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Alkaline Hydrolysis of *N*-Ethyl-2,4-dinitroacetanilide

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The alkaline hydrolyses of anilides have been studied extensively,[2-4] but those of anilides bearing ortho substituents seem to be a rather unexplored field.[5] As was shown for *p*-nitroacetanilide (1),[4,6-8] the reaction mechanism of the base-catalyzed hydrolyses of anilides with strongly electron-withdrawing substituents on the phenyl moiety differs somewhat from the general one[2] (Scheme I). The difference is caused by higher acidity of leaving-group nitroanilines. While the k_2 step is said to be a subject of general acid catalysis, the breakdown of doubly charged intermediate (k_3') occurs smoothly without any catalytic assistance.

The results obtained in the case of the alkaline hydrolysis of *N*-ethyl-2,4-dinitroacetanilide (**2**) are expected to conform to the reaction mechanism proposed for all other anilides, but the rate-determining step may change for such sterically hindered derivatives. That this prediction is fulfilled will be developed in latter sections.

Results

Kinetic Runs. The hydrolysis of **2** with a large excess of hydroxide ion was followed spectrophotometrically in water containing 0.05% (v/v) of acetonitrile (μ = 0.8 M, NaCl), and the reaction showed very good pseudo-first-order kinetics. Table I shows the sodium hydroxide concentration dependence of k_ψ (pseudo-first-order constant). At every temperature studied the pseudo-first-order rate constant (k_ψ) showed a nonlinear dependence (concave upward) on the hydroxide ion concentration (Table I). Calculated k_ψ values were obtained from eq 1 by using those of k_1, k_2/k_{-1}, and k_3/k_{-1} (Table II and Scheme II). The agreement between the observed and calculated k_ψ values is fairly satisfactory.

If the hydrolysis of **2** follows Scheme I, eq 1 holds,[2,4]

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

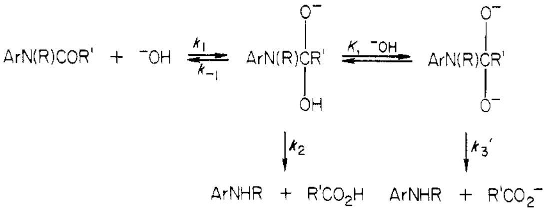
$$a = k_2/k_{-1},\ b = k_3/k_{-1}$$

which applies to the alkaline hydrolyses of almost all formanilides or acetanilides. The above-described dependence supports the correctness of eq 1 very well. In order to obtain detailed information about the mechanism, we studied the hydroxide ion concentration dependence of $k_\psi/[^-\mathrm{OH}]$ at 50 °C (Figure 1; curve is convex upward). The result clearly shows that eq 2 holds very well. The

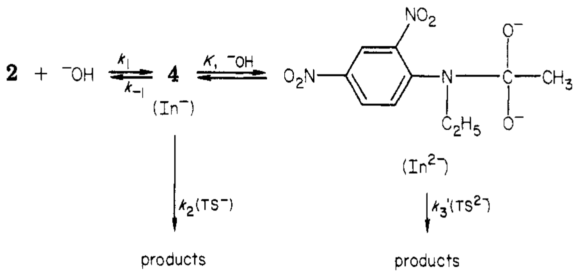
$$\frac{k_\psi}{[^-\mathrm{OH}]} = k_1\frac{a + b[^-\mathrm{OH}]}{1 + a + b[^-\mathrm{OH}]} \qquad (2)$$

data in Table I were used to calculate the kinetic parameters, k_1, a, and b of eq 1. The calculations were performed by the nonlinear least-squares method (with a HITAC 8800/8700 located at the Computer Center of the University of Tokyo, Program SALS MODEL[9]). The initial values necessary for calculation were estimated from the plots of $k_\psi/[^-\mathrm{OH}]$ vs. $[^-\mathrm{OH}]$ (Figure 1). The k_1 values and partioning ratios are shown in Table II, in which the kinetic parameters at 20 °C are extrapolated from Arrhenius plots (Figure 2; but the log (k_2/k_{-1}) vs. $1/T$ plot is not shown). Activation parameters are listed in Table II.

Scheme I



Scheme II[a]



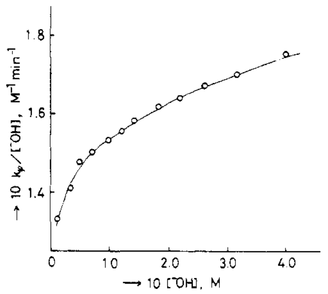


Figure 1. Relationship between $k_\psi/[^-\mathrm{OH}]$ and $[^-\mathrm{OH}]$ at 50 °C.

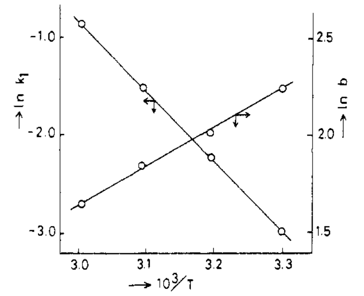


Figure 2. Arrhenius plots.

Salt Effects. A negative salt effect was observed (Table III): the k_ψ value at μ = 0.05 M decreases by ca. 23% at μ = 0.80 M. This effect might arise from the ionic nature of **2**, which is composed of the *Z* and *E* isomers.[10,11] The NMR spectra show that the singlets of the acetyl methyl protons appear at δ 2.20 and 1.82 for the (*Z*) and (*E*) isomers, respectively, with the ratio (*Z*/*E*) being 1.35.

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Table I. Rate Constants for the Alkaline Hydrolysis of *N*-Ethyl-2,4-dinitroacetanilide (2)[a]

10^2[$^-$OH], M	10^3k_ψ, min^{-1} obsd	10^3k_ψ, min^{-1} calcd[c]	10^2[$^-$OH], M	10^3k_ψ, min^{-1}[b] obsd	10^3k_ψ, min^{-1}[b] calcd[c]
	20 °C			30 °C	
3.00	0.705	0.379	3.00	0.896	0.907
5.00	0.768	0.673	5.00	1.56	1.58
7.00	1.17	0.991	7.00	2.36	2.30
10.0	1.62	1.50	10.0	3.54	3.44
12.0	2.01	1.86	12.0	4.26	4.24
14.0	2.46	2.23	14.0	5.04	5.06
18.0	3.09	2.99	18.0	6.74	6.75
22.0	3.95	3.77	22.0	8.26	8.50
26.0	4.55	4.57	26.0	10.3	10.3
32.0	5.86	5.80	32.0	12.9	13.0
40.0	7.56	7.47	40.0	16.9	16.8
	40 °C			50 °C	
3.00	2.11	2.11	1.00	1.34	1.40
5.00	3.58	3.61	3.00	4.24	4.32
7.00	5.28	5.17	5.00	7.40	7.35
10.0	7.66	7.61	7.00	10.5	10.5
12.0	9.25	9.29	10.0	15.2	15.3
14.0	11.1	11.0	12.0	18.6	18.7
18.0	14.4	14.5	14.0	22.1	22.1
22.0	18.1	18.2	18.0	29.4	29.1
26.0	22.1	21.9	22.0	35.6	36.3
32.0	27.7	27.7	26.0	43.8	43.7
40.0	35.6	35.5	32.0	53.7	55.0
			40.0	70.6	70.5
	60 °C				
3.00	9.12	9.47		60 °C	
5.00	10.0	16.0	18.0	62.5	62.0
7.00	22.6	22.7	22.0	76.8	77.0
10.0	32.9	33.1	26.0	92.2	92.4
12.0	40.6	40.1	32.0	115	116
14.0	47.7	47.3	40.0	147	148

[a] [*2*]$_0$ 5 × 10^{-5} M; μ = 0.8 (NaCl). [b] Estimated limit of error ±1.5%. [c] Calculated from eq 1 by using the values of k_1 and k_2/k_{-1} shown in Table II.

Table II. k_1 Values, Partitioning Ratios, and Activation Parameters for the Alkaline Hydrolysis of *N*-Ethyl-2,4-dinitroacetanilide (2)

(A) Rate Data

temp, °C	10^2k_1, M^{-1} min^{-1}	k_2/k_{-1}	k_3/k_{-1} M^{-1}
20[a]	2.20 ± 0.03	1.00 ± 0.13	11.5 ± 3.1
30	5.05 ± 0.04	1.21 ± 0.17	9.3 ± 2.5
40	10.8 ± 0.7	1.65 ± 0.25	7.3 ± 2.1
50	21.7 ± 0.3	1.78 ± 0.56	6.3 ± 3.5
60	46.0 ± 5.8	2.03 ± 0.60	5.2 ± 2.6
	(B) Thermodynamic Data		
E, kcal mol^{-1}	14.7 ± 1.0	3.3 ± 2.4	−3.7 ± 7.0
$\Delta H^\ddagger$, kcal mol^{-1}	14.1 ± 1.0	2.7 ± 2.4	−4.4 ± 7.0
$\Delta S^\ddagger_{303}$, eu	−9.8 ± 3.4	−49 ± 8	−68 ± 23

[a] Extrapolated values.

Solvent Isotope Effects. At 36 °C the solvent isotope effect ($k_\psi^{H_2O}/k_\psi^{D_2O}$) was 0.68, 0.69, and 0.72 at [$^-$OH] of 0.1, 0.0398, and 0.023 M, respectively. The effect results from rate-determining addition of hydroxide ion, which is in accord with a slope of unity in the plot of log k_ψ vs. log [$^-$OH].[2,4,6]

Discussion

Reaction Mechanism. The plots of k_ψ/[$^-$OH] against [$^-$OH] demand the presence of an intermediate and its hydroxide ion catalyzed breakdown (Figure 1), so one can generally adopt Scheme I and therefore calculate the partitioning of the intermediate using eq 1.

Table III. Salt Effects on the Alkaline Hydrolysis of *N*-Ethyl-2,4-dinitroacetanilide (2) at 40 °C

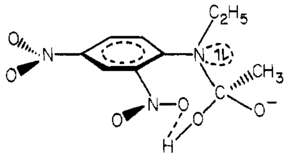
μ (NaCl), M	10^3k_ψ, min^{-1}	μ (NaCl), M	10^3k_ψ, min^{-1}
0.05	4.67	0.50	4.00
0.10	4.55	0.80	3.58
0.30	4.18		

[a] [**2**]$_0$ = 5 × 10^{-5} M; [$^-$OH] = 5.00 × 10^{-2} M.

The rate constant of intermediate formation (k_1) is ca. 4 times smaller than that reported for 1[4] (k_1 = 0.221 M^{-1} min^{-1}; a = 0.077; b = 10.6 at 30 °C). This shows a different result from what can be expected from the pK_a values of *N*-ethyl-2,4-dinitroaniline (15.2)[12] and *p*-nitroaniline (18.4).[15] Furthermore, the pattern of intermediate breakdown is also different from that for 1. It should be noted here that the k_2/k_{-1} value observed for 2 is ca. 16 times larger than that for 1, and, therefore, even at low [$^-$OH] the intermediate breakdown is not a rate-determining step, in due consideration of the slope of unity for the log k_ψ vs. log [$^-$OH] plot.

The NMR studies of *N*-methyl-2-nitroacetanilide[16] revealed the presence of the rotational barriers about the carbon (C_1)-nitrogen (amino) bond, so the π-electron system of the acetamide group is effectively decoupled from the electron-withdrawing effects of an aryl substituent. Since the latter rotational barrier is imposed only by steric requirements,[16] it would increase when *N*-methyl group is replaced by an *N*-ethyl one. Although the NMR spectra of 2 showed a very similar pattern to that of *N*-methyl-2,4-dinitroacetanilide (3),[16] the observed coalescence temperature was higher for 2 than for 3, showing the presence of a rotational barrier in 2 (see Experimental Section). Therefore, the lower reactivity of 2 could be interpreted to mean a decrease in the activating effect of the nitro groups due to a loss in coplanarity of the benzene moiety and the double bond character of the amide bond (C⌐N). Both isomers *Z* and *E* are considered to be less reactive toward alkaline hydrolyses.

Examination of the molecular model of the intermediate for 2 shows that the rotation around the ring carbon (C_1)–nitrogen (amino) bond is still strongly hindered, so that the electron-withdrawing character of the dinitro aromatic system should not affect the reaction site too much. On the other hand, such a structure can be stabilized by an intramolecular hydrogen bond between the 2-nitro oxygen and the hydroxyl hydrogen atoms (4, Scheme II). As a result, when 4 converts to the products, greater steric strain is released than when the intermediate from 1 does. Balance of release of steric strain and stabilization by hydrogen bonding (with the former being



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(12) The pK_a value for *N*-ethyl-2,4-dinitroaniline can be estimated from both the pK_a of *N*-ethyl-*p*-nitroaniline[13] and the linear free energy relationships derived for the pK_a of nitro anilines.[14,15]

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predominant) may correspond to the result that **4** converts to the products faster than the intermediate from **1** does.

Applying Kurz's theory of transition-state acidities,[17a] one can consider the dissociation of TS^- to TS^{2-} as shown in eq 3, from which eq 4 is derived (Scheme II). K_w is the

$$TS^- \overset{K_a^*}{\rightleftharpoons} TS^{2-} + H^+ \tag{3}$$

$$K_a^* = (k_3/k_2)K_w \tag{4}$$

ionic product of water. The pK_a^* values (30 °C) calculated for **2** and **1** are 13.0 and 11.8,[18] respectively, which are close to those of 2-chloro (pK_a 14.31)[19] and 2,2-dichloroethanols (pK_a 12.89)[20] and larger than those of phenols[21] and carboxylic acids.[22] The ratio of $[TS^-]$ to $[TS^{2-}]$ for **2** can be obtained by use of the pK_a^* value. Those values at 30 °C are calculated as 3.98, 0.63, and 0.32 at $[^-OH]$ = 0.030, 0.220, and 0.400 M, respectively. That is to say, at low $[^-OH]$ **4** mainly decomposes to the products via the k_2 step, and at high $[^-OH]$ it decomposes mainly via the k_3 step.

Transition States. The k_3/k_{-1} and k_2/k_{-1} values (Table II) show that both pathways are important for the breakdown of **4**, and a large and negative ΔS^{*}_{303} strongly suggests that some water molecules are involved in TS^- and TS^{2-}.[23]

On the other hand, it has been proved that the k_2 step is generally assisted by the general-acid catalysis, and the k_3 step involves proton transfer (for a "poor" leaving group) or solvation to a cleaving bond (for a "good" leaving group).[24]

Solvent Isotope Effects. The inverse isotope effect seems to be caused mainly by $k_1^{H_2O}/k_1^{D_2O}$ (ca. 0.74 was reported by Kershner and Schowen[17b]), because the addition step (k_1) is rate-determining.[2,4,6] Reactions of this type have been suggested to involve inverse isotope effects.[25] An example is the reacton of 2-chloroethanol with base, giving ethylene oxide.[25-27] Furthermore, it has been discussed in detail that this effect is expected in the alkaline hydrolyses of amides.[28-30]

Negative Salt Effect. The observed salt effects are consistent with the existence of a partial positive charge on either the carbonyl carbon or the amide nitrogen. That is, the former charge would disappear from the reactant to the transition state. Furthermore, **2** exists in two isomers ([*Z*] and [*E*]) in polar solvents (see the NMR spectra of **2** in Experimental).[31] The two isomers have the $>C{=}N^+<$ resonance form. Therefore, a positive charge on the amide nitrogen would decrease from the reactant to the transition state. Such a decrease in positive charge would correspond to the negative salt effect.

Experimental Section

Materials. *N*-Ethyl-2,4-dinitroacetanilide (**2**) was prepared from *N*-ethyl-2,4-dinitroaniline in acetic anhydride containing a very small amount of H_2SO_4.[32] Three subsequent recrystallizations from ethanol gave a pure product: mp 111.5-112 °C (uncor); IR ($CHCl_3$) $\nu_{C=O}$ 1675 cm^{-1}; NMR (Me_2SO-d_6, 40 °C) δ 1.10 (3 H, br, m, $CH_2C\mathbf{H}_3$), 1.75, 2.16 (3 H, 2 br s, $COCH_3$) [corresponding to the forms *E* and *Z*, respectively ($[Z]/[E]$ = 1.35)], 3.8 (2 H, br m, $C\mathbf{H}_2CH_3$), 7.89, 8.58, 8.68 (3 × 1 H, d, q, d, AMX aromatic system, J_{AM} = 8.5 Hz, J_{MX} = 2 Hz, J_{AX} = 0); NMR (Me_2SO-d_6, 72 °C) δ 1.10 (3 H, *t*, $CH_2C\mathbf{H}_3$, J = 7 Hz), 1.97 (3 H, s, $COCH_3$), 3.76 (2 H, q, $C\mathbf{H}_2CH_3$, J = 7 Hz), 7.84, 8.52, 8.72 (3 × 1 H, d, q, d, J_{AM} = 8 Hz, J_{MX} = 2 Hz, J_{AX} = 0). Anal. Calcd for $C_{10}H_{11}N_3O_5$: C, 47.44; H, 4.38; N, 16.60. Found: C, 47.56; H, 4.37; N, 16.48.

Acetonitrile was dried with calcium hydride, distilled, and stored over molecular sieves. Sodium hydroxide used was 0.1 N standard solution (Wako). Sodium chloride used was a Wako guaranteed reagent. Deuterium oxide (99.175% D) and sodium deuterium oxide (40% solution) from Merck were used. These materials were handled with syringes and serum-capped volumetric flasks.

Kinetics. The reaction rates were measured spectrophotometrically at 360 nm with a Hitachi 139 spectrophotometer equipped with a thermostated cell compartment with temperature control to within ±0.05 °C. Prepared sodium hydroxide solutions were standardized with 0.01 N HCl and the 3-mL portions were thermostated in a stoppered cell. After 1.5 μL of 0.1 M stock solution of **2** in acetonitrile had been added, the reaction was calculated with the Guggenheim method. All rate constants listed are averages of two or more runs, their agreement usually being within ±1.5%. The activation energies and entropies were calculated as described by Bunnett.[33]

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(18) The value for **1** was obtained with k_2/k_{-1} and k_3/k_{-1} as reported by DeWolfe and Newcomb[4] and the one for **2** with the *a* and *b* values in Table II.

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Hydride Shifts in Cyclohexyl Tosylate Solvolysis in Fluorinated Alcohols[1]

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Hydride shifts from positions beyond $C\beta$ to a carbonium ion center are usually considered to be a unique feature of medium-ring solvolysis reactions, where transannular proximity can lead to such rearrangements.[2] Acyclic as well as cyclohexyl derivatives show a very small hydride shift contribution besides 1,2-migration.[3] No tertiary

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