

Mechanism of the Hydrolysis of 2-Phenyl-4H,5H,6H-3-methyl-3-thiazinium Perchlorate Derivatives

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Received May 27, 1999

Hydrolysis reactions of 2-phenyl-4H,5H,6H-3-methyl-3-thiazinium perchlorate (PTP) and its derivatives at various pH have been investigated kinetically. The hydrolysis is quantitative, producing *N*-3-mercaptopropyl-*N*-methylbenzamide as the only product in the all pH ranges. The observed rate of hydrolysis of PTP was always of the first-order. For hydrolysis from PTP, Hammett ρ values were 0.53, 0.84 and 1.13 for pH 5.0, 8.0, and 10.0, respectively. Bronsted β value was 0.53 for general base catalysis. This reaction is catalyzed by general base at low acetate concentration. However, as the amount of base becomes larger, the rate of hydrolysis reaction approaches the limiting values. The plot of $\log k$ vs. pH shows that the rate constants (k_i) are two different regions in the profile; one part is directly proportional to hydroxide ion concentration and the other is not. On the bases of these results, the plausible hydrolysis mechanism and a reaction equation were proposed: Below pH 4.5, the hydrolysis was initiated by the addition of water to α -carbon. Above pH 9.0, the hydrolysis was proceeded by the addition of hydroxide ion to α -carbon. However, in the range of pH 4.5-8.0, these two reactions occurred competitively.

Introduction

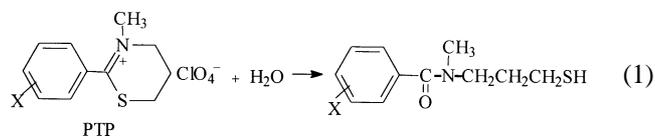
Thiazolium salts are versatile catalysts for many organic and biochemical reactions. The best known representative of these compounds is thiamine pyrophosphate (vitamin B₁), which acts as cofactor in some important enzymatic reactions.¹

Up to the present only derivatives of completely unsaturated heterocyclic bases, such as those of the pyridine, quinoline, thiazole and benzothiazole series, have been used for the preparation of cyanine dyes. It was therefore of interest to examine the reactivity of methyl group in quaternary salts of 2-alkylthiazoline, since the nucleus of this base is partly saturated. The dyes derived from 2-alkylthiazoline are of special interest because they absorb at shorter wave lengths than the corresponding derivatives of any other heterocyclic base thus far applied to cyanine dye formation. The dyes are also photographic sensitizers, some being of considerable power.²

In spite of many uses of thiazolines and thiazines as dye, medicament, sensitizer and intermediates in organic synthesis,^{3a-3c} two compounds have been the subject of only a few kinetic studies.^{4a-4c}

Martin and Herdick^{4a} studied mechanism for the hydrolysis of 2-methyl-thiazoline in acidic solution. They found that the hydrolysis of its is sensitive to the reaction conditions and the structure of the substrates.

In this paper, we wish to reveal the mechanism of hydrolysis of 2-phenyl-4H,5H,6H-3-methyl-3-thiazinium perchlorate (PTP) based on the substituent effect, Bronsted plot and general base catalysis effect on the rate constant and its change with pH (eq. 1).



Experimental Section

General procedure. All of the reagents were commercially available and used without further purification. Kinetic runs were obtained from a Hitachi Recording spectrophotometer 150-20 with thermostated cuvette holders. All of the buffer solutions were prepared from reagent grade chemicals and the ionic strength was kept constant to 0.1 M by adding sodium chloride.

Synthesis of PTP. PTP and its derivatives were prepared through four-step reactions which started from the reaction of 3-bromopropylamine hydrobromide with benzyl chloride derivatives by the well-known method.^{2,3c,5}

Product of hydrolysis. PTP (3.0 g, 0.01 mol) was dissolved in 50 mL of a buffer solution (pH = 9.0) of boric acid and sodium hydroxide. The resultant solution was stirred for 10 hrs at room temperature and was acidified with 6 N HCl at pH 2.0. The resulting solution was extracted with diethyl ether (50 mL), washed with water, dried over anhydrous MgSO₄. The organic layer was evaporated to give *N*-3-mercaptopropyl-*N*-methylbenzamide as a color liquid: IR (neat, cm⁻¹): 2250 (SH), 1640 (C=O); ¹H NMR (DMSO-*d*₆) δ 7.3 (s, 5H, phenyl), 3.5 (br m, 2H, N-CH₂), 3.0 (s, 3H, N-CH₃), 2.5 (br m, 2H, S-CH₂), 1.8 (m, 2H, CH₂), 1.5 (s, 1H, SH).

Kinetic studies. Kinetic runs were made in water at 25 °C. The PTP was introduced as 1 mL of 2.0 × 10⁻³ M metha-

nolic solution in 100 mL of final aqueous solution and the flask was quickly shaken. Each aliquot (3.0 mL) of the solution was removed from the volumetric flask at time intervals and was placed in a quartz cuvette. The decrease of absorption at the wavelength of maximum (H: $\lambda_{\max} = 258$ nm, *p*-CH₃: $\lambda_{\max} = 264$ nm, *p*-Cl: $\lambda_{\max} = 262$ nm, *p*-NO₂: $\lambda_{\max} = 260$ nm,) for the PTP and its derivatives with time was monitored.

Results and Discussion

Determination of rate constants. The initial concentration of PTP (2.0×10^{-5} M) was kept constant over wide pH range. As shown in Figure 1, the observed rates of PTP was always of the first-order. The first-order rate constants (k_{obs}) obtained from the slope at various pH are given in Table 1 and Figure 2 shows pH-log (rate) profile of this reaction. First-order rate constants of the PTP derivatives were also determined by the same way.

Substituent effects. As shown in Figure 3, Hammett ρ values were 0.53, 0.84 and 1.13 for pH = 5.0, 8.0, and 10.0, respectively. This result indicates that the rate of addition is accelerated by electron withdrawing groups at all pH ranges, and that the addition reaction proceeds through similar substituent effect in acidic, neutral, and basic media.

General base catalysis. To make sure that this reactions catalyzed by general base, the rate constants were determined at various acetate ion concentration at pH 4.78. As shown in Figure 4, this reaction is catalyzed by general base at low acetate ion concentration. However, as the amount of base becomes larger, the rate of addition reaction approaches the limiting values. The influence of base strength variation for the rate of this reaction was also studied, the results are summarized in Table 2. The Bronsted plot for hydrolysis from PTP is linear with excellent correlation (Figure 5, $\beta = 0.53$ ($r = 0.999$)).

Rate equation and mechanism. As shown in Figure 2, the plot of $\log k$ vs. pH is not linear; From pH 0.0 to 4.5, the $\log k_t$ remains constant. However, from pH 4.5 to 8.0, the \log

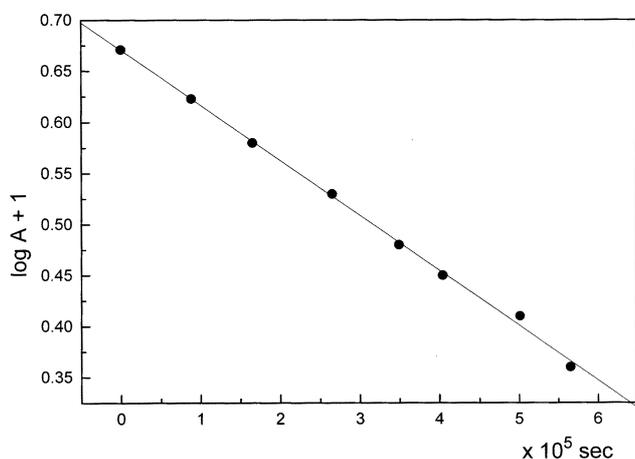


Figure 1. Plot of log absorbance vs. time for the hydrolysis of PTP at pH 5.0 and 25 °C.

Table 1. Rate constants for the hydrolysis of PTP at various pH and 25 °C

pH	Buffer Solution	$k_t (\text{sec}^{-1}) \times 10^7$	
		obsd	calcd
0.0	HCl	2.70	2.93
0.5	HCl	2.72	2.93
1.0	HCl	2.90	2.93
1.5	HCl	2.92	2.93
2.0	HCl	2.94	2.93
2.5	HCl	3.00	2.94
3.0	HCl	3.09	2.95
3.5	HOAc + NaOAc	3.12	2.99
4.0	HOAc + NaOAc	3.25	3.12
4.5	HOAc + NaOAc	3.90	3.52
5.0	HOAc + NaOAc	4.90	4.59
5.5	HOAc + NaOAc	7.10	6.87
6.0	HOAc + NaOAc	10.5	9.90
6.5	HOAc + NaOAc	12.0	12.2
7.0	KH ₂ PO ₄ + K ₂ HPO ₄	13.2	13.9
7.5	KH ₂ PO ₄ + K ₂ HPO ₄	15.5	16.4
8.0	KH ₂ PO ₄ + K ₂ HPO ₄	21.3	23.2
8.5	KH ₂ PO ₄ + K ₂ HPO ₄	36.7	44.6
9.0	H ₃ BO ₃ + NaOH	106	111
9.5	H ₃ BO ₃ + NaOH	309	323
10.0	H ₃ BO ₃ + NaOH	980	993
10.5	H ₃ BO ₃ + NaOH	3350	3110
11.0	NaOH	10200	9810
11.5	NaOH	32000	30900
12.0	NaOH	100000	97000

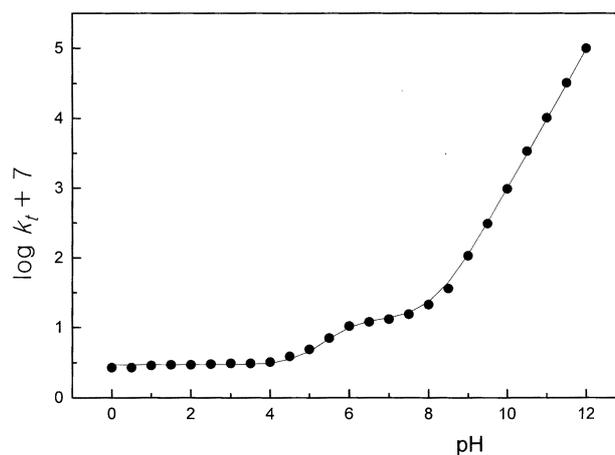


Figure 2. pH-log (rate) profile for the hydrolysis of PTP at 25 °C. Circles are experimental points and the solid line is drawn according to equation (10).

k_t increases gradually and above pH 8.5, the slope is 1.0, *i.e.*, k_t is directly proportional to the hydroxide ion concentration.

The rate observed constants (k_t) can be divided into two parts, each representing a different mechanism.

$$k_t = k_{10} + k_{\text{OH}}[\text{OH}^-] \quad (2)$$

where k_{10} is the first order rate constant for the spontaneous

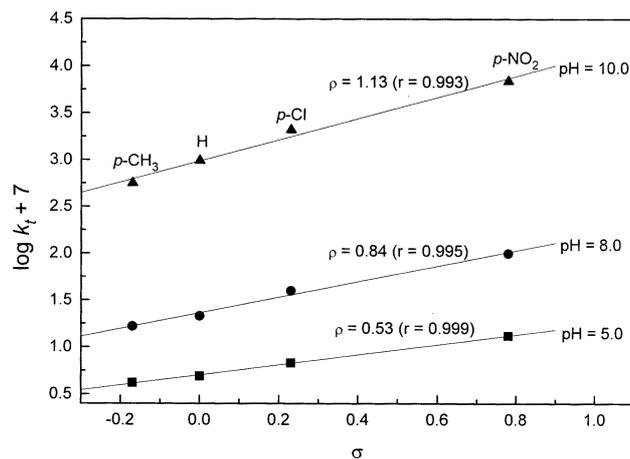


Figure 3. Hammett plots for the hydrolysis of PTP at pH 5.0, 8.0, and 10.0.

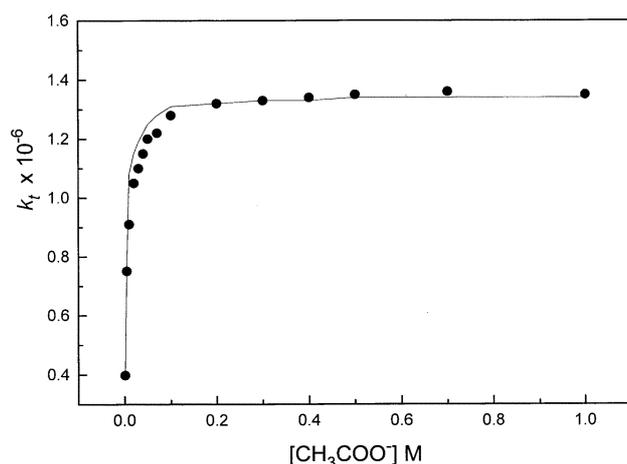


Figure 4. General base catalyzed hydrolysis of PTP at pH 4.78 and 25 °C. Circles are experimental points and the curve is drawn according to equation (11-3).

Table 2. Effect of base strength upon the $k_1/k_{-1} \cdot k_t^B$ values for the hydrolysis of PTP at 25 °C

base	$^a pK_a$	$k_1/k_{-1} \cdot k_2^B (\text{sec}^{-1})$
H ₂ O	-1.7	1.01×10^{-6}
ClCH ₂ COO ⁻	2.82	1.35×10^{-4}
CH ₃ COO ⁻	4.75	1.40×10^{-3}
Pyridine	5.36	4.20×10^{-3}
Lutidine	6.64	1.03×10^{-2}
H ₂ PO ₄ ⁻	7.32	4.50×10^{-2}
OH ⁻	15.7	1.51×10^3

^aReference 6.

hydrolysis and k_{OH} is the catalytic rate constant for the base catalyzed reactions.

At high pH, since the rate constant is directly proportional to the hydroxide ion concentration, the following reaction mechanism is proposed.

Although tetrahedral intermediate(II) was never directly detected in aqueous media, its half-life was estimated by indirect kinetics.^{7a-7c} Several authors assumed the rate-limit-

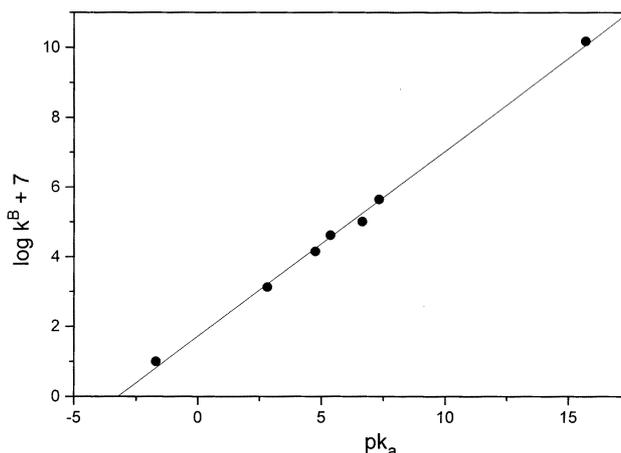
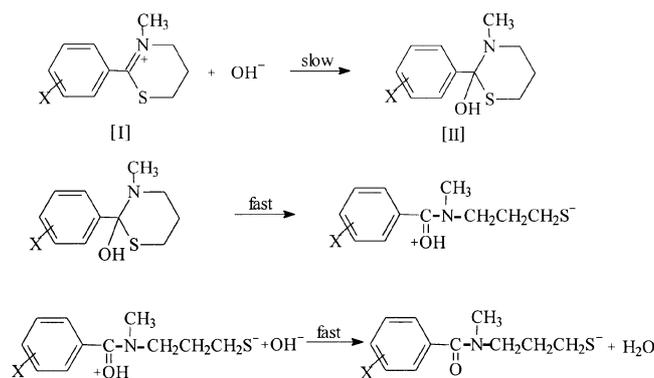


Figure 5. Plot of $\log k_t^B$ vs. pK_a of the bases for hydrolysis of PTP at 25 °C.



Scheme 1

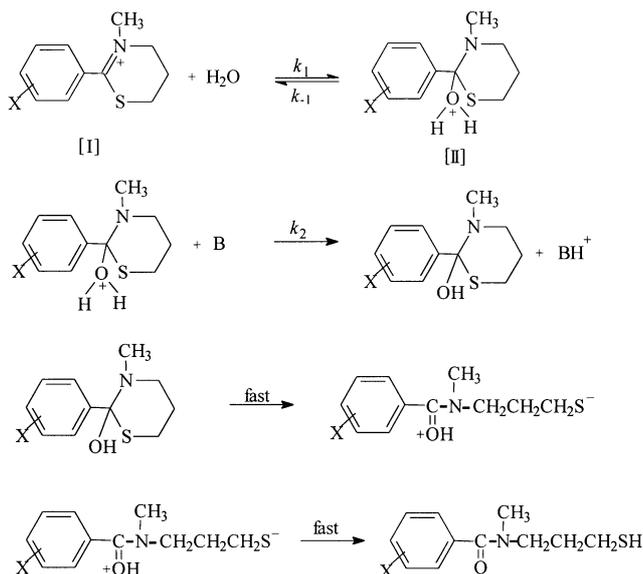
ing step of above mechanism to be the formation of pseudo-base (II) by nucleophilic addition of OH⁻ while also assuming that the ring opening with proton loss is too fast to be measured by conventional techniques.^{7b} Since the rate of addition reaction is accelerated by the electron withdrawing group with $\rho = 1.13$ at pH 10.0, the attack of hydroxide ion is the rate determining step in alkaline pHs.

At low pH, either the hydroxide ion or water may be added to PTP. However, the first possibility has been ruled out because the hydroxide ion concentration is much smaller than that of water *i.e.*, $k_t = k_{10}$ at pH < 3. The most plausible mechanism under acidic condition is shown in Scheme 2.

This mechanism is similar to that suggested by Martin *et al.*^{4a} for the hydrolysis of thiazoline and oxazoline in acidic media. They have also proved the existence of tetrahedral intermediate(II) formed by the addition of water to the substrate.

As the concentration of general base increases, the addition of water becomes the rate controlling step and the rate would approach the limiting value k_1 . This is in good agreement with the observed results (Figure 4). But, if the concentration of general base is low, the rate determining step may be changed to the second step.

If the reaction proceeds as shown in Scheme 2, one can apply steady-state approximation with respect to [II].⁸ The rate equation can be expressed as Eq. (3).



$$\text{Rate} = -\frac{[\text{PTP}]}{dt} = k_{10}[\text{PTP}] \quad (3)$$

$$= \frac{k_1 k_2 \Sigma[\text{B}]}{k_{-1} + k_2 \Sigma[\text{B}]} [\text{PTP}] \quad (4)$$

$$\frac{1}{k_{10}} = \frac{k_{-1} + k_2 \Sigma[\text{B}]}{k_1 k_2 \Sigma[\text{B}]} \quad (5)$$

$$\frac{1}{k_{10}} = \frac{1}{k_1} + \frac{1}{\left(\frac{k_1}{k_{-1}}\right) k_2 \Sigma[\text{B}]} \quad (6)$$

From the Eq. (6), it can be shown that if the concentration of general base is high ($k_2[\text{B}] \gg k_{-1}$), then $k_{10} = k_1$. Therefore, if the concentration of general base is high, k_{10} will take $1.35 \times 10^{-6} \text{ sec}^{-1}$ which is the limiting value of general base catalysis in Figure 4.

If water and hydroxide ion are the only general bases present, Eq. (6) becomes

$$\frac{1}{k_{10}} = \frac{1}{k_1} + \frac{1}{\left(\frac{k_1}{k_{-1}}\right) \{k_2^{\text{H}_2\text{O}} [\text{H}_2\text{O}] + k_2^{\text{OH}^-} [\text{OH}^-]\}} \quad (7)$$

Below pH 3.0, the concentration of hydroxide ion is negligible, then Eq. (7) becomes

$$\frac{1}{k_{10}} = \frac{1}{k_1} + \frac{1}{\left(\frac{k_1}{k_{-1}}\right) \{k_2^{\text{H}_2\text{O}} [\text{H}_2\text{O}]\}} \quad (8)$$

The value of $(k_1/k_{-1})k_2^{\text{H}_2\text{O}}$ can be determined from the $k_1 = 1.35 \times 10^{-6} \text{ sec}^{-1}$ and the observed rate constant (k_t) = $2.94 \times 10^{-7} \text{ sec}^{-1}$ at pH = 2.0. The value is $3.44 \times 10^{-7} \text{ sec}^{-1}$. By the substituting $k_t = 1.2 \times 10^{-6} \text{ sec}^{-1}$ at pH = 6.5 into equation (7), $(k_1/k_{-1})k_2^{\text{OH}^-} = 3.32 \times 10^2 \text{ sec}^{-1}$ can be obtained. As a result k_{10} becomes,

$$\frac{1}{k_{10}} = \frac{1}{1.35 \times 10^{-6}} + \frac{1}{3.44 \times 10^{-7} + 3.32 \times 10^2 [\text{OH}^-]}$$

$$\frac{1}{k_{10}} = \frac{1.69 \times 10^{-6} + 3.32 \times 10^2 [\text{OH}^-]}{4.64 \times 10^{-13} + 4.48 \times 10^{-4} [\text{OH}^-]}$$

$$k_{10} = \frac{4.64 \times 10^{-13} + 4.48 \times 10^{-4} [\text{OH}^-]}{1.69 \times 10^{-6} + 3.32 \times 10^2 [\text{OH}^-]} \quad (9)$$

At pH 10.0, where rate is directly proportional to hydroxide ion concentration, $k_t = 9.80 \times 10^{-5} \text{ sec}^{-1}$. By substituting above data into Eq. (2), $k_{\text{OH}^-} = 9.80 \times 10^{-1} \text{ sec}^{-1}$ can be obtained.

As a result, over all-rate equation constant becomes;

$$k_{10} = \frac{4.64 \times 10^{-13} + 4.48 \times 10^{-4} [\text{OH}^-]}{1.69 \times 10^{-6} + 3.32 \times 10^2 [\text{OH}^-]} + 9.80 \times 10^{-1} [\text{OH}^-] \quad (10)$$

Table 1 and Figure 2 show that the values of over-all rate constant, k_t calculated by Eq. (10) are in good agreement with observed values.

Similarly, the rate equation obtained for the hydrolysis of PDP derivatives; *p*-CH₃:

$$k_t = \frac{4.53 \times 10^{-13} + 2.72 \times 10^{-4} [\text{OH}^-]}{1.56 \times 10^{-6} + 2.11 \times 10^2 [\text{OH}^-]} + 6.27 \times 10^{-1} [\text{OH}^-]$$

p-Cl:

$$k_t = \frac{8.17 \times 10^{-13} + 1.06 \times 10^{-3} [\text{OH}^-]}{2.33 \times 10^{-6} + 5.60 \times 10^2 [\text{OH}^-]} + 2.07 [\text{OH}^-]$$

p-NO₂:

$$k_t = \frac{2.04 \times 10^{-12} + 6.34 \times 10^{-3} [\text{OH}^-]}{4.08 \times 10^{-6} + 1.81 \times 10^3 [\text{OH}^-]} + 6.90 [\text{OH}^-]$$

If acetate ion is present as a general base catalyst, Eq. (6) becomes

$$\frac{1}{k_{10}} = \frac{1}{k_1} + \frac{1}{\left(\frac{k_1}{k_{-1}}\right) \{k_1^{\text{H}_2\text{O}} [\text{H}_2\text{O}] + k_2^{\text{OH}^-} [\text{OH}^-] + k_2^{\text{OAc}^-} [\text{OAc}^-]\}} \quad (11)$$

From the value of $k_1 = 1.35 \times 10^{-6} \text{ sec}^{-1}$, $(k_1/k_{-1})k_2^{\text{H}_2\text{O}} [\text{H}_2\text{O}] = 3.44 \times 10^{-7} \text{ sec}^{-1}$, $(k_1/k_{-1})k_2^{\text{OH}^-} = 3.32 \times 10^{21} \text{ sec}^{-1}$, $[\text{CH}_3\text{COO}^-] = 0.1 \text{ M}$, $[\text{OH}^-] = 6.03 \times 10^{-10} \text{ M}$ and observed rate constant k_t , the value of catalytic constant of acetate ion $(k_1/k_{-1})k_2^{\text{OAc}^-} = 2.42 \times 10^{-4} \text{ sec}^{-1}$, can be obtained. By substituting above data into equation (10), k_{10} is given by the following Eq. (11-1).

$$\frac{1}{k_{10}} = \frac{1.89 \times 10^{-6} + 2.42 \times 10^{-4} [\text{OAc}^-]}{7.34 \times 10^{-13} + 3.27 \times 10^{-10} [\text{OAc}^-]} \quad (11-1)$$

$$k_{10} = \frac{7.34 \times 10^{-13} + 3.27 \times 10^{-10} [\text{OAc}^-]}{1.89 \times 10^{-6} + 2.42 \times 10^{-4} [\text{OAc}^-]} \quad (11-2)$$

As a result, over-all rate constant becomes;

$$k_t = \frac{7.34 \times 10^{-13} + 3.27 \times 10^{-10}[\text{OAc}^-]}{1.89 \times 10^{-6} + 2.42 \times 10^{-4}[\text{OAc}^-]} + 9.80 \times 10^{-1}[\text{OH}^-] \quad (11-3)$$

Figure 4 shows that the values of over-all rate constant, k_t calculated by Eq. (11-3) are in good agreement with the observed values.

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