tables I and II.

(c) Unified Approach to Predicting the Mechanism of Base Hydrolysis of Amides. The more complete mechanism for base hydrolysis of amides (eq 3)[1e,3,18] is an expansion of that given in eq 1. In unbuffered media, steady-state treatment gives the following:

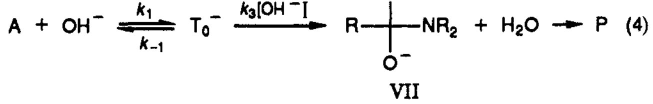


$$\mathrm{RC(=O)NR_1R_2} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{T_0^-}{\mathrm{R{-}C(O^-)(OH){-}NR_1R_2}} \left.\begin{array}{l} \xrightarrow{k_2} \\ \xrightarrow{k_3[\mathrm{OH^-}]} \\ \xrightarrow{k_B[\mathrm{B}]} \\ \xrightarrow{k_{BH}[\mathrm{BH}]} \end{array}\right\} \mathrm{RCO_2^-} + \mathrm{HNR_1R_2} \quad (3)$$

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

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

and if $k_2 \gg k_3[\mathrm{OH^-}]$ (as in the case of the presently discussed toluamides), $k_{ex}/k_{hyd} = k_{-1}/2k_2$. Terms second-order in [OH$^-$] are reported for the hydrolysis of acetanilides,[1e] formanilides,[3] trifluoroacetanilides,[18] and acetyl- or benzoylpyrroles.[19] This is interpreted in terms of a mechanism (eq 4) wherein a second OH$^-$



$$\mathrm{A + OH^-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} T_0^- \xrightarrow{k_3[\mathrm{OH^-}]} \mathrm{R{-}C(O^-)_2{-}NR_2} + \mathrm{H_2O} \longrightarrow \mathrm{P} \quad (4)$$

VII

removes a proton from a reversibly formed T_0^- to yield a dianion VII, which subsequently expels amide ion, with or without general-acid assistance by solvent. At high [OH$^-$], this trapping of T_0^- effectively halts the reversal and the kinetics become first-order in [OH$^-$] so that formation of T_0^- is the rate-limiting step.

N methylation of formanilides[3] and acetanilides[18,20] tends to decrease the k_{-1}/k_2 ratio so that reversibility from T_0^- is diminished, but not eliminated, relative to the corresponding N–H derivative. This type of N-substitution behavior is also seen for T_0^- produced from benzamides and toluamides as determined from the diminished k_{ex}/k_{hyd} ratio in passing from secondary to tertiary derivatives.[1,2,6,7] N-Methylacetanilides and *N*-methylformanilides can show evidence of second-order terms in [OH$^-$], although this is generally observed only at high pH since the k_3/k_{-1} ratio is <1 M^{-1}.[1e,20]

Finally, many amides such as benzamides,[1,2] toluamides,[6,7] and simple aliphatic amides[21] do not exhibit second-order [OH$^-$] terms under any presently investigated conditions. This requires that the associated T_0^- (or its kinetic equivalent) is sufficiently reactive to break down to products without the assistance of a second OH$^-$. For the above amides, T_0^- may or may not be reversibly formed depending on the relative k_{-1} and k_2 barriers, but this can only be probed by ^{18}O-exchange experiments since reversal is transparent to the hydrolysis kinetics.

The pertinent question is what factors influence the relative k_{-1}, k_2, and k_3 barrier heights, and when one can anticipate large amounts of ^{18}O exchange. We deal with a systematic comparison of tertiary toluamides, since solvation and steric differences would complicate a generalized comparison of primary, secondary, and tertiary amides. The kinetic, KIE, and ^{18}O-exchange studies for I, II,[7] V,[6b] and III suggest that both the exchange and hydrolysis transition states have one incorporated OH$^-$ and that breakdown to product proceeds via an anionic form having a protonated N in place prior to rate-limiting C–N cleavage. For amides where the basicity of the corresponding secondary amine is high (e.g., $\mathrm{H_2N^+(CH_3)_2}$, pK_a = 10.64; $\mathrm{H_2N^+(CH_2)_4}$, pK_a = 11.27[22]), N protonation followed by breakdown to products via paths b and d (Figures 2 and 3) is faster than reversion to starting materials and little or no ^{18}O exchange is observed. Reduction in the pK_a of the amine such as is brought about by the β-CF$_3$ unit in III ($\mathrm{H_2N^+(Et)CH_2CF_3}$, p$K_a$ = 6.3) destabilizes any N-protonated form and concomitantly raises the k_2 barrier leading to products from T_0^-. ^{18}O exchange will be observed, but the k_{ex}/k_{hyd} ratio will be independent of [OH$^-$] since both transition states have one incorporated OH$^-$. Decreasing the pK_a of the amine leads to a

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further destabilization of the N-protonated forms and associated k_2 transition states. At the same time, those factors that inhibit N protonation will also acidify the remaining OH group of T_0^- and facilitate departure of the N either in an anionic form that may be H bonded to solvent or with general-acid catalysis, but requiring no prior complete protonation.[23] In this case, the hydrolysis kinetics will exhibit second-order terms: ^{18}O exchange and substantial reversal of T_0^- will be observed at low [OH$^-$], with diminishing amounts occurring as the [OH$^-$] is raised. In the limit at high [OH$^-$], each time T_0^- is formed it is immediately converted to VII and reversal is eliminated.

For *p*-nitroacetanilide, exactly the above situation is observed[1c] where k_{ex}/k_{hyd} varies from 1.6 to 0.17 as [OH$^-$] changes from 0.02 to 0.24 M. Similarly, it is reported that *N*-benzoyl- and *N*-toluoylpyrrole[19b] exhibit hydrolysis kinetics with a second-order dependence on [OH$^-$], merging into a first-order dependence with increasing [OH$^-$], consistent with the above mechanism: ^{18}O-exchange studies were not reported,[19] but the mechanism demands that these must follow the expected pattern.

The change in mechanism between III and *N*-benzoyl- or *N*-toluoylpyrrole results from the low basicity of the latter amine (pK_a(conjugate acid) = −3.80[24]). Thus, within the tertiary toluamide or benzamide series the point of transition between the first- and second-order hydrolysis mechanism occurs when the departing amine has a basicity intermediate between those of pyrrole and *N*-ethyl-*N*-(trifluoroethyl)amine.

Conclusions

1. Tertiary toluamide III exhibits substantial ^{18}O exchange accompanying hydrolysis in base at 100 °C. Exchange and hydrolysis are both first-order in [OH$^-$]; $k_{ex}/k_{hyd} = 33.4 \pm 1.6$. Amide III is at least as, or more, sterically demanding than *N*,*N*-dimethyltoluamide (I) or *N*-toluoylpyrrolidine (II) but exhibits 2300–3500-fold more exchange than the latter two amides. Thus, in contrast to analyses based upon the stereoelectronic theory preferred by Deslongchamps,[4] conformational mobility of the anionic tetrahedral intermediate (T_0^-) is not the dominant factor in determining whether a tertiary amide will or will not exhibit ^{18}O exchange accompanying hydrolysis. Rather, amine leaving ability is the crucial factor, and this depends on basicity, with the least basic amine having the poorest leaving ability.

2. The solvent kinetic isotope effects on the exchange and hydrolysis processes for III are $(k_{ex})_{H/D} = 0.90 \pm 0.05$ and $(k_{hyd})_{H/D} = 1.05 \pm 0.04$. The predominantly rate-limiting step for exchange is k_1, the attack of OH$^-$, while the rate-limiting step for hydrolysis is k_2, the breakdown of the anionic tetrahedral intermediate(s) to product. Analysis of the SKIE in terms of isotopic fractionation factors indicates that the small observed isotope effect on k_{hyd} is most consistent with breakdown via one or both of two anionic but N-protonated forms, an anionic zwitterion (T_{ZW}^-) or a zwitterionic OH$^-$ H-bonded encounter complex.

3. The observed SKIE on k_{ex} indicates the following: (a) the ^{16}O and ^{18}O atoms in T_0^- are in protonic equilibrium and (b) the intermediate that leads to exchange is on the hydrolytic pathway (i.e., T_0^-). If either of these circumstances were not true, then there would be substantially less ^{18}O exchange in D_2O.

4. Base hydrolysis of tertiary amides can exhibit first- or second-order terms in [OH$^-$], and whether ^{18}O exchange is observed depends upon the relative barrier heights for the transition states leading away from T_0^- to starting materials or products. Amides containing amines with low basicity are more prone to ^{18}O exchange than those containing amines with high basicity since breakdown to product proceeds via an anionic intermediate with a protonated N. When the amine basicity is intermediate between that of pyrrole or *N*-ethyl-*N*-(trifluoroethyl)amine, the hydrolytic mechanism will exhibit second-order terms in [OH$^-$] and there will be observed ^{18}O exchange that decreases with increasing [OH$^-$].

Acknowledgment. We gratefully acknowledge the financial assistance of the University of Alberta and Natural Sciences and Engineering Research Council of Canada. We are also indebted to Professor R. E. D. McClung (Department of Chemistry, University of Alberta) for the line-shape analysis used in determining the barriers to rotation of III.

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Bond Dissociation Energies and Kinetics for the Reaction of $W(CO)_5$ with the Unlikely Ligands N_2O and CF_2Cl_2

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Abstract: Transient infrared spectroscopy has been used to study reactions of $W(CO)_5$, the coordinatively unsaturated tungsten carbonyl generated by 351- or 355-nm photolysis of $W(CO)_6$. $W(CO)_5$ is highly reactive toward CO, CF_2Cl_2, and N_2O with bimolecular rate constants of 1.4 ± 0.1, 1.2 ± 0.2, and $0.5 \pm 0.1 \times 10^{-10}$ cm^3 molecule^{-1} s^{-1}, respectively, at 298 K. Infrared absorptions for the transiently stable $W(CO)_5(CF_2Cl_2)$ and $W(CO)_5(N_2O)$ complexes were observed. The rate of dissociative loss of the CF_2Cl_2 and N_2O ligands from these complexes can be determined by observation of the rate of regeneration of $W(CO)_6$ in a reaction mixture consisting of $W(CO)_5L$, CO, and L, where L is either CF_2Cl_2 or N_2O. The bond dissociation energy for the loss of the chlorofluorocarbon ligand from $W(CO)_5(CF_2Cl_2)$ is 19.6 ± 0.6 kcal/mol. A bond dissociation energy was estimated for the loss of the N_2O ligand from $W(CO)_5(N_2O)$.

I. Introduction

Knowledge of gas-phase transition-metal carbonyl chemistry has been expanded by the use of transient infrared spectroscopy. Information about the structures and reactivities of short-lived, unsaturated metal carbonyl species is now directly available from this technique.[1,2] Up to this point transient infrared studies of gas-phase metal carbonyl photofragments have largely centered

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