Kinetics and Mechanism of Alkaline Hydrolysis of *N*-(2-Bromoethyl)phthalamic Acid

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The extensive mechanistic studies of aqueous cleavage of the amide bond[1-11] have been the subject of significant interest for the past nearly three decades partly because such bond cleavage is involved in the degradation of peptides and proteins. The alkaline hydrolyses of various substituted acetanilides have been most extensively studied. Biechler and Taft[12] were the first to propose the formation of oxy dianionic tetrahedral intermediates in the alkaline hydrolysis of substituted acetanilides. They considered ionized substrate as unreactive toward the product formation. Mader[13] has, however, presented evidence that ionized substituted anilide also give products. Recently, we have studied the aqueous cleavage of phthalimide in a strongly alkaline medium.[14] In this paper we described the observed results and the probable mechanisms for alkaline hydrolysis of *N*-(2-bromoethyl)phthalamic acid.

Experimental Section

Materials. *N*-(2-Bromoethyl)phthalimide (NBPH) was obtained from Eastman Chemical Co., and its stock solution was prepared in absolute ethanol. All other reagents used were of reagent grade.

Kinetics. All the kinetic runs were carried out at 25 °C keeping ionic strength constant at 2.0 M by the use of potassium chloride. For a typical kinetic run the reaction mixture containing sodium hydroxide and potassium chloride was equilibrated at 25 °C for about 10 min. The reaction was then initiated by adding 25 μL of 0.01 M NBPH solution to the reaction mixture. The total volume of the reaction mixture containing 1% ethanol was 2.5 mL. The appearance of phthalic acid was monitored spectrophotometrically at 265 nm using a Cary 16 UV–visible spectrophotometer. The temperature of the reaction mixture was controlled by the use of the thermostated cell compartment of the spectrophotometer. The kinetic conditions employed were such that the formation of intermediate product, *N*-(2-bromoethyl)phthalamic acid (1), from NBPH was more than 2.7×10^3 times faster than its further conversion to phthalic acid. The observed data obeyed a first-order rate law, and the observed pseudo-first-order rate constants (k_{obsd}) were evaluated from eq 1 using

$$A_{obsd} = \epsilon_{app}x_0[1 - \exp(-k_{obsd}t)] + A_0 \qquad (1)$$

a nonlinear least-squares technique.[15] In eq 1, ϵ_{app} (apparent extinction coefficient), k_{obsd}, and A_0 (absorbance at $t = 0$) were considered as unknown parameters, and x_0 represents the initial concentration of NBPH. Almost all the kinetic runs were carried out in duplicate, and the average deviations were less than 4% for most of the runs.

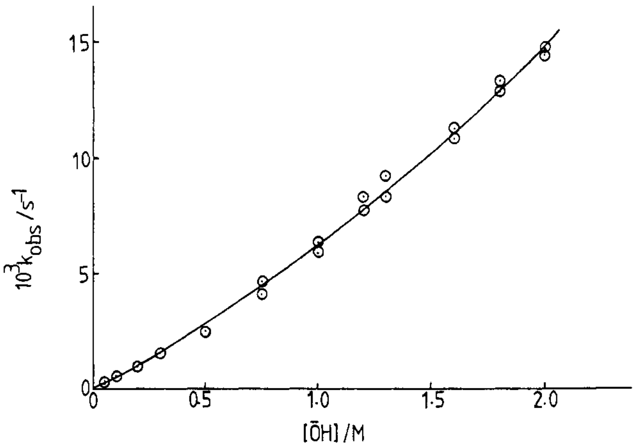
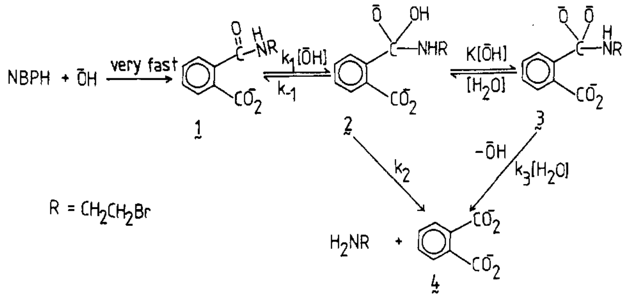


Figure 1. Dependence of k_{obsd} on $[OH^-]$ for the aqueous cleavage of *N*-(2-bromoethyl)phthalamic acid. The solid line is drawn through the least-squares calculated points using eq 2 with $A = 5.03 \times 10^{-3}$ M^{-1} s^{-1} and $B = 1.18 \times 10^{-3}$ M^{-2} s^{-1}.

Scheme I



Results and Discussion

The reaction rate for the second step of hydrolysis of NBPH was studied within the sodium hydroxide ion concentration range of 0.05–2.0 M at 25 °C. The results are shown in Figure 1. The first-order rate constants were empirically fitted to eq 2 within the $[OH^-]$ range of 0.05–2.0

$$k_{obsd} = A[OH^-] + B[OH^-]^2 \qquad (2)$$

M. The kinetic electrolyte effect as a possible cause for the deviations of the observed points from linearity is presumably unlikely because no such deviations were observed in the alkaline hydrolyses of methyl *p*-hydroxybenzoate[16] and monomethyl phthalate[17] within the sodium hydroxide ion concentration range of 0.02–2.0 M at a constant ionic strength of 2.0 M maintained by KCl. The unknown empirical parameters *A* and *B* were calculated by the use of the least-squares technique and the respective values thus obtained are $(5.03 \pm 0.26) \times 10^{-3}$ M^{-1} s^{-1} and $(1.18 \pm 0.16) \times 10^{-3}$ M^{-2} s^{-1}. The spontaneous reaction can be neglected compared to $A[OH^-] + B[OH^-]^2$ within the $[OH^-]$ range of the present study. The mechanism of the second step of hydrolysis of NBPH is shown in Scheme I.

Considering intermediates 2 and 3 as transient reactive species and applying the steady-state approximation, one can get eq 3.

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(1) DeWolfe, R. H.; Newcomb, R. C. *J. Org. Chem.* **1971**, *36*, 3870 and references therein.

(2) (a) Pollack, R. M.; Dumsha, T. C. *J. Am. Chem. Soc.* **1973**, *95*, 4463. (b) *FEBS Lett.* **1974**, *38*, 292. (c) *J. Am. Chem. Soc.* **1975**, *97*, 377.

(3) Pollack, R. M. *J. Org. Chem.* **1974**, *39*, 2108.

(4) Stauffer, C. E. *J. Am. Chem. Soc.* **1972**, *94*, 7887; *Ibid.* **1974**, *96*, 2489.

(5) Menger, F. M.; Donchue, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 432.

(6) Yamana, T.; Mizukami, Y.; Tsuji, A.; Yasuda, Y.; Masuda, K. *Chem. Pharm. Bull.* **1972**, *20*, 881.

(7) Khan, M. N.; Khan, A. A. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1176; *Indian J. Chem.* **1975**, *13*, 485.

(8) Khan, M. N.; Ahmed, R.; Khan, A. A. *Indian J. Chem.* **1976**, *14A*, 961.

(9) Bruice, P. Y.; Mautner, H. G. *J. Am. Chem. Soc.* **1973**, *96*, 1582.

(10) Drake, D.; Schowen, R. L.; Jayaraman, H. *J. Am. Chem. Soc.* **1973**, *95*, 454.

(11) Komiyama, M.; Bender, M. L. *Bioorg. Chem.* **1978**, *7*, 133.

(12) Biechler, S. S.; Taft, R. W. *J. Am. Chem. Soc.* **1957**, *79*, 4927.

(13) Mader, P. M. *J. Am. Chem. Soc.* **1965**, *87*, 3191.

(14) Khan, M. N.; Khan, A. A. *J. Chem. Soc., Perkin Trans. 2* **1979**, 796.

(15) Khan, M. N.; Olagbemiro, T. O.; Umar, U. Z. *Tetrahedron* **1983**, *39*, 811.

(16) Khan, M. N.; Olagbemiro, T. O. *J. Chem. Res.* (*Synop.*) **1985**, 166.

(17) Khan, M. N., unpublished observations.

0022-3263/85/1950-5859$01.50/0

$$k_{\text{obsd}} = \frac{k_1[\text{OH}^-][k_2 + k_3K[\text{OH}^-]]}{k_{-1} + k_2 + k_3K[\text{OH}^-]} \tag{3}$$

The value of k_{-1}/k_2 could be estimated by a procedure described as follows. In the scheme, k_{-1} and k_2 represent the rate constants for the expulsion of leaving groups OH (pK_a of H_2O is 15.7) and RNH (pK_a of RNH_2 is ~27), respectively. The pK_a of $C_6H_5NH_2$ is 27,[18] and σ_I values for C_6H_5 and CH_2CH_2Br are nearly same (Appendix). The push provided by the other groups attached to the reaction center in the expulsion of the leaving groups in the k_{-1} step and k_2 step may be expected to be same, but the higher acidity of H_2O compared to that of RNH_2 could result in k_{-1} being significantly larger than k_2. However, the relatively larger leaving ability of OH group compared to RNH group from **2**, based on the difference of pK_a of their conjugate acids, could be partially off set by the larger carbon basicity of oxyanions than that of amines, for a given proton basicity. It may be worth mentioning here that an approximate value of k_{-1}/k_2 might be calculated from the Jencks' equation (eq 4),[19] which is derived for

$$\log (k_O/k_N) = -0.9\text{p}K_O + 0.7\text{p}K_N + C_t \tag{4}$$

acetate esters. In eq 4, $k_O \equiv k_{-1}$ and $k_N \equiv k_2$. If we assume that the eq 4 is valid for the present system, then the ratio k_{-1}/k_2 may be estimated to be 2.5×10^2 considering pK_O = 15.7, pK_N = 27, and $C_t = -2.40$. Although this analysis is far from exact, it indicates that $k_{-1} > k_2$.

It appears from structures **2** and **3** that k_3 may be larger than k_2 because of the relatively larger push experienced by the leaving group in the k_3 step. But $K[\text{OH}^-]$ should be far less than unity because $K = (K_a/K_w)[H_2O]$ where K_a is the ionization constant of the hydroxyl group of **2**. The value of K_a is estimated to be significantly smaller than K_w (Appendix). Thus, it may not be unreasonable to assume that $k_3K[\text{OH}^-]$ might not be very different from k_2 even at the highest concentration of $[\text{OH}^-]$ attained in the present study. These conclusions lead to a conceivable assumption that $k_{-1} > (k_2 + k_3K[\text{OH}^-])$, and application of this assumption reduces eq 3 to eq 5. Similar assumption has been considered recently by Young et al.[20] to explain the observed k_{obsd}–$[\text{OH}^-]$ profile for the cleavage of dichloro-*N*-methylacetanilide. Equation 5 is similar to eq 2 with $A = k_1k_2/k_{-1}$ and $B = k_1k_3K/k_{-1}$. The observed value of k_1k_2/k_{-1} of 5.03×10^{-3} M^{-1} s^{-1} may be compared with the hydroxide ion catalyzed bimolecular rate constants, k_{OH}, for aqueous cleavages of benzamide ($k_{OH} = 1.5 \times 10^{-3}$ M^{-1} s^{-1} at 100.4 °C)[21] and phthalamic acid ($k_{OH} = 5.9 \times 10^{-5}$ M^{-1} s^{-1} at 85 °C).[14] The estimated value of k_{-1}/k_2 of 2.5×10^2 could be used to calculate k_1 from the observed value of A and the value thus obtained is ~1.2 M^{-1} s^{-1}. The value of k_1 of 1.2 M^{-1} s^{-1} is ~18 times smaller than the k_1' (21.9 M^{-1} s^{-1}) obtained for the cleavage of NBPH. Although the estimated value of k_{-1}/k_2 is not very reliable, the ratio k_1'/k_1 of ~18 is not unreasonable because hydroxide ion attack at carbonyl carbon may not be very sensitive to the pK_a of the leaving group.

$$k_{\text{obsd}} = (k_1/k_{-1})[k_2 + k_3K[\text{OH}^-]][\text{OH}^-] \tag{5}$$

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Appendix

Estimation of pK_a of Hydroxyl Group of 2. Following the approach of Fox and Jencks,[22] the approximate pK_a of the hydroxyl group of species **2** has been estimated as follows. The values of σ_I for $NHCH_2CH_2Br$ and *o*-$O_2CC_6H_4^-$ substituents are not known and the value of σ_I for O^- substituent is −0.12.[23] On the basis of values of σ_I for NH_2, $NHNH_2$, NMe_2, and CH_2CH_2Br of 0.12, 0.15, 0.06, and 0.08, respectively, it may not be unreasonable to take σ_I for $NHCH_2CH_2Br$ as 0.14 which is between the values of σ_I for NH_2 and $NHNH_2$. [The value of σ_I for Br is 0.44, and making the allowance of falloff factor of 2.0 per methylene group,[22] σ_I for CH_2CH_2Br could be estimated to be 0.11. But σ_I for Cl is 0.46 and σ_I for CH_2Cl is 0.17, which indicate that the falloff factor is ~2.7. Using this value of falloff factor, σ_I for CH_2CH_2Br was found to be 0.06. The average value (0.08) of 0.11 and 0.06 could be considered as the appropriate value of σ_I for CH_2CH_2Br.] Again, on the basis of a pK_a of 15.7 for CH_3OH[24] and σ_I of −8.2,[22] correction for O^-, $NHCH_2CH_2Br$ and C_6H_5 substituents $(-8.2 \times (-0.12 + 0.14 + 0.10) = -1.0)$ gives a pK_a of 14.7 for hydroxyl group of $O^-C(C_6H_5)(NHCH_2CH_2Br)OH$. The replacement of *o*-H by *o*-CO_2^- may be assumed to increase pK_a of the hydroxyl group of $O^-C(C_6H_5)(NHCH_2CH_2Br)OH$ by ~1.3 pK, the difference between pK_2 of phthalic acid (5.51)[25] and pK_a of benzoic acid (4.19).[25] Thus, the estimated pK_a of the hydroxyl group of **2** is 16.0 (=14.7 + 1.3). Although the estimated value of 16 for pK_a of hydroxyl group of **2** is not very reliable for various reasons such as relatively unreliable value of σ_I for the electrically charged group[23] O^-, it certainly indicates that pK_a > pK_w.

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[18] Broxton, T. J.; Deady, L. W.; Rowe, J. E. *J. Org. Chem.* **1980**, *45*, 2404 and reference cited therein.

[19] Gressor, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963.

[20] Young, J. K.; Pazhanisamy, S.; Schowen, R. L. *J. Org. Chem.* **1984**, *49*, 4148.

[21] Bunton, C. A.; Nayak, B.; O'Connor, C. *J. Org. Chem.* **1968**, *33*, 572.

[22] Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436.

[23] Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley: New York, 1975.

[24] Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.

[25] Weast, R. C., Ed. "CRC Handbook of Chemistry and Physics"; CRC Press Inc.: Cleveland, OH, 1982.

Addition of Cyclopropylphosphonates to Aldehydes

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Cyclopropylphosphonates are not easily obtainable by C–P bond-forming reactions,[1] and their synthetic application has scarcely been investigated. The previous paper[2] described the reductive phosphonation of *gem*-dibromocyclopropanes with trialkyl phosphite, triethylamine, and water to afford dialkyl cyclopropylphosphonates under mild reaction conditions. We now report the reaction of

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[1] Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. Reid, J. R.; Marmor, R. S. *Ibid.* **1978**, *43*, 999.

[2] Hirao, T.; Hagihara, M.; Ohshiro, Y.; Agawa, T. *Synthesis* **1984**, 60.

[3] Baker, R.; Sims, R. J. *Synthesis* **1981**, 117.

0022-3263/85/1950-5860$01.50/0