C-C Bond Fission in Carboxamides. Kinetic Studies on Alkaline Hydrolysis of Substituted α-Nitroisobutyranilides

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Alkaline hydrolysis of substituted α-nitroisobutyranilides, trichloroacetanilide and trifluoroacetanilide was studied kinetically at various hydroxyl ion concentrations in 10% aqueous dioxane. The formation of phenylcarbamate ion as an intermediate was confirmed on hydrolysis of the α-nitroisobutyranilides and trichloroacetanilide but not trifluoroacetanilide. All the substituted α-nitroisobutyranilides except the *p*-nitro derivative were found to undergo C–C bond fission exclusively. Trichloroacetanilide and the *p*-nitro derivative of α-nitroisobutyranilide underwent both C–C and C–N bond fission. The mechanism of C–C bond fission in the hydrolysis of α-nitroisobutyranilides was explained on the basis of the solvent isotope effect as a fast reversible addition of a hydroxyl ion followed by a rate-determining decomposition of the tetrahedral addition intermediate to form a phenylcarbamate ion and a carbanion.

Alkaline hydrolysis of anilides containing strongly electron attracting groups in the acylic part of the molecule has been studied extensively by many workers, but the only reaction pathway so far proposed is C–N bond fission to give carboxylate anion and aniline as primary products.

The only exception to this pathway is that deduced from the brief description of Eriksson and Holst[1] of a distinct odour of phenyl isocyanide and formation of chloride ion during the alkaline hydrolysis of trichloroacetanilide, but these authors did not discuss the origin of these compounds.

Previously we found an unusual C–C bond fission besides the usual C–N bond fission during studies on alkaline hydrolysis of α-nitroisobutyramide[2] and trichloroacetanilide,[3] and showed the origin of phenyl isocyanide and chloride ion in the latter case.

The present work was on alkaline hydrolysis of substituted α-nitroisobutyranilides to examine C–C bond fission in the alkaline hydrolysis of carboxamides. Use of substituted anilides facilitated studies on the effect of structural change on the hydrolysis and provided much information on the mechanism of the reaction.

Experimental

Materials. α-Nitroisobutyranilides were prepared by condensation of α-nitroisobutyryl chloride, obtained by a known method,[4] with appropriate anilines in dichloromethane at 0°C in the presence of potassium carbonate. They were recrystallized from appropriate solvents. The results of analyses are shown in Table 1. Trichloroacetanilide[5] and trifluoroacetanilide[6] were prepared by a known method and gave the expected analytical values. Deuterium oxide (99.75% D_2O) and NaOD (in 99.75% D_2O) were obtained from Merck and Co., Inc. The inorganic compounds used were of reagent grade.

Apparatus. Spectroscopic measurements were carried out with a Shimadzu, type QV-50, spectrophotometer. A Metrohm pH-meter, type E-300B, with a combined electrode was used for pH measurements.

Kinetic Measurements. Kinetic measurements were made spectrophotometrically at 50±0.02°C in 10% (V/V) aqueous dioxane unless otherwise specified. The ionic strength of the reaction mixture was adjusted to 0.9 by addition of potassium chloride except for $[OH^-]>0.9$M. The initial concentration of anilides was in the range 10^{-3} to 10^{-4}M. The concentration of sodium hydroxide was estimated with sulfamic acid. In a typical run, a volume of about 85 m*l* of sodium hydroxide solution, with the desired amount of potassium chloride, was put into a 100 m*l* volumetric flask and warmed to 50±0.02°C in a water bath. A volume of 10 m*l* of anilide in dioxane and the necessary amount of sodium hydroxide solution to make up the volume, both at 50°C, were added to the flask. The resulting mixture was quickly shaken, and then stood in the bath. At appropriate intervals 0.50 m*l* of the solution was pippetted into 5 m*l* of 1N HCl and the absorbance due to unreacted anilide was measured. The rate constant of the reaction was obtained graphically using the usual pseudo-first order kinetic treatment. The absorption maxima of the anilides used are shown in Table 1. With the *m*-nitro derivative, the absorption of *m*-nitroaniline overlaps that of the anilide in acidic solution, so the above method was not applicable. Hence *m*-nitroaniline was converted into its diazonium salt in 1N-HCl solution, and the absorption of this salt at 540 mμ was followed. *m*-Nitrophenylcarbamic acid was rapidly converted into *m*-nitroaniline under these condition and hence the amount of diazonium salt observed corresponded to the sum of the amounts of aniline and phenylcarbamic acid present in the reaction mixture.

Phenylcarbamate ion in the reaction mixture was separated and determined by the method of Christenson.[7] The rate of decomposition of phenylcarbamate ion (k_6 in Table 4) was measured with phenyl isocyanate.

Acid Dissociation Constants. pK_a values for the α-nitroisobutyranilides were determined from the change in the absorbance with pH. Stock solutions of an anilide were mixed with appropriate buffers and the absorbances of the anilide in its undissociated form were measured at its λ_{max} shown in Table 1. Error due to the time lapse between mixing and reading the absorbance was corrected by extrapolation of values to zero time.

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[1] S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, **20**, 1892 (1966).

[2] M. Masui, H. Sayo, H. Ohmori, and T. Minami, *Chem. Commun.*, **1969**, 404.

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[7] I. Christenson, *Acta Chem. Scand.*, **18**, 904 (1964).

TABLE 1. MELTING POINTS, ANALYTICAL RESULTS AND ABSORPTION MAXIMA OF α-NITROISOBUTYRANILIDES, $Me_2C(NO_2)CONHC_6H_4X$

X	mp, °C	Calcd. % C	Calcd. % H	Calcd. % N	Found, % C	Found, % H	Found, % N	λ_{max}, mμ
p-OMe	73 — 74	55.45	5.92	11.76	55.46	5.86	11.90	239
p-Me	115 —116	59.45	6.35	12.60	59.62	6.25	12.63	238
m-Me	107 —108	59.45	6.35	12.60	59.56	6.23	12.45	237
H	104 —105	57.68	5.81	13.46	57.89	5.80	13.63	235
p-Cl	121 —122.5	49.48	4.57	11.55	49.63	4.84	11.46	242
m-Cl	134.5—136	49.48	4.57	11.55	49.42	4.52	11.47	240
m-NO_2	135 —136	47.43	4.38	16.60	47.41	4.37	16.67	235
p-NO_2	137.5—139	47.43	4.38	16.60	47.14	4.26	16.45	304

Results

Hydrolysis of Substituted α-Nitroisobutyranilides. The rate of hydrolysis of all α-nitroisobutyranilides used was first-order in the anilide at constant hydroxyl ion concentration. The final products were 2-nitropropane aci-ion, substituted aniline and carbonate ion. The observed pseudo-first-order rate constant, k_{obs}, approaches a limiting value with increase in hydroxyl ion concentration, as shown in Fig. 1 and Table 2. These limiting values, k_{limit}, are also summarized in Table 2. A similar phenomenon was observed by Erikson and Holst on hydrolysis of trichloro- and trifluoroacetanilide.[1] The effect of the initial concentration on k_{obs} was examined with concentrations of 2×10^{-4} to 8×10^{-4}M of unsubstituted α-nitroisobutyranilide at a hydroxyl ion concentration of 0.9M and $\mu=0.9$: no effect was observed. Change in ionic strength between 0.9 and 3.6 had no effect on k_{obs} for hydrolysis of the same anilide at a hydroxyl ion concentration of 0.9M. Substituted phenylcarbamate ion was detected by the method of Christenson[7] in the reaction mixture during the hydrolysis, and its concentration increased with time, up to a maximum, and then decreased slowly towards zero at infinite time. A typical example of the hydrolysis of unsubstituted α-nitroisobutyranilide is shown in Fig. 2. The time when the phenylcarbamate ion reaches its maximum concentration is given in Table 3, as t_{max}, with the relative concentration of phenylcarbamate ion at this time. The maximum concentration of phenylcarbamate ion increased with the concentration of hydroxyl ion.

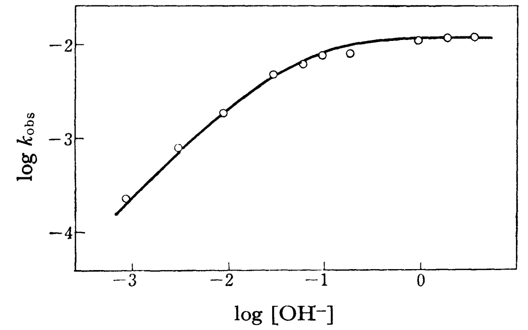


Fig. 1. Plot of log k_{obs} against log $[OH^-]$ in the alkaline hydrolysis of α-nitroisobutyranilide. The line is calculated from Eq. (16) and parameter values in Table 2.

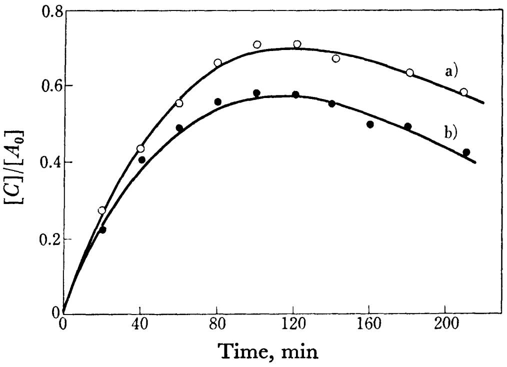


Fig. 2. Time-dependences of the concentration of phenylcarbamate ion during hydolysis of α-nitroisobutyranilide.
a) $[OH^-]=1.8$M, b) $[OH^-]=0.9$M

TABLE 2. PSEUDO-FIRST-ORDER RATE CONSTANTS, k_{obs}, AND LIMITING VALUES OF k_{obs}, k_{limit}, FOR THE HYDROLYSIS AND DISSOCIATION CONSTANTS OF ANILIDES, $RCONHC_6H_4X$, AT 50°C

	$[OH^-]$, M[a] R	$Me_2C(NO_2)$								CCl_3	CF_3
	X	*p*-OMe	*p*-Me	*m*-Me	H	*p*-Cl	*m*-Cl	*m*-NO_2	*p*-NO_2	H	H
10^3k_{obs}, min^{-1}	3.6	12.8			11.9						
	1.8	10.4	12.4	12.4	11.6	9.36	7.74	7.29	8.75		
	0.9	9.6	10.1	12.3	10.8	8.26	6.93	7.57	8.54	117	291
	0.09	4.1	4.86	7.13	7.11	5.57	3.92	6.67		93	230
	0.009	1.77	1.48	2.41	1.84	2.35	3.00	3.57	7.95	17	63.2
	0.0027	0.32	0.54	0.67	0.77	1.64	1.74	1.99			
	0.0009	0.11	0.17	0.17	0.21	0.37	0.75	1.15	6.28		
10^3k_{limit}, min^{-1}		14.0	13.0	12.4	12.0	9.5	7.8	7.6	8.8		
pK_a		12.1	12.0	12.0	11.8	11.6	11.4	11.0	10.3	9.98[b]	9.51[b]

a) $\mu=0.9$ except for $[OH^-]>0.9$ M, containing 10% (v/v) dioxane. b) Data from Ref. 1 at 25°C

TABLE 3. VALUES OF t_{max}, $[C]_{max}/[A_0]$ AND $(k_{obs}-\lambda)$ FOR THE HYDROLYSIS OF ANILIDES AT 50°C, $\mu=0.9$

R	X	$[OH^-]$ M	t_{max} obsd. min	t_{max} calcd. min	$[C]_{max}/[A_0]$[a)]	$10^3\times(k_{obs}-\lambda)$ min^{-1}
$Me_2C(NO_2)$	*p*-OMe	0.9	100		0.79	0
	p-Me	0.9	100		0.34	0
	m-Me	0.9	90		0.64	0
	H	1.8	120	150	0.71	0
		0.9	110	118	0.58	0
		0.09	100	108	0.43	0
		0.009	80	90	0.08	0
	p-Cl	0.9	140		0.67	0
	m-Cl	0.9	150		0.60	0
	m-NO_2	0.009	200		0.30	0
	p-NO_2	0.9	140		0.17	5.14
		0.009	130		0.26	2.54
CCl_3	H	0.9	27	26	0.40	60
		0.09	27	25	0.30	60
		0.009	40	42	0.09	10.5

a) $[C]_{max}$ represents the concentration of phenylcarbamate ion at $t=t_{max}$; $[A_0]$ is the initial concentration of total anilide.

Acid Dissociation Constants. The acid dissociation constants of α-nitroisobutyranilides are summarized in Table 2. A plot of the acid dissociation constants for substituted α-nitroisobutyranilides against the Hammett σ values was linear with $\rho=+1.19$ (figure not shown). With the *p*-nitro derivative, use of the σ^- value fitted the line better.

Decomposition of Phenylcarbamate Ion. In aqueous alkaline solution phenyl isocyanate is rapidly transformed to phenylcarbamate ion, and the latter decomposes gradually to give aniline and carbonate ion.[7,8] The rate of the decarboxylation reaction was measured at 50—70°C. The pseudo-first-order rate constants are summarized in Table 4.

TABLE 4. PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE DECOMPOSITION OF PHENYLCARBAMATE ION k_6 at 50°C

$[OH^-]$, M[a)]	1.9	0.9	0.18	0.09	0.009
10^3k_6, min^{-1}	3.31	6.50	8.56	11.8	35.0

a) $\mu=0.9$ except for $[OH^-]>0.9$ M, containing 10% (v/v) dioxane.

Hydrolysis of Trichloro- and Trifluoroacetanilide. Table 2 also shows data for the hydrolysis of trichloro- and trifluoroacetanilide. The rates obtained at 25°C are in fairly good agreement with those reported previously.[1)] A considerable amount of phenylcarbamate ion was obtained on hydrolysis of trichloroacetanilide, and the amount increased to a maximum as in the case of α-nitroisobutyranilides (Table 3). Thus it seems that the reaction pathway for the hydrolysis of trichloroacetanilide is comparable to that of α-nitroisobutyranilides. However, with trifluoroacetanilide, the concentration of phenylcarbamate ion was very low during the run and so no maximum was observed.

TABLE 5. RATE CONSTANTS k_{obs} AND ACTIVATION PARAMETERS FOR THE HYDROLYSIS OF ANILIDES $RCONHC_6H_5$, $[OH^-]=0.9$M, $\mu=0.9$

	Temp. (°C)	R: $Me_2C(NO_2)$	CCl_3	CF_3
10^3k_{obs}, min^{-1}	25		10.0	33.7
	35		27.0	85.0
	50	10.8	117	291
	60	28.7		
	70	80.6		
E_a, kcal/mol		21.8	18.9	16.4
$\Delta S^{\neq}$, e.u.		−10.5	−14.7	−20.5

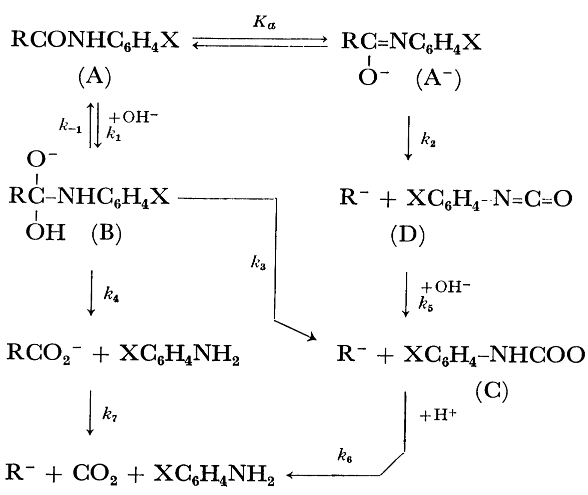
The rate of aniline formation was essentially the same as that of disappearance of anilide. The results suggest that a C–C bond fission similar to that with trichloroacetanilide scarcely occurs during hydrolysis of trifluoroacetanilide.

Activation Parameters. The activation parameters for the hydrolysis of α-nitroisobutyranilide, trichloroacetanilide and trifluoroacetanilide are shown in Table 5. They were obtained at a hydroxyl ion concentration of 0.9M, where the observed pseudo-first-order rate constant is very close to its limiting value, k_{limit}.

Solvent Isotope Effect. Solvent isotope effects on the hydrolysis of α-nitroisobutyranilide, trichloroacetanilide and trifluoroacetanilide were examined at a hydroxyl ion concentration of 1.8M, where $k_{obs}=k_{limit}$ was valid for each of these compound. The $k_{obs}(H)/k_{obs}(D)$ ratio was 1.10 ± 0.07 for α-nitroisobutyranilide, 1.33 ± 0.06 for trifluoroacetanilide and 1.39 ± 0.04 for trichloroacetanilide.

Discussion

Formation of phenylcarbamate ion as an intermediate and other results suggest the following reaction pathway for the hydrolysis of α-nitroisobutyranilides:



Scheme 1

(The possibility that step k_3 involves a term catalyzed by hydroxyl ion cannot be excluded at this point.

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8) E. Mohr, *J. Prakt. Chem.*, [2] **73**, 177 (1906); C. Naegeli, A. Tyabji, L. Conrad, and F. Litwan, *Helv. Chim. Acta*, **21**, 1100 (1938).

This will be discussed later.) A similar step to that involving formation of phenyl isocyanate (D) as an intermediate has been demonstrated in the hydrolysis of carbamic acid esters.[7] Assuming that B is in a steady state, the observed pseudo-first-order rate constant (k_{obs}) for the disappearance of total anilide is given by Eq. (1).

$$k_{obs} = \frac{K_w}{K_a + a_H}\left(\frac{k_1 k_3}{k_{-1}+k_3+k_4} + \frac{k_1 k_4}{k_{-1}+k_3+k_4}\right) + \frac{k_2 K_a}{K_a + a_H} \tag{1}$$

where K_a is the dissociation constant defined in Eq. (2), K_w is the ionic product of water, and a_H is the activity of hydronium ion.

$$K_a = \frac{[A^-]a_H}{[A]} \tag{2}$$

The conversion of phenyl isocyanate into phenylcarbamate ion has been reported to be very rapid in alkaline solution,[7,8] and hence D can also be considered to be in a steady-state. The rate of the change in C is given by Eq. (3).

$$\frac{d[C]}{dt} = \lambda[A_0]e^{-k_{obs}t} - k_6[C], \tag{3}$$

where $$\lambda = \frac{K_w}{K_a + a_H}\cdot\frac{k_1 k_3}{k_{-1}+k_3+k_4} + \frac{k_2 K_a}{K_a + a_H} \tag{4}$$

and $[A_0]$ is the initial concentration of total anilide, so that

$$[C] = \frac{\lambda[A_0]}{k_{obs} - k_6}(e^{-k_6 t} - e^{-k_{obs}t}). \tag{5}$$

We now define t_{max} as the time for C to reach its maximum concentration, and $[C]_{max}$ as the concentration of C at this time. When $t = t_{max}$, then $d[C]/dt = 0$ is valid. Substituting [C] from equation (5) in equation (3) and solving about t_{max} gives Eq. (6).

$$t_{max} = \frac{\ln k_{obs} - \ln k_6}{k_{obs} - k_6} \tag{6}$$

The t_{max} calculated in Table 3 was obtained using experimental values of k_{obs} (Table 2), k_6, measured separately (Table 4),[9] and Eq. (6). The good agreement between the observed and calculated values substantiates the above equations.

From Eq. (3)

$$\lambda[A_0]e^{-k_{obs}\cdot t_{max}} - k_6[C]_{max} = 0$$

$$\lambda = k_6\frac{[C]_{max}}{[A_0]}e^{k_{obs}\cdot t_{max}} \tag{7}$$

Thus the value of λ can be calculated from experimental values. By subtracting Eq. (4) from Eq. (1), we obtain Eq. (8).

$$k_{obs} - \lambda = \frac{K_w}{K_a + a_H}\cdot\frac{k_1 k_4}{k_{-1}+k_3+k_4}. \tag{8}$$

As shown in Table 3, the values of $k_{obs} - \lambda$ for the substituted α-nitroisobutyranilides are essentially zero within the limits of experimental error except with the *p*-nitro derivative. This strongly suggests that the hydrolysis of these compounds proceeds exclusively through pathways involving phenylcarbamate ion as an intermediate, that is, k_1 or k_4 is negligible. If $k_4 \simeq 0$, Eq. (1) can be reduced to Eq. (9). (As will be discussed later, the experimental results obtained were not explained successfully when $k_1 \simeq 0$).

$$k_{obs} = \frac{K_w}{K_a + a_H}\,\frac{k_1 k_3}{k_{-1}+k_3} + \frac{k_2 K_a}{K_a + a_H} \tag{9}$$

From Eq. (9)

$$\frac{k_1 k_3 K_w}{k_{-1}+k_3} + k_2 K_a = k_{obs}(K_a + a_H) \tag{9'}$$

TABLE 6. VALUES OF $k_{obs}(K_a + a_H)$ FOR THE HYDROLYSIS OF α-NITROISOBUTYRANILIDE AT VARIOUS HYDROXYL ION CONCENTRATIONS AT 50°C

$[OH^-]$, M	3.6	1.8	0.9	0.09	0.054	0.009	0.0009
$10^{14}k_{obs}(K_a + a_H)$, M·min^{-1}	1.90	1.88	1.80	1.77	1.84	1.97	1.95

As shown in Table 6, the value of $k_{obs}(K_a + a_H)$ does not change with hydroxyl ion concentration within the limits of experimental error, and hence the left hand side of Eq. (9′) can also be regarded as constant. Since mechanistically k_1, k_{-1}, and k_2 should be constants, two possibilities may be considered. First, k_3 does not contain a term dependent on hydroxyl ion concentration; that is, k_3 is also a constant. If this is not the case, $k_3 \gg k_{-1}$ should be true to make the term constant. In Eq. (9) the first term represents the rate constant for disappearance of total anilide through the tetrahedral intermediate (B), and the second term that for disappearance through phenyl isocyanate (D). It is difficult to decide which step is predominant, but solvent isotope effects should afford a clue to this problem. Tobias and Kézdy have reported a method for determining whether carbanions are intermediates in the hydrolysis of esters with labile α protons.[10] This method would be applicable in the present case.

In the pH region where $K_a \gg a_H$ Eq. (9) can be simplified to Eq. (10).

$$k_{obs} = k_{limit} = \frac{K_w}{K_a}\cdot\frac{k_1 k_3}{k_{-1}+k_3} + k_2 \tag{10}$$

If only step k_2 is operative,

$$k_{obs} = k_2$$

Since no proton transfer is involved in this step, it is expected that $k_{obs}^{H_2O}/k_{obs}^{D_2O} = 1$.[10] On the other hand, if step k_3 is actually operative, the observed isotope effect should be

$$k_{obs}^{H_2O}/k_{obs}^{D_2O} = (k^{H_2O}/k^{D_2O})(K_w^{H_2O}/K_w^{D_2O})(K_a^{D_2O}/K_a^{H_2O}), \tag{11}$$

where $k = k_1 k_3/(k_{-1} + k_3)$.

The values of $K_w^{H_2O}/K_w^{D_2O}$ and $K_a^{H_2O}/K_a^{D_2O}$ at 50°C were estimated by the method of Swain, Kuhn and Schowen[11] to be 5.8 and 3.05, respectively. The

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[9] k_6 is the pseudo-first-order rate constant for the decomposition of phenylcarbamic acid and varies with hydroxyl ion concentration in a complicated manner. No further investigation was carried out, since the absence of information on the detailed nature of k_6 would not affect the conclusion.

[10] P. S. Tobias and F. J. Kézdy, *J. Amer. Chem. Soc.*, **91**, 5171 (1969).

[11] C. G. Swain, D. A. Kuhn, and R. L. Schowen, *ibid.*, **87**, 1553 (1965).

value of $K_w{}^{H_2O}/K_w{}^{D_2O}$ at 25°C estimated by the same method is 6.75, which is in good agreement with the reported value of 6.67 ($K_w{}^{D_2O}/K_w{}^{H_2O}=0.15$).[12] This seems to substantiate the above assumptions. Using these values and Eq. (11), we get

$$k_{obs}^{H_2O}/k_{obs}^{D_2O} = 1.9(k_1{}^{H_2O}/k_1{}^{D_2O}) \qquad (12)$$

where $k_3 \gg k_{-1}$, and another Eq. (13) where $k_{-1} \gg k_3$.

$$k_{obs}^{H_2O}/k_{obs}^{D_2O} = 1.9\times(k_1k_3/k_{-1})^{H_2O}/(k_1k_3/k_{-1})^{D_2O} \qquad (13)$$

It has been reported that an inverse isotope effect is involved in a process in which hydroxyl ion attacks a carbon atom, and the expected maximum isotope effect in such a process should be 1.7^{-1}.[13] Equation (12) is, then

$$k_{obs/obs}^{H_2O/D_2O} = 1.9/1.7^{\beta} \qquad (14)$$

where β represents the degree of bond formation in the transition state, that is $0 \leqq \beta \leqq 1$.[11] As discussed above step k_3 does not involve a term catalyzed by hydroxyl ion when Eq. (13) holds, and hence no solvent isotope effect is expected as in step k_2. Thus Eq. (13) becomes

$$k_{obs}^{H_2O}/k_{obs}^{D_2O} = 1.9/1.7 \doteqdot 1.12 \qquad (15)$$

The observed solvent isotope effects were 1.33 and 1.39 for trifluoroacetanilide and trichloroacetanilide, respectively. On hydrolysis of these two anilides, at the lyoxide ion concentration used in this study the attack of hydroxyl ion on the anilide was shown to be rate-determining.[1] The observed values are in the range expected from Eq. (14). In the hydrolysis of trichloroacetanilide, therefore, the possibility of phenylcarbamate ion being produced through step k_2 seems unlikely. If it is not the case, the observed solvent effect should be smaller than that for trifluoroacetanilide, because more than one third of the whole reaction proceeds through phenylcarbamate ion.

The solvent isotope effect observed in the hydrolysis of α-nitroisobutyranilide at a lyoxide ion concentration of 1.8M was 1.10, which is very close to the value expected from Eq. (15). The results strongly suggest that the hydrolysis of α-nitroisobutyranilide mainly proceeds through the tetrahedral addition intermediate (B), and the rate of decomposition of this intermediate to phenylcarbamate ion is slower than that of liberation of hydroxyl ion to give the original anilide, that is, $k_{-1} \gg k_3$.

The value of activation entropy, $\Delta S^{\neq} = -10.5$ eu., also seems to support this view. In the hydrolysis of carbamic acid esters, those hydrolyzed *via* a reaction pathway with an isocyanate intermediate like step k_2 in Scheme 1, have positive $\Delta S^{\neq}$ values, and those having negative $\Delta S^{\neq}$ values have been stated to be hydrolyzed *via* a tetrahedral addition intermediate.[7] The $\Delta S^{\neq}$ values of several of the latter esters are less negative than that of α-nitroisobutyranilide. If step k_2 in Scheme 1 actually operates in the hydrolysis of α-nitroisobutyranilide, the value of $\Delta S^{\neq}$ should be positive. The possibility that the reaction occurs *via* both pathways, k_2 and k_3, is not completely eliminated, but it seems extremely likely that step k_2 is not the main pathway.

From the above discussion Eq. (9) may be reduced to Eq. (16).

$$k_{obs} = \frac{K_w}{K_a + a_H} \cdot \frac{k_1k_3}{k_{-1}}. \qquad (16)$$

Using the values of k_{limit} (Table 2), K_a (Table 2), and K_w, the value of k_1k_3/k_{-1} is calculated to be 0.347 min^{-1} for the hydrolysis of α-nitroisobutyranilide. The solid line in Fig. 1 is calculated from Eq. (16) and these values. This calculated line agrees well with the observed rate constants.

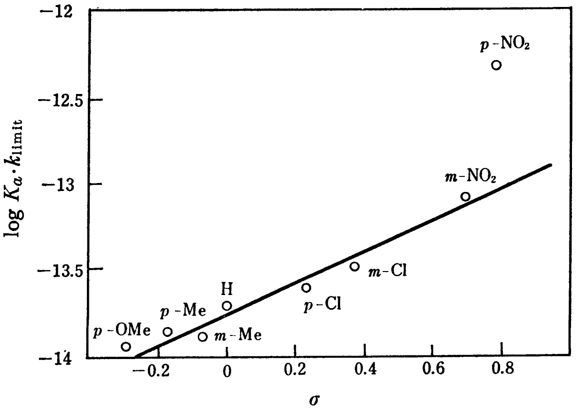

Fig. 3. Plot of $k_{limit} \cdot K_a$ against σ.

A plot of the value $k_1k_3K_w/k_{-1}$ ($=k_{limit} \cdot K_a$) for the substituted α-nitroisobutyranilides against Hammett σ values was essentially linear with $\rho=0.83$ (Fig. 3) except for the *p*-nitro derivative. The upward deviation observed with this anilide was reduced when the σ^- value was used. However, it is doubtful whether this treatment is adequate in the present case. Since the value of $k_{obs}-\lambda$ for the *p*-nitro derivative (Table 3) is more than half that of k_{obs} at 0.9M hydroxyl ion concentration, a considerable amount of C–N bond fission, that is normal hydrolysis, occurs in the hydrolysis. This fact seems compatible with the observed deviation in Fig. 3. In the hydrolysis of substituted acetanilide, the *p*-nitro derivative reacts appreciably faster than the rate predicted from the rates observed with other anilides, and thus a new mechanism was introduced to interpret the hydrolysis of anilides with strongly electron withdrawing substituents on the phenyl ring.[14] The C–N bond in the *p*-nitro derivative of α-nitroisobutyranilide must be activated by the *p*-nitro group more than that in other derivatives, and hence normal hydrolysis becomes possible to some extent.

It is interesting to compare the results obtained with trifluoroacetanilide, trichloroacetanilide and α-nitroisobutyranilide. In the hydrolysis of the trifluoro-derivative, no C–C bond fission was observed, that is the reaction was normal. With the trichloro-derivative, the ratio of C–C bond fission to C–N bond fission is more than one third. With the α-nitroisobutyr-deriv-

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TABLE 7. ACTIVATION ENERGIES FOR DECARBOXYLATION OF CARBOXYLIC ACIDS RCO_2H

R	Solvent	E_a, kcal/mol	Ref.
CF_3	Ethylene glycol	42.0	16
CCl_3	Ethylene glycol	31.6	16
CCl_3	Ethyl alcohol	31.0	17
CCl_3	Water	36.3	17, 18
CBr_3	Water	33.0	18
$Me_2C(NO_2)$	Water	22.5	19

atives, the reaction proceeds exclusively through C–C bond fission except with the *p*-nitro-derivative. A similar phenomenon was observed in studies on the formation of a tetrahedral addition intermediate of ethyl acetate derivatives.15) The addition compound from ethyl trichloroacetate was found to decompose *via* C–C bond fission to give ethyl carbonate, whereas that from ethyl trifluoroacetate did not.

The value of activation energy for the decarboxylation of the carboxylic acids shown in Table 7 are interesting. The order of facility of C–C bond fission coincides with that observed in the present study. It seems clear from the above considerations that C–C bond fission increases with stability of the carbanion formed.

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