Substituent Effects and Solvent Isotope Effects in the Basic Methanolysis of Amides[1,2]

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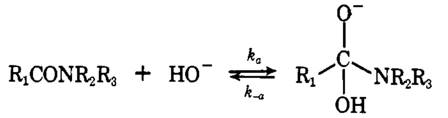
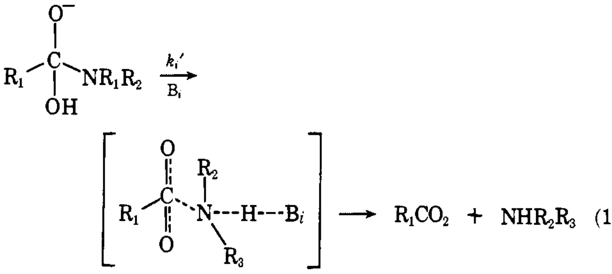
Abstract: Anilides $XC_6H_4N(CH_3)COCF_3$ undergo methoxide-catalyzed methanolysis in CH_3OH and CH_3OD with second-order rate constants given by $k^x{}_{CH_3OH} = 0.056 + 0.043 \times 10^{2.90\sigma_x}$ M^{-1} sec^{-1} and $k^x{}_{CH_3OD} = 0.028 + 0.049 \times 10^{2.9\sigma_x}$ M^{-1} sec^{-1}. The reaction shows general base catalysis in buffered solution. The tetrahedral methoxide adduct decomposes to products in a rate-determining process by parallel pathways involving either predominant proton transfer ($\rho = 0$, $k^H{}_{CH_3OH}/k^H{}_{CH_3OD} = 2$) or predominant C–N bond cleavage with solvation catalysis ($\rho = 2.9$, $k^H{}_{CH_3OH}/k^H{}_{CH_3OD} = 0.88$).

A mechanism which we previously advanced[4] for the hydrolytic cleavage of amides by a base catalyst (eq 1) involved the formation of a transition state (II) (and conceivably an intermediate of similar structure) in which both oxygens of the tetrahedral intermediate (I) have been deprotonated. The kinetic law of eq 2, where k_{obsd} is the observed rate constant and k_i represents the overall rate processes for the conversion of the reactants into the transition state which leads to products [*i.e.*, k_i equals $(k_i'k_a/k_{-a})$], gives the observed first-order rate constant for the base-catalyzed hydrolysis of amides.


(1a)

I

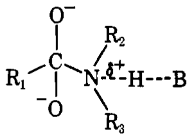

(1b)

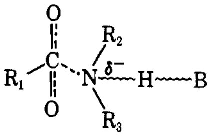
II

$$k_{obsd} = \frac{k_a[HO^-]\{\Sigma_i k_i[B_i]\}}{k_a + \Sigma_i k_i[B_i]} \qquad (2)$$

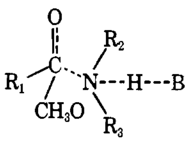
In eq 1 and 2, B_i can represent water, hydroxide ion, or a general base. At low base concentrations, the water-catalyzed elimination step is rate determining. For intermediate concentrations of base, the base-catalyzed elimination becomes the rate-determining step. At sufficiently high concentrations of base, $\Sigma_i k_i[B_i] \gg k_{-a}$ and a change from rate-determining elimination to rate-determining addition is observed.[5]

On the basis of substituent effects and solvent isotope effects,[6] it was deduced that two different elimination mechanisms existed, as evidenced by (a) a break in the Hammett plot and (b) a corresponding shift in the solvent isotope effect. For electron-donating substituents in R_3, proton transfer was rate determining (transition state III), while for electron acceptors, heavy-atom reorganization dominated, with the proton remaining in a stable potential (transition state IV).


III


IV

If the ionizable proton in I were replaced by a nonionizable group, as in the methoxide-catalyzed methanolysis reaction, then the mechanism clearly must change. But if its major features are preserved (transition state V, dotted lines representing *either* full or partial bonds), then some predictions are possible. The reaction should show simple general base catalysis (*i.e.*, $[CH_3O^-][BH^+] \propto [B]$) rather than general base catalysis superimposed on specific hydroxide catalysis, as found in the hydrolysis reaction.[7]


V

The kinetics should therefore be simple and the rate constants readily determined with good precision. It might also be expected that a shift in mechanism with substitituents in R_3 would occur, as in hydrolysis, from dominant proton transfer with electron donors to dominant heavy-atom reorganization with electron acceptors. The substituent effects and solvent isotope effects on the kinetics of the base-catalyzed methanolysis of these amides are therefore reported and discussed here.

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[1] This research was supported by grants from the National Science Foundation, the National Institutes of Health, and the General Research Fund of the University of Kansas. Data reduction was carried out in the Computation Center of the University of Kansas.

[2] Amide Hydrolysis. V. For part IV, see L. D. Kershner and R. L. Schowen, *J. Amer. Chem. Soc.*, **93**, 2014 (1971).

[3] Holder of a Research Career Development Award of the National Institute of General Medical Sciences.

[4] R. L. Schowen, H. Jayaraman, L. Kershner, and G. W. Zuorick, *J. Amer. Chem. Soc.*, **88**, 4008 (1966).

[5] R. L. Schowen, H. Jayaraman, and L. Kershner, *ibid.*, **88**, 3373 (1966).

[6] L. D. Kershner and R. L. Schowen, *ibid.*, **92**, 2014 (1970).

[7] R. L. Schowen and G. W. Zuorick, *ibid.*, **88**, 1223 (1966).

Table I. Salt Effects Negligible in the Methanolysis of $XC_6H_4N(CH_3)COCF_3$ in Sodium Methoxide Solutions (0.01–0.2 *M*) at 25.0 ± 0.1°

X	k_2,[a] M^{-1} sec^{-1}	k_2,[b] M^{-1} sec^{-1}
m-Cl	0.513 ± 0.015	0.533 ± 0.010 (0.563 ± 0.012)[c]
H	0.104 ± 0.002	0.1002 ± 0.0006
m-CH$_3$	0.0833 ± 0.0018	0.0828 ± 0.0015

[a] No attempt was made to keep ionic strength constant throughout the range of base concentrations. [b] Ionic strength maintained at 0.25 *M* with added lithium perchlorate. [c] Ionic strength held at 0.40 *M* with added lithium perchlorate.

Table II. First-Order Rate Constants (sec^{-1}) for the General Base Catalyzed Methanolysis of *m*-Chloro-*N*-methyl-2,2,2-trifluoroacetanilide Using Triethylamine and Triethylamine Hydrochloride[a]

$10^6 k_{obsd}$, sec^{-1}	[B], *M*	[BH$^+$], *M*	$10^7 \cdot$ [CH$_3$O$^-$],[b] *M*
3.92 ± 0.08	0.100	0.005	9.4
2.92 ± 0.07	0.075	0.0035	9.4
2.14 ± 0.06	0.050	0.0025	9.4
1.09 ± 0.04	0.025	0.00125	9.4

[a] Error limits are standard deviations. [b] Calculated from the pK_b of triethylamine in methanol (7.33) as determined by an indicator method.

Table III.[a] Second-Order Rate Constants (M^{-1} sec^{-1}) and Solvent Isotope Effects for the Base-Catalyzed Methanolysis of $XC_6H_4N(CH_3)COCF_3$ in CH_3OH and CH_3OD at 25.0 ± 0.1°

X	k_{CH_3OH}	k_{CH_3OD}	k_{CH_3OH}/k_{CH_3OD}
m-NO$_2$	5.750 ± 0.073	8.130 ± 0.56	0.707 ± 0.08
m-Br	0.524 ± 0.004	0.464 ± 0.008	1.13 ± 0.03
p-Cl	0.265 ± 0.017	0.274 ± 0.013	0.97 ± 0.11
p-Br	0.349 ± 0.005	0.346 ± 0.026	1.01 ± 0.10
m-Cl	0.513 ± 0.015	0.430 ± 0.018	1.19 ± 0.07
m-OCH$_3$	0.110 ± 0.003	0.101 ± 0.004	1.09 ± 0.07
H	0.104 ± 0.002	0.0899 ± 0.002	1.16 ± 0.05
m-CH$_3$	0.0833 ± 0.0018	0.0595 ± 0.0018	1.40 ± 0.05
p-CH$_3$	0.0729 ± 0.0005	0.0451 ± 0.0013	1.62 ± 0.04
p-OCH$_3$	0.0564 ± 0.0006	0.0321 ± 0.0006	1.76 ± 0.04

[a] Error limits are standard deviations.

Results

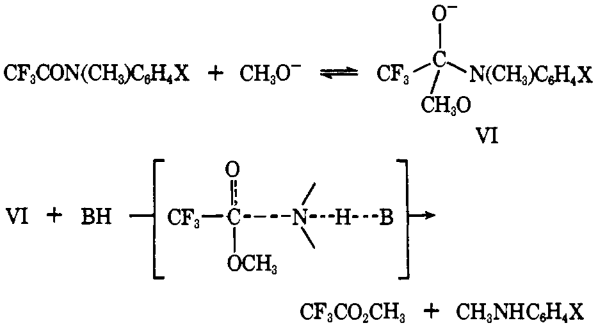
Kinetics. The reaction of methanol and methanol-*O-d* with aryl-substituted *N*-methyl-2,2,2-trifluoroacetanilides, catalyzed by methoxide ion, eq 3 (L = H or D), was first order in methoxide ion and first order in substrate amide. The second-order rate constants were determined by a linear least-squares fitting of k_{obsd} as a function of methoxide ion concentrations from 0.01 to 0.20 *M* (for X = *m*-NO$_2$, 0.002–0.02 *M*; for all X in CH$_3$OD, 0.025–0.10 *M*). First-order rate constants, obtained at about seven methoxide ion concentrations for each compound with the ionic strength varying according to the concentration of methoxide ion, were very linear in base concentration throughout the entire range. Runs at constant ionic strength showed the absence of any significant salt effect (Table I). The reaction exhibits simple general base catalysis (Table II).

$$XC_6H_4N(CH_3)COCF_3 + CH_3OL \xrightarrow{CH_3O^-} XC_6H_4NLCH_3 + CF_3COOCH_3 \quad (3)$$

Isotope Effects. The methoxide-catalyzed methanolysis of aryl-substituted *N*-methyl-2,2,2-trifluoroacetanilides in methanol and methanol-*O-d* was found to yield the isotope effects given in Table III.

Discussion

Mechanism. The expulsion of the $XC_6H_4NCH_3^-$ group from the tetrahedral intermediate VI (eq 5) should be far more difficult than expulsion of the less basic CH_3O^- group (eq 4), so that decomposition of VI



(4)

VI

(5)

to products should be the rate-determining step. This expectation is confirmed by the faster rates in CH$_3$OH than in CH$_3$OD for most compounds (Table III). In contrast, the methanolysis reactions of esters[8] in which the carbonyl addition step has been shown by isotopic labeling to be rate determining are faster in CH$_3$OD than in CH$_3$OH by factors of 1.5–2.1. The normal isotope effects also suggest that departure of the $XC_6H_4NCH_3^-$ is electrophilically assisted by solvent. This is fully consistent with the observation of simple general base catalysis, resulting from superimposition of general acid catalysis in the decomposition of VI upon the methoxide dependence of its formation. The mechanism is then that of eq 4 and 5 with the kinetic law of eq 6, where the k_e and k_i are for breakdown of VI. The rate constants k_{CH_3OH} and k_{CH_3OD} of Table III are thus equal to $k_a k_e/k_{-a}$ and refer to conversion

$$k_{obsd} = \frac{k_a}{k_{-a}}[CH_3O^-]\{k_e + \sum_i k_i[B_iH]\} \quad (6a)$$

$$k_{obsd} = \frac{k_a k_e}{k_{-a}}[CH_3O^-] + \sum_i \frac{k_a k_i}{k_{-a}}[B_i] \quad (6b)$$

of original reactants (methoxide ion and amide) into the activated complex for decomposition of VI to products.

Substituent Effects. Figure 1 shows a Hammett plot of the second-order rate constants in both CH$_3$OH and CH$_3$OD. As in the hydrolysis reaction,[6] the substituent effect is very small for electron donors and very large for electron-attracting substituents in the phenyl ring. If the upward break in the Hammett plot results from a change in mechanism from rate-determining proton transfer (mechanism I) to rate-determining heavy-atom reorganization (mechanism II), then the rate constants $k^x{}_{CH_3OL}$ (L = H or D) can be represented as a sum of rate constant $k^x{}_{1L}$ for mechanism I, presumed to obey a linear Hammett relation with slope ρ_{1L}, and $k^x{}_{2L}$ for mechanism II, presumed to obey a different linear Hammett relation with slope ρ_{2L} (eq 7). This is found: the lines drawn in Figure 1

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[8] C. G. Mitton, M. Gresser, and R. L. Schowen, *J. Amer. Chem. Soc.*, **91**, 2045 (1969).

$$k^{x}{}_{\mathrm{CH_3OL}} = k^{x}{}_{1\mathrm{L}} + k^{x}{}_{2\mathrm{L}} \tag{7a}$$

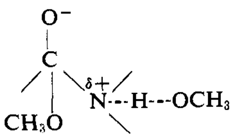
$$k^{x}{}_{\mathrm{CH_3OL}} = k^{\mathrm{H}}{}_{1\mathrm{L}}10^{\rho_{1\mathrm{L}}\sigma_x} + k^{\mathrm{H}}{}_{2\mathrm{L}}10^{\rho_{2\mathrm{L}}\sigma_x} \tag{7b}$$

are plots of eq 8 and 9 which show that $\rho_{1\mathrm{H}} = \rho_{1\mathrm{D}} = 0$

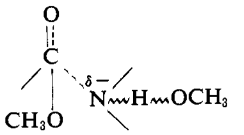
$$k^{x}{}_{\mathrm{CH_3OH}} = 0.056 + 0.043 \times 10^{2.9\sigma_x} M^{-1}\ \mathrm{sec}^{-1} \tag{8}$$

$$k^{x}{}_{\mathrm{CH_3OD}} = 0.028 + 0.049 \times 10^{2.9\sigma_x} M^{-1}\ \mathrm{sec}^{-1} \tag{9}$$

and $\rho_{2\mathrm{H}} = \rho_{2\mathrm{D}} = 2.9$. We therefore propose the valence isomeric activated complex structures VII for mechanism I ($\rho = 0$, dominant for $\sigma_x < 0$; presumably δ^+ in VII is about equal to the small positive charge on the initial-state amide nitrogen) and VIII for mechanism II ($\rho = 2.9$, dominant for $\sigma_x > 0$). Proton transfer dominates in VII so that a large solvent isotope effect is expected for mechanism I, while heavy-atom reorganization with solvation catalysis dominates in VIII, so that a small solvent isotope effect is expected for mechanism II.



VII



VIII

Isotope Effects. From the $k^{\mathrm{H}}{}_{1\mathrm{L}}$ and $k^{\mathrm{H}}{}_{2\mathrm{L}}$ values in eq 8 and 9, we calculate $k^{\mathrm{H}}{}_{1\mathrm{H}}/k^{\mathrm{H}}{}_{1\mathrm{D}} = 0.056/0.028 = 2$ for mechanism I and $k^{\mathrm{H}}{}_{2\mathrm{H}}/k^{\mathrm{H}}{}_{2\mathrm{D}} = 0.043/0.049 = 0.88$ for mechanism II. Now these isotope effects are products of an inverse isotope effect[9] of 2.3 on the quantity k_a/k_{-a} and a normal isotope effect on k_e. Thus, $k_e{}^{\mathrm{CH_3OH}}/k_e{}^{\mathrm{CH_3OD}}$ is about 4.6 for mechanism I and 2 for mechanism II. The value of 4.6 is easily ascribable to a primary isotope effect in VII, while we assign the value of 2 to a hydrogen-bonding contribution in VIII. A forthcoming paper will treat these effects in detail.

Experimental Section

Materials. The aryl-substituted *N*-methyl-2,2,2-trifluoroacetanilides were prepared as described by Kershner and Schowen.[6] Solvent methanol was from Allied Chemical and Dye Co., both the reagent grade absolute and reagent grade distilled over Mg being used, with no distinction appearing in the rate constants. The methanol-*O-d* (Diaprep. Inc.) was carefully distilled from barium nitrate (J. T. Baker Chemical Co.). Sodium methoxide solutions in both methanol and methanol-*O-d* were prepared in essentially the same way with the exception that in methanol-*O-d* the solutions were handled in a drybox or transferred by syringe from serum-capped volumetric flasks. Small pieces (<1 g each) of cleaned metallic sodium were added to approximately 1 l. (250 ml in the case of methanol-*O-d*) of solvent and allowed to react. Less concentrated base solutions were prepared by dilution of buret-measured aliquots of the stock base solution. For standardization, 2–5-ml aliquots of base solutions were added to approximately 50 ml of doubly distilled water and potentiometrically titrated against a solution of 0.0500 *M* potassium acid phthalate (Baker and Adamson Primary Standard).

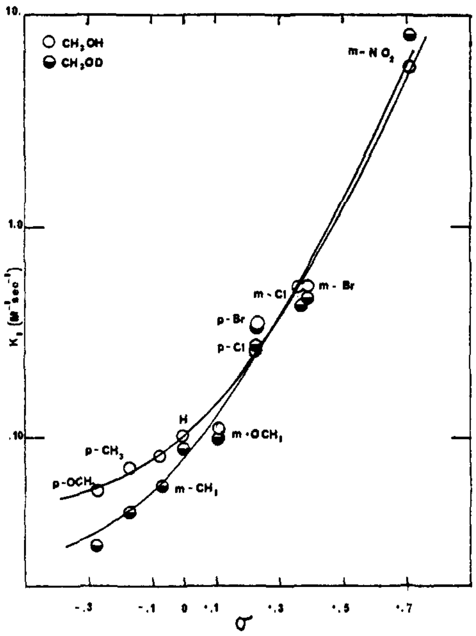


Figure 1. Hammett plot of the data for methoxide-catalyzed methanolysis of $\mathrm{XC_6H_4N(CH_3)COCF_3}$ in light and heavy methanol. The solid lines are plots of eq 8 and 9.

Kinetics. Solvolysis reaction rates were determined following the spectrophotometric procedure outlined by Kershner and Schowen.[6]

General Base Catalysis. Buffer solutions were prepared by dissolving an appropriate amount of triethylamine hydrochloride (Eastman White Label, recrystallized from 60% ethanol–water) in methanol and neutralizing a portion of the salt with a standard solution of sodium methoxide followed by volumetric dilution. The kinetics was followed by a modification of the spectrophotometric procedure described above, the reaction progress being monitored by manual null adjustment of the Cary 16 spectrophotometer, rather than by using a strip chart recorder. Rate constants were determined by linear least-squares fit of the integrated first-order kinetic law.

pK_b of Triethylamine in Methanol. Standard buffer solutions of triethylamine and triethylamine hydrochloride were prepared in a concentration range of 0.100–0.075 *M* in base component and 0.005–0.0036 *M* in acid component. The *p*-nitrophenol–*p*-nitrophenoxide (8.63×10^{5} *M*, $\lambda_{\max}$ 390 nm, $\epsilon \simeq 1.27 \times 10^{5}\ M^{-1}\ \mathrm{cm}^{-1}$, p$K_b$ = 6.05 ± 0.12 for the anion[11]) indicator system was used to determine pK_b = 7.33 ± 0.12 for triethylamine in methanol.

Acknowledgment. We are happy to thank Professor R. W. Taft of the University of California, Irvine, for his kindness and for his clever and useful criticism of this paper.

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[9] The value 2.3 is calculated from More O'Ferrall's fractionation factor of 0.72 for the methoxide ion,[10] assuming triple solvation: $(0.72)^3 = 1\ 2.3$.

[10] R. A. More O'Ferrall, *J. Chem. Soc. D*, 114 (1969).

[11] M. Jacobson, unpublished determination. *Cf.* C. H. Rochester and B. Rossall, *J. Chem. Soc. B*, 743 (1967) (pK_b = 5.4); B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Amer. Chem. Soc.*, 88, 1911 (1966) (pK_b = 5.7).