Alkaline Hydrolyses of *N*-Alkyl-2,4-dinitroacetanilides

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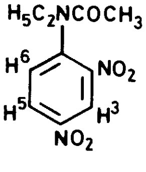
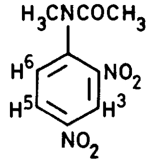
The alkaline hydrolysis in protium and deuterium oxides of *N*-alkyl-2,4-dinitroacetanilides (alkyl; methyl and hydrogen) proceeds *via* the rate-limiting formation of a tetrahedral intermediate, which decomposes to give products with water (k_2 process) and hydroxide catalysis (k_3 process), the latter process being predominant. Solvent isotope effects for both processes are *ca.* 3.0 (60 °C). Breakdown of the tetrahedral intermediate proceeds by two pathways with the transition states involving C–N bond breakage to give a hydrogen-bonded anilide ion intermediate.

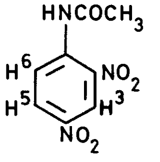
To date, many reports and reviews have appeared on the alkaline hydrolysis of amides.[1] Recently, the effects of amide structure, hydroxide ion concentration, solvent composition, and other variables on the alkaline hydrolysis of amides have been the subject of a number of studies. The alkaline hydrolysis of amides are generally considered to be sensitive to both polar and steric effects of acyl substituents. We have already reported on the alkaline hydrolysis of *N*-ethyl-2,4-dinitroacetanilide (**1**) and it was found that the substituents on the amido nitrogen atom and phenyl moiety considerably affect the rate of hydrolysis.[2] Although the investigations on the substituent effects on the amido nitrogen atom and phenyl moiety of acetanilides were published,[3–8] they were somewhat less than systematic. This paper reports on the substituent effects of the following acetanilides on their rates of alkaline hydrolyses.



(**1**)



(**2**)



(**3**)

Experimental

Materials.—*N*-Methyl-2,4-dinitroaniline (MDA) was synthesized from chloro-2,4-dinitrobenzene and methylamine according to the method of Bogoslovskii and Tsil'man[9] [75.1%; m.p. 174—175 °C (from ethanol) (lit.,[9] 176—177 °C)]. Compound (**2**) was synthesized from MDA and acetic anhydride in the presence of a small amount of concentrated H_2SO_4 (three or four drops) according to the method described in the literature[2] (63.4%), m.p. 75—76 °C (Found: C, 45.0; H, 3.85; N, 17.5. Calc. for $C_9H_9N_3O_5$: C, 45.19; H, 3.77; N, 17.60%); δ(Me_2SO; 60 MHz) 2.17 (3 H, s, $COCH_3$), 3.48 (3 H, s, NCH_3), 7.97 (1 H, d, *J* 4 Hz, 6-H), and 8.70 (2 H, m, 3- and 5-H, overlapped).

2,4-Dinitroacetanilide (**3**).—Compound (**3**) was synthesized from 2,4-dinitroaniline and acetic anhydride according to the method given for compound (**2**) (93.2%), m.p. 118.5—119 °C (lit.,[10] 121 °C); δ(Me_2SO; 60 MHz) 2.17 (3 H, s, $COCH_3$), 8.04 (1 H, d, $J_{5,6}$ 4.1 Hz, 6-H), 8.56 (1 H, dd, $J_{5,6}$ 4.1, $J_{3,5}$ 1.1 Hz, 5-H), 8.72 (1 H, d, $J_{3,5}$ 1.1 Hz, 3-H), and 10.71 (1 H, s, NH).

Table 1. pK_a Values of 2,4-dinitroacetanilide (**3**)

Temp./°C	pK_a[a]
20	10.90
30	10.69
40	10.61
50	10.40

[a] Estimated limit of error ±0.05.

pK_a *Measurements.*—The pK_a values were examined for compound (**3**). The term K_a is defined as the equilibrium constant for the reaction $ArNHCOCH_3 + H_2O \rightleftharpoons ArN^-COCH_3 + H_3O^+$ (Ar = 2,4-dinitrophenyl). Glycine, sodium chloride, and sodium hydroxide were used for the preparation of buffer solutions. The absorbances for the undissociated and dissociated compound (**3**) (d_M and d_I) were measured in water (pH 7.0) and in a 2M-aqueous sodium hydroxide. The pK_a values were calculated according to equation (1) (Table 1).

$$\mathrm{p}K_a = \mathrm{pH} + \log\frac{d_I - d}{d - d_M} \qquad (1)$$

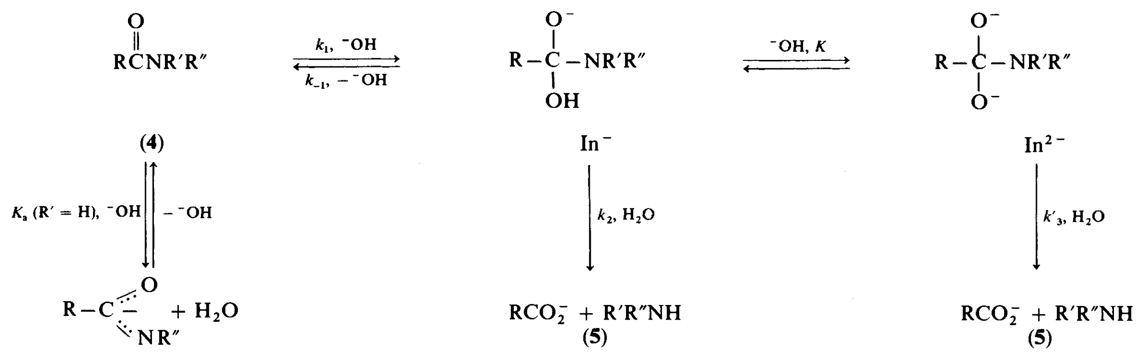
d = absorbance at each pH value

Rate Measurements.—A sample solution was prepared as follows. An acetonitrile solution of the anilide (0.1M; 1.5 μl) was placed in a quartz cell (3 ml) containing the prescribed concentration of aqueous sodium hydroxide (3 ml) kept at constant ionic strength (0.8M; NaCl). The time-dependent increase in the absorption maximum of the corresponding aniline formed were measured with a Hitachi 124 spectrophotometer.

Rate constants were calculated by the Guggenheim method.[11]

Results

Absorption Spectra.—The time-dependent spectral changes were measured for the reactions of (**2**) and (**3**) with an excess of sodium hydroxide (Figures 1 and 2 respectively). With compound (**2**), the spectral change was found to be moderate; the absorption (d) is to *N*-methyl-2,4-dinitroaniline (Figure 1). With compound (**3**), the spectral change differed slightly from that for (**2**) in that the absorption (b) appeared just after addition of sodium hydroxide, an observation attributed to the



Scheme 1.

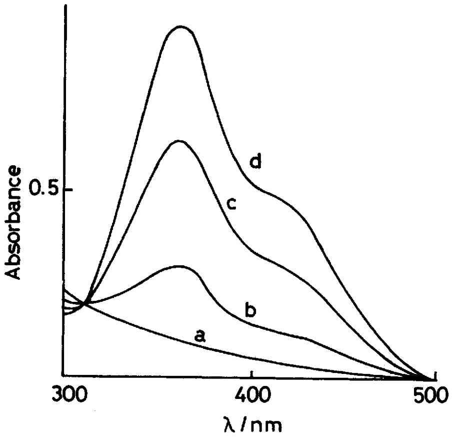


Figure 1. Time-dependent spectral changes for the alkaline hydrolysis of *N*-methyl-2,4-dinitroacetanilide (**2**) (3×10^{-5}M) at 30 °C ([⁻OH] = 0.1M): a; 2 and b; 10 min after addition of sodium hydroxide, c; 45 min, d; 19 h

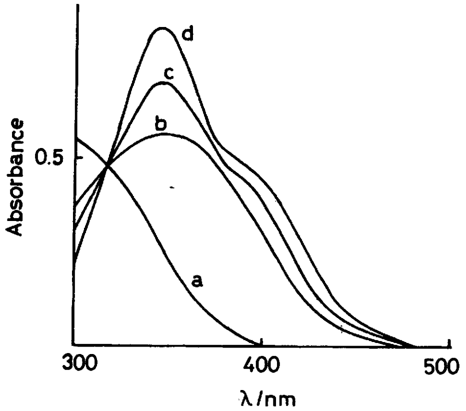


Figure 2. Time-dependent spectral changes for the reaction of 2,4-dinitroacetanilide (**3**) (3.0×10^{-5}M) at 30 °C ([⁻OH] = 0.1M): a; 3 min and b; just after addition of sodium hydroxide, c; 40 min and d; 22 h

formation of the conjugate base of (**3**) (Figure 2). The spectral change (b) ⟶ (c) ⟶ (d) was relatively slow, where the absorption (d) was due to 2,4-dinitroaniline.

From these results and the wealth of information already obtained,[1-8] the reaction sequence shown in the Scheme in unbuffered solutions was deduced.

Rate Constants.—According to the Scheme, acetanilide hydrolysis proceeds by reversible, base-catalysed formation of the tetrahedral intermediate (In⁻), which decomposes to give products. Assuming the validity of the steady-state approximation for the concentration of In⁻, this mechanism leads to the expression for the observed first-order rate constant, k_ψ, for acetanilide hydrolysis in alkaline solution [equation (2)]. In

$$k_\psi = \frac{k_1[^-\mathrm{OH}]}{1 + \dfrac{K_a[^-\mathrm{OH}]}{K_W}} \, \frac{k_2 + k_3[^-\mathrm{OH}]}{k_{-1} + k_2 + k_3[^-\mathrm{OH}]} \qquad (2)$$

equation (2) k_3 refers to Kk_3' (Scheme), which holds for the following equations. The dependence of k_ψ on [⁻OH] is shown in Table 2 with *N*-methyl-2,4-dinitroacetanilide (**2**). If an acetanilide is so weakly acidic ($K_a[^-\mathrm{OH}]/K_W \ll 1$) or has no hydrogen on the amido nitrogen atom, then equation (2) is simplified to equation (3). Equation (4) is derived by dividing both sides of equation (3) by [⁻OH]. Therefore the relationship between $k_\psi/[^-\mathrm{OH}]$ and [⁻OH] should be convex upward (not shown). Equation (5) is derived by rearranging equation (4).

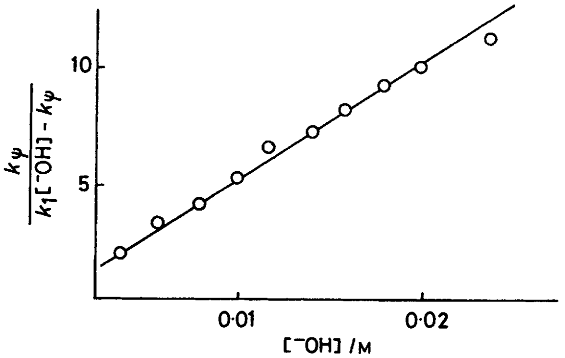


Figure 3. Relationship between $k_\psi/(k_1[^-\mathrm{OH}] - k_\psi)$ and [⁻OH] in the alkaline hydrolysis of *N*-methyl-2,4-dinitroacetanilide (**2**) at 75 °C

$$k_\psi = k_1[^-\mathrm{OH}]\frac{\mathrm{a} + \mathrm{b}[^-\mathrm{OH}]}{1 + \mathrm{a} + \mathrm{b}[^-\mathrm{OH}]} \qquad (3)$$

$$\mathrm{a} = \frac{k_2}{k_{-1}};\ \mathrm{b} = \frac{k_3}{k_{-1}}$$

$$\frac{k_\psi}{[^-\mathrm{OH}]} = k_1\frac{\mathrm{a} + \mathrm{b}[^-\mathrm{OH}]}{1 + \mathrm{a} + \mathrm{b}[^-\mathrm{OH}]} \qquad (4)$$

$$\frac{k_\psi}{k_1[^-\mathrm{OH}] - k_\psi} = \mathrm{a} + \mathrm{b}[^-\mathrm{OH}] \qquad (5)$$

Table 2. Hydroxide concentration dependence of the rate constants for the alkaline hydrolysis of *N*-methyl-2,4-dinitroacetanilide (**2**)[a]

	k_ψ.[b]/min^{-1}			k_ψ.[b]/min^{-1}	
[$^-$OH]/M	Observed	Calc.[c]	[$^-$OH]/M	Observed	Calc.[c]
	50 °C			60 °C	
0.009 50	0.005 56	0.005 54	0.001 95	0.001 71	0.001 34
0.0190	0.0112	0.0113	0.003 90	0.003 73	0.003 35
0.0285	0.0171	0.0172	0.005 85	0.005 60	0.005 59
0.0380	0.0232	0.0231	0.007 80	0.007 91	0.007 92
0.0475	0.0292	0.0291	0.009 75	0.009 93	0.0103
0.0570	0.0352	0.0351	0.0117	0.0128	0.0127
0.0665	0.0412	0.0412	0.0136	0.0151	0.0151
0.0760	0.0478	0.0473	0.0156	0.0177	0.0176
0.0855	0.0531	0.0533	0.0176	0.0197	0.0201
0.0950	0.0598	0.0594	0.0195	0.0226	0.0225
0.145	0.0924	0.0916	0.0214	0.0251	0.0249
			0.0254	0.0296	0.0300
			0.0292	0.0354	0.0348
	70 °C			75 °C	
0.002 05	0.003 51	0.003 90	0.003 90	0.007 68	0.007 77
0.003 06	0.005 52	0.005 85	0.005 85	0.0131	0.0130
0.003 86	0.007 20	0.007 99	0.007 99	0.0189	0.0190
0.006 21	0.0122	0.009 98	0.009 98	0.0245	0.0246
0.0133	0.0265	0.0117	0.0117	0.0297	0.0294
0.0201	0.0405	0.0140	0.0140	0.0360	0.0360
0.0482	0.0980	0.0158	0.0158	0.0412	0.0411
0.0676	0.138	0.0180	0.0180	0.0675	0.0674
0.0772	0.158	0.0200	0.0200	0.0532	0.0532
0.0965	0.198	0.0239	0.0239	0.0642	0.0644

[a] $[(\mathbf{2})]_0 = 2.5 \times 10^{-5}$M; $\mu = 0.8$M (NaCl); solvent H_2O–CH_3CN (99.95:0.05 v/v%). [b] Estimated limit of error ±1.0%. [c] These k_ψ values were calculated by substituting the data in Table 3 into equation (4).

From equation (5) the relationship between $k_\psi/(k_1[^-OH] - k_\psi)$ and $[^-OH]$ is expected to be linear (Figure 3). Although a and b are normally obtainable from the intercept and slope of this line, this was not so in this instance. Therefore the following method was used: the $k_\psi/[^-OH]$ value obtained when $[^-OH]$ was changed to infinity in equation (4) was used as the initial value of k_1, and then by substituting this initial k_1 value and the k_ψ values at two arbitrary hydroxide concentrations into equation (5), the simultaneous simple equations with respect to a and b were obtained. The a and b values obtained by solving the equations were used as initial values.

The k_1, a, and b values in Table 3 were derived by substituting these initial k_1, a, and b values in equation (4) and using the non-linear least-squares method.[12,*] The Arrhenius plot (not shown) then gave the activation parameters (Table 4).

With 2,4-dinitroacetanilide (**3**) the pre-equilibrium (Scheme) exists. As the conjugate base [corresponding to (**6**)] of (**3**) is known to be inactive towards hydrolysis,[8] an increase in the absorbance at 346 nm can be expected to obey pseudo-first-order kinetics. By a procedure similar to that used for (**2**) equation (6) is derived, from which the relationship between k_ψ

$$\frac{k_\psi}{k_1[^-OH]} = 1 + \frac{K_a}{K_W}[^-OH]\frac{a + b[^-OH]}{1 + a + b[^-OH]} \qquad (6)$$

and $[^-OH]$ is expected to be convex upward (not shown). The dependence of k_ψ on $[^-OH]$, rate constants (k_1, a, and b), and activation parameters are shown in Tables 5, 3, and 4, respectively. The k_1, a, and b values were derived by computer calculations as with (**2**) (Table 3). The a values at 50, 60, and 70 °C and the b values at 60 and 70 °C could not be accurately determined. The activation parameters for the k_1 stage at 30 °C are shown in Table 4, which indicates that the $\Delta H^\ddagger$ value decreases in the order of (**1**) > (**2**) > (**3**). Therefore, the bulkiness of alkyl substituents on the amido nitrogen atom was found to affect k_1 in a systematic manner.

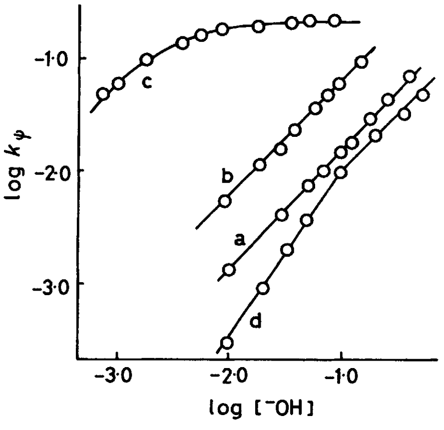


Figure 4. Relationship between log k_ψ and log $[^-OH]$ for various acetanilides: a; *N*-ethyl-2,4-dinitroacetanilide (**1**), b; *N*-methyl-2,4-dinitroacetanilide (**2**), c; 2,4-nitroacetanilide (**3**), and d; 4-nitroacetanilide (**7**)

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* This program[12] was devised by Dr. T. Nakagawa, Department of Chemistry Faculty of Science, Tokyo University, to whom the author (S. S.) is very much indebted.

Table 3. Rate constants and rate ratios for various acetanilides

Acetanilide	Temp./°C	k_1/M^{-1} min^{-1}	a(k_2/k_{-1})	b(k_3/k_{-1})/M^{-1}
N-Ethyl-2,4-dinitroacetanilide (**1**)^{a}	60	0.460	2.03	5.25
	30	0.051	1.21	9.33
	25	0.033^{e}		
	20	0.022	1.00	11.5
N-Methyl-2,4-dinitroacetanilide (**2**)	60	1.28	0.255	459
	50	0.649	6.95	209
	30	1.172^{e}	*f*	*f*
	25	0.119^{e}	*f*	*f*
2,4-Dinitroacetanilide (**3**)	60	128	*f*	3 190
	50	75.3	*f*	4 030
	30	27.0^{e}	*f*	*f*
N-Methyl-4-nitroacetanilide (**8**)^{b}	25	0.048	1.3	4.4
4-Nitroacetanilide (**7**)^{c}	30	0.221	0.007	10.6
Acetanilide (**9**)^{d}	25	0.004 71	0.097	0.041

^{a} Reference 2. ^{b} Reference 14. ^{c} Reference 13. ^{d} Reference 8. ^{e} Interpolated value. ^{f} Not determined.

Table 4. Activation parameters for the alkaline hydrolysis of nitro-substituted acetanilides (30 °C)

	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	$\Delta G^{\ddagger}$/kJ mol^{-1}
N-Ethyl-2,4-dinitroacetanilide (**1**)^{a}	59.0 ± 4.2	−110 ± 4.2	92.0 ± 15.9
N-Methyl-2,4-dinitroacetanilide (**2**)	52.3 ± 4.6	−121 ± 4.5	89.1 ± 18.4
2,4-Dinitroacetanilide (**3**)	40.6 ± 2.0	−119 ± 19	76.1 ± 7.9

^{a} Cited from reference 2.

Table 5. Hydroxide concentration dependence of the rate constants for the alkaline hydrolysis of 2,4-dinitroacetanilide (**3**)

	k_{ψ},^{b}/min^{-1}			k_{ψ},^{b}/min^{-1}	
[$^{-}$OH]/M	Observed	Calc.^{c}	[$^{-}$OH]/M	Observed	Calc.^{c}
	45 °C			50 °C	
0.003 79	0.0452	0.0455	0.001 92	0.0488	0.0490
0.005 69	0.0506	0.0507	0.003 84	0.0755	0.0756
0.007 58	0.0523	0.0524	0.005 77	0.0865	0.0866
0.009 48	0.0556	0.0554	0.007 69	0.0907	0.0908
0.0190	0.0602	0.0600	0.009 61	0.0868	0.0870
0.0379	0.0642	0.0641	0.0186	0.0912	0.0913
0.0560	0.0651	0.0652	0.0373	0.0956	0.0957
0.0758	0.0659	0.0660	0.0559	0.100	0.101
0.0839	0.0658	0.0660	0.0652	0.0990	0.103
0.0932	0.0658	0.0648	0.0746	0.101	0.105
			0.0932	0.0995	0.106
	60 °C			70 °C	
0.001 97	0.099	0.100	0.003 73	0.260	0.261
0.003 94	0.140	0.142	0.005 59	0.308	0.307
0.005 91	0.160	0.161	0.007 46	0.320	0.322
0.007 46	0.166	0.167	0.009 32	0.348	0.350
0.009 32	0.180	0.182	0.0186	0.391	0.392
0.0186	0.198	0.200	0.0373	0.427	0.429
0.0373	0.210	0.211	0.0559	0.424	0.425
0.0559	0.212	0.213	0.0652	0.422	0.427
0.0746	0.216	0.217	0.0746	0.426	0.428
0.0932	0.216	0.220	0.0839	0.449	0.450
			0.0932	0.430	0.455

^{a} [(**3**)]$_0$ = 3.0 × 10^{-5}M; μ = 0.8M (NaCl); solvent H_2O–CH_3CN (99.95:0.05 v/v%). ^{b} Estimated limit of error ±1.1%. ^{c} These k_{ψ} values were calculated by substituting the data in Table 3 into equation (4).

Discussion

Reaction Order.—In order to clarify the dependence of k_{ψ} on [$^{-}$OH], log k_{ψ} was plotted against log [$^{-}$OH] (Figure 4). With 4-nitroacetanilide (**7**)[13] the slope is *ca.* 2 at lower [$^{-}$OH], whereas it was *ca.* 1 at higher [$^{-}$OH], indicating that the rate-limiting step shifts from the $^{-}$OH-catalysed decomposition of In^{-} (k_3 process) to the addition of $^{-}$OH to the carbonyl carbon atom of (**7**) [the k_1 stage, corresponding to (**4**) in the Scheme].

On the other hand, with compounds (**1**) and (**2**) the slope is *ca.* 1, indicating the rate-limiting addition of $^{-}$OH to the carbonyl carbon atom, and with (**3**) the slope changes from *ca.* 1

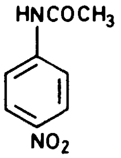
Table 6. Solvent isotope effects in the alkaline hydrolysis of *N*-alkyl-2,4-dinitroacetanilides at 60 °C

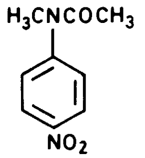
Acetanilide	Solvent	k_1/M^{-1} min^{-1}	a(k_2/k_{-1})	b(k_3/k_{-1})/M^{-1}
N-Methyl-2,4-dinitroacetanilide (**2**)	D_2O	1.56 ± 0.01	0.75 ± 0.5	1 440 ± 250
	H_2O	1.28 ± 0.04	0.26 ± 0.10	460 ± 190
2,4-Dinitroacetanilide (**3**)	D_2O	130 ± 4	17.9 ± 6.4	9 900 ± 2 300
	H_2O	128 ± 1	6.1 ± 2.1	3 190 ± 808

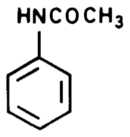
to *ca.* 0 with increased [$^-$OH], indicating that the addition of $^-$OH to the carbonyl carbon atom is rate-limiting and that the pre-equilibrium favours the conjugate base [corresponding to (**6**) in the Scheme] of (**3**) with increased [$^-$OH]. This result is consistent with equation (6).

Rate Constants.—The rate constants and ratios are listed in Table 3 with those of the related acetanilides. For compounds (**1**), (**2**), and (**3**), k_1 decreases in the order (**3**) > (**2**) > (**1**), which corresponds to the order of $\Delta H^{\ddagger}$ [(**1**) > (**2**) > (**3**)], as opposed to the order of $\Delta S^{\ddagger}$ (Table 4). These results show that in the formation of In$^-$ the bulkier *N*-ethyl group exerts a steric effect on the carbonyl carbon atom.[2] These results are also reflected on the a and b values, *i.e.* decreased $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$, with increased stability of In$^-$, and an increase in the b/a value [at 60 °C: 2.6, 1 800, and >3 190 for (**1**), (**2**), and (**3**), respectively]. In other words, the decomposition of In$^-$ mainly occurs *via* the k_3 process involving the hydrogen abstraction by $^-$OH from In$^-$ followed by C–N bond fission of In^{2-}, which shows that as In$^-$ becomes more stable, *i.e.* exists longer, the k_3 process predominates. This tendency is also seen with compounds (**8**)[14] and (**7**) (Table 3).

When an NO_2 group is introduced on to the 4-position of compound (**9**), the k_1 value increases *ca.* 47-fold [(**7**) and (**9**)], although the reaction temperatures are different (Table 3). This is at least partly attributed to the electron-withdrawing effect of the 4-NO_2 group.[13]


(**7**)


(**8**)


(**9**)

Solvent Isotope Effects.—The hydrolyses of compounds (**2**) and (**3**) in protium and deuterium oxide showed the isotope effects given in Table 6. The $k_\psi(H_2O)$ value at [$^-$OH] 0.0117M and the $k_\psi(D_2O)$ value at [$^-$OD] 0.0112M were 0.0128 and 0.0166 min^{-1}, respectively. Then, the $k_\psi(D_2O)/k_\psi(H_2O)$ value is 1.3, which agrees fairly well with the $k_1(D_2O)/k_2(H_2O)$ value (1.2). With (**3**), the $k_\psi(H_2O)$ value at [$^-$OH] 0.001 97M and the $k_\psi(D_2O)$ value at [$^-$OD] 0.002 05M were 0.0998 and 0.0086 min^{-1}, respectively. Therefore, the $k_\psi(D_2O)/k_\psi(H_2O)$ ratio was 0.89, which approximately agrees with the $k_1(D_2O)/k_1(H_2O)$ value (1.0). With (**1**), the $k_\psi(D_2O)/k_\psi(H_2O)$ value was 1.4, 1.4, and 1.4 at [$^-$OH] of 0.100, 0.0398, and 0.023M, respectively.[2] The similarity of these isotope effects shows that the addition of $^-$OH to the carbonyl carbon atom is rate-limiting with (**1**), (**2**), and (**3**), (a, b, and c in Figure 4).[1b,13]

Structure of TS 1.—The processes in which $^-$OH is bound to a substrate generally proceed twice as rapidly in deuterium oxide than in protium oxide if binding is complete.[15] If the order of the new bond is x, then the isotope effect $k_1(D_2O)/k_1(H_2O)$ can be expressed as 2^x.[15] In turn, the order of the new bond can be estimated if the isotope effect is measured. With (**1**), (**2**), and (**3**), the bond orders were found to be 0.48, 0.26, and 0.16, respectively. The value (0.48) for (**1**) is a little uncertain, because the $k_\psi(D_2O)/k_\psi(H_2O)$ [not $k_1(D_2O)/k_1(H_2O)$] ratio was used in the calculation, which is considered fairly reasonable from a consideration of the results with (**2**) (Table 6).

Table 7. Acid dissociation constants for the transition state (TS 2) and *N*-alkyl-2,4-dinitroanilines

Acetanilide	pK_a*[a]	pK_{HA}[b]
N-Ethyl-2,4-dinitroacetanilide (**1**)	12.6	15.3
N-Methyl-2,4-dinitroacetanilide (**2**)	9.8	15.2
2,4-Dinitroacetanilide (**3**)	[c]	15.0

[a] At 60 °C. [b] K_{HA} is defined as the equilibrium constant for the reaction ArNHR + $H_2O \rightleftharpoons$ ArNR$^-$ + H_3O^+.[18–20] All acidity constants were at 25 °C. [c] Not measured.

The transition state for addition (TS1) can be assumed to resemble the reactant rather than the intermediate In$^-$ bearing in mind the bond orders. Relatively large isotope effects, therefore, would not be obtained in the k_1 stage.

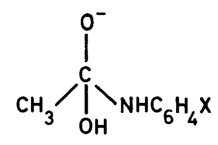
Acid Dissociation of TS 2 to TS 3.—According to Kurz's excellent theory of transition-state acidities,[16] the dissociation of TS 2 (transition state in the k_2 process) to TS 3 (transition state in the k_3 process) to give a proton and TS 3 is expressed as in equation (7). The K_a* values are given by equation (8) (K_W; the autoprotolysis constant of water) and shown in Table 7.

$$(\mathrm{TS}\ 2)^- + H_2O \overset{K_a^*}{\rightleftharpoons} (\mathrm{TS}\ 3)^{2-} + H_3O^+ \qquad (7)$$

$$K_a^* = \frac{k_3}{k_2}K_W \qquad (8)$$

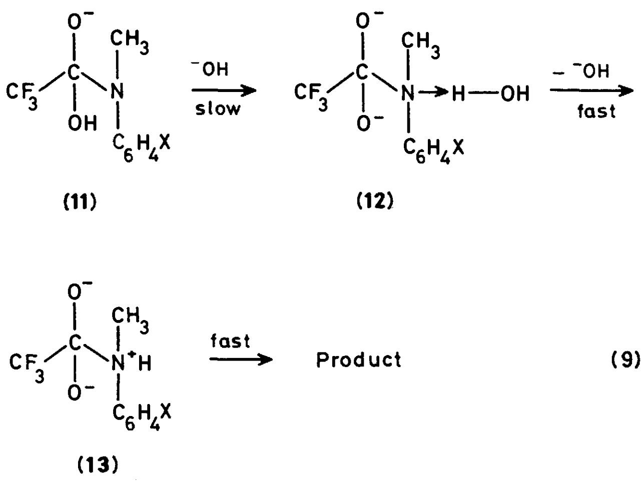
For compounds (**1**) and (**2**), the pK_a* values differ by a factor of *ca.* 3 from each other, although the pK_{HA} values are almost identical. This factor is considered to be independent of the electron-donating effects of the *N*-alkyl substituents (C_2H_5 or CH_3) on the dissociation of the hydroxy proton (corresponding to that of In$^-$) of TS 2. On the other hand, it could be reasonably assumed that the C (carbonyl carbon)–N (amido nitrogen) bond is partially broken in TS 2.[17] As a result, the bond in TS 2 would be broken to a greater extent in (**1**) than in (**2**) owing to the bulkier *N*-ethyl substituent, causing the transmission of the electron-attracting power of 2,4-dinitrophenyl group to reduce, which would, in turn, increase the pK_a (reducing the acidity).

Structure of TS 2 and TS 3.—Bender and Thomas[21] proposed a simple proton transfer for the rate-limiting decomposition of the tetrahedral intermediate (**10**) (corresponding to In$^-$) in the alkaline hydrolysis of 4-substituted acetanilides. Later, in the alkaline hydrolyses of substituted *N*-methyltrifluoroacetanilides, Schowen *et al.*[6] postulated this

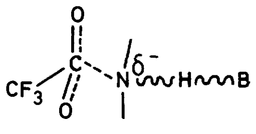


(10)

proton transfer for the rate-determining decomposition of the intermediate (*11*) (corresponding to In^-) to generate the other intermediate (**12**) (corresponding to In^{2-}) giving (**13**), and, then, products as in equation (9). Their proposal was based on the general catalysis of the decomposition of (**11**) in buffered solutions and reasonably large solvent isotope effects on k_2 [(**11**) $\longrightarrow$ products] and k_3 [(**11**) $\longrightarrow$ (**12**) $\longrightarrow$ (**13**) $\longrightarrow$ products].[6]



(9)



(14)

In more recent work Schowen *et al.* proposed the detailed structures for TS 2 (k_2 process) and TS 3 (k_3 process), to which the basicities of the aniline moiety were strongly related.[17] As they proposed, if $pK_b > 9$ (K_b is defined as the equilibrium constant for the reaction $ArNHR + H_3O^+ \rightleftharpoons ArNH_2R^+ + H_2O$) then (**14**) is a reliable representation of TS 2 (B; H_2O) and TS 3 (B; ^-OH) (the broken and wavy lines represents bond-breakage and catalyst solvation respectively). This also is the case with the present results and is consistent with the $a(D_2O)/a(H_2O)$ and $b(D_2O)/b(H_2O)$ values (Table 6).

In conclusion, the general base-catalysed hydrolysis can be assumed to take place *via* the k_2 process by considering the $a(D_2O)/a(H_2O)$ (larger than 1) and pK_a values and the sodium hydroxide concentrations used in the experiments (Table 2 and 5).

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Received 23rd *June* 1986; *Paper* 6/1266