of the acetyl group had an overall negative effect on the antimalarial potency of this series of thiosemicarbazones.

**Antibacterial Activity**—In the assessment of the antibacterial activity of the 2-(α-hydroxyacetyl)pyridine thiosemicarbazones (Table III), the strong inhibitory effect of the 2-acetylpyridine thiosemicarbazones seen against *N. gonorrhoeae* and *N. meningitidis* (3) was also observed here. Most of the 2-(α-hydroxyacetyl)pyridine compounds had MIC values of <0.1 μg/mL against these bacterial species, and in a few instances the degree of inhibition was slightly superior to that observed with the 2-acetylpyridine thiosemicarbazones.

Against *S. aureus*, several of the 2-(α-hydroxyacetyl)pyridine thiosemicarbazones, *i.e.*, IIf, h, and j, had MIC values of 0.5–1 μg/mL. Again, there were several instances in which inhibitory activity superior to the 2-acetylpyridine thiosemicarbazones (*i.e.*, in IId, e, h, and k) was seen.

## CONCLUSIONS

The biological data for the newly synthesized 2-(α-hydroxyacetyl)pyridine thiosemicarbazones indicates that $N^4$,$N^4$-disubstitution provides optimal *in vivo* and *in vitro* antimalarial and antibacterial activities. The introduction of a hydroxy function into the α-position of 2-acetylpyridine thiosemicarbazones results in compounds with increased solubility, decreased host toxicity, and in some instances, improvement of antimalarial and antibacterial activity *in vitro*. However, this is offset by the concomitant decrease in *in vivo* antimalarial effects. These results suggest that pharmacological parameters, such as tissue distribution and the rate of metabolism, play an essential role in determining the *in vivo* antimalarial activity, as well as host toxicity, of this series of compounds.

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# Kinetics and Mechanism of the Alkaline Hydrolysis of Maleimide


**M. NIYAZ KHAN**



Received August 23, 1983, from the *Department of Chemistry, Bayero University, Kano, Nigeria.* Accepted for publication March 21, 1984.



**Abstract** □ The kinetics of hydrolysis of maleimide was carried out within the $[OH^-]$ range of $2.46 \times 10^{-6}$ to 2.0 M at 30°C. The observed pseudo-first-order rate constants, $k_{obs}$, follow the empirical equation: $k_{obs} = (A_1[OH^-] + A_2[OH^-]^2)/(1 + A_3[OH^-])$. Both ionized and un-ionized forms of maleimide have been suggested to be involved in hydrolysis. The nucleophilic attacks by hydroxide ion at the carbonyl carbon of both ionized and un-ionized maleimide and by water at the carbonyl carbon of ionized maleimide to form tetrahedral intermediates are considered to be the rate-determining steps. The observed results obtained at different 1,4-dioxane–water compositions have revealed an increase in $k_{obs}$ with a decrease in 1,4-dioxane content which could be attributed to the higher polarity of the transition state compared with the reactant state.



**Keyphrases** □ Maleimide—kinetics, mechanism of hydrolysis □ Hydrolysis maleimide, effect of temperature


Many compounds containing an imide group act as drugs (1). *N*-Ethylmaleimide is of interest because of its rapid and Michael-type reaction with the sulfhydryl group of proteins (2, 3). Usually, the alkaline hydrolysis of amides and imides have been found to occur by a stepwise mechanism involving the tetrahedral intermediate (I) (4). Biechler and Taft (5) were the first to propose an additional oxydianionic tetrahedral intermediate (II) in the alkaline hydrolysis of trifluoroacetanilide. Later, II was found to exist in many acyl transfer reactions where the acyl substrates contained electron-withdrawing substituents and hydrolytic conditions covered a reasonable range of $[OH^-]$ (6). Recently, we have observed II in the alkaline hydrolysis of methyl-*o*-methoxybenzoate (7). In the continuation of our work on mechanistic studies on aqueous cleavage of amides (8) and imides (9) in a highly alkaline medium, we initiated this study to determine if an intermediate (II) exists and to study the nature of the rate-determining step.


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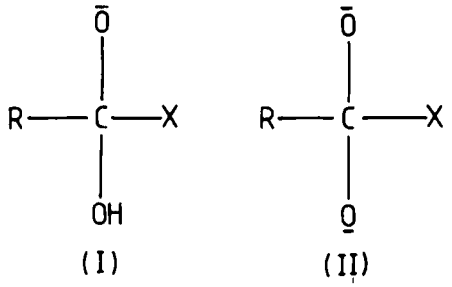


(I) (II)

## EXPERIMENTAL SECTION

**Materials**—Reagent grade maleimide, 2-amino-2-methyl-1,3-propanediol and Tris were obtained commercially[1]. All other reagent grade chemicals were obtained commercially[2] and were used without further purification. Glass-distilled water was used throughout the studies. Buffer solutions were prepared by partial neutralization.

**Kinetic Measurements**—For a typical kinetic run, 47.5 mL of a mixture containing sodium hydroxide or buffer solutions of desired pH and potassium chloride to maintain the ionic strength was incubated at 30°C in a thermostatic water bath[3] for ~10–15 min. The reaction was started by adding 2.5 mL of 0.0125 M solution of maleimide prepared in 100% 1,4-dioxane. An aliquot (~2.5 mL) was withdrawn from the mixture and was quickly transferred to a 3-mL quartz cuvette kept preincubated (30°C) in the thermostatic cell holder of a spectrophotometer[4]. The temperature was maintained electronically by a temperature-control unit of the spectrophotometer[4]. The progress of the reaction was followed by monitoring the disappearance of maleimide spectrophotometrically[4] at 300 nm.

The observed pseudo-first-order rate constants, $k_{obs}$, were calculated from:

$$A_{obs} = E_{app}X_0 \exp(-k_{obs}t) + A_\infty \qquad \text{(Eq. 1)}$$

where $X_0$ is the initial concentration of substrate; $A_{obs}$ and $A_\infty$ are the absorbance values at any time $t$ and $t = \infty$, respectively; and $E_{app}$ represents the apparent molar extinction coefficient. The nonlinear least-squares technique[5] was used to calculate three unknown parameters ($k_{obs}$, $E_{app}$, and $A_\infty$) from Eq. 1. The calculated values of $A_\infty$ were compared with the corresponding $A_{obs}$ obtained after ~10 half-lives of the reactions; they were almost the same. Most of the kinetic runs were carried out for more than 6 half-lives and fitting of the observed data to Eq. 1 was good for all runs. Maleamic acid and maleic acid are expected to have similar extinction coefficients at 300 nm and therefore, the hydrolysis of maleamic acid could not complicate the simple first-order kinetics. Furthermore, the bimolecular rate constant for alkaline hydrolysis was found to be $2.2 \times 10^{-4}$ $M^{-1}$ $s^{-1}$ at 65°C (10). This indicates that the rate constant obtained at even the highest [$OH^-$] (2.0 M) and at 30°C, is nearly 70-fold larger than the corresponding rate constant for the hydrolysis of maleamic acid obtained at 65°C.

Because of the low aqueous solubility of maleimide, its $pK_a$ was determined with a spectrophotometric technique (11). The value of the ionization constant, $K_a$, was 3.30 (±0.53) $\times 10^{-10}$ M at 30°C.

**Product Characterization**—A typical absorption wavelength for a cyclic imide group is 300 nm, while an amide group generally does not absorb here. Therefore a decrease in absorption peak at 300 nm should demonstrate the cleavage of the imide bond. We carried out experiments, described below, to determine the quantitative yield of the suspected product, maleamic acid.

One milliliter of 0.0125 M maleimide at 30°C was added to a mixture (total volume 19 mL) containing 0.03 M NaOH. The mixture (1 mL) was withdrawn at 25 min and was analyzed for ammonia by the nesslerizing technique (8, 12). The analysis revealed the absence of any detectable amount of ammonia formed within the 25-min period. After more than 12 half-lives of the first step of hydrolysis (25 min), 1.0 mL of 10.5 M HCl was added to the mixture. The mixture was made acidic because the acid-catalyzed hydrolysis of maleamic acid is substantially accelerated due to intramolecular carboxyl group participation (13). The recovery of ammonia was 95% at 300 min, 99% at ~21 h, and ~99% at ~41 h. Similar results were obtained for another reaction carried out at 0.2 M NaOH (other conditions similar to those described above). To substantiate the observation that no detectable ammonia formed within 25 min after the start of the reaction in basic medium, we performed a kinetic run at 30°C with a mixture containing 2.0 M NaOH and $6.25 \times 10^{-4}$ M maleimide. The reaction was carried out for >72 h; the observed pseudo-first-order rate constant was 1.62 (±0.19) $\times 10^{-3}$ $min^{-1}$ which could be compared with the literature value ($25.8 \times 10^{-3}$ $min^{-1}$) obtained at 65°C (10). To determine the rate constant for acid-catalyzed hydrolysis of the intermediate product maleamic acid, we carried out a kinetic run containing $5.952 \times 10^{-4}$ M maleimide and 0.03 M NaOH at 30°C. After 24 min, 1.0 mL of 10.5 M HCl was added to the mixture. The reaction was followed for more than 10 half-lives; the observed pseudo-first-order rate constant was 5.34 (±0.04) $\times 10^{-3}$ $min^{-1}$. This result could be compared with the literature values $5.28 \times 10^{-3}$ $min^{-1}$ (14) and $3.16 \times 10^{-3}$ $min^{-1}$ (12).

We also carried out the hydrolysis of maleimide in the presence of 1.0 M HCl at 30°C. The observed result has shown the absence of any detectable amount of ammonia formed within 525 min after the start of the reaction and only ~14, ~37, and ~46% ammonia was recovered at 23, 73, and 97 h, respectively. This indicates that the acid-catalyzed hydrolysis of maleimide is much slower than the base-catalyzed hydrolysis.

## RESULTS

The alkaline hydrolysis of maleimide was carried out within the hydroxide ion concentration range $2.460 \times 10^{-6}$–2.0 M at 30°C. The range $2.460 \times 10^{-6}$–$5.382 \times 10^{-4}$ M was attained by carbonate, 2-amino-2-methyl-1, 3-propanediol and Tris buffer solutions while the range of 0.002–2.0 M was maintained by sodium hydroxide solution. The ionic strength of the reaction medium was kept constant at 1.0 M in the presence of buffer components and 2.0 M in presence of sodium hydroxide. The observed pseudo-first-order rate constants at pH 8.57 and 8.08 (Table I) were obtained in the presence of 0.5 M carbonate buffer. The contribution of buffer catalysis to $k_{obs}$ at these pH values could be assumed to be negligible compared with both $OH^-$ and water catalyses because even within the 10.42–9.37 pH range the increase in total buffer concentration from 0.1 to 0.7 M has increased $k_{obs}$ only by 6–18%. The observed data as summarized in Table I were found to be best fitted to the empirical:

$$k_{obs} = \frac{A_1[OH^-] + A_2[OH^-]^2}{1 + A_3[OH^-]} \qquad \text{(Eq. 2)}$$

**Table I—Effect of Hydroxide Ion Concentration on the Aqueous Cleavage of Maleimide** [a]

| [$OH^-$], M | $10^3 k_{obs}$, $s^{-1}$ | $10^3 k^b_{calcd}$, $s^{-1}$ |
|---|---|---|
| $2.460 \times 10^{-6}$ [d] | 0.1514 ± 0.0058 [c] | 0.1730 |
| $3.243 \times 10^{-6}$ | 0.1750 ± 0.0030 | 0.2270 |
| $6.872 \times 10^{-6}$ | 0.3300 ± 0.0055 | 0.4650 |
| $7.603 \times 10^{-6}$ | 0.3124 ± 0.0023 | 0.5111 |
| $1.352 \times 10^{-5}$ | 0.6510 ± 0.0190 | 0.8630 |
| $2.276 \times 10^{-5}$ | 0.9310 ± 0.0480 | 1.346 |
| $4.800 \times 10^{-5}$ | 2.059 | 2.346 |
| $7.711 \times 10^{-5}$ | 2.633 ± 0.042 | 3.184 |
| $1.207 \times 10^{-4}$ | 4.057 | 4.013 |
| $2.000 \times 10^{-4}$ | 5.484 | 4.910 |
| $5.382 \times 10^{-4}$ | 7.312 | 6.247 |
| 0.002 [d] | 7.558 ± 0.102 | 7.094 |
| 0.01 | 7.643 ± 0.017 | 7.475 |
| 0.03 | 7.989 ± 0.030 | 7.758 |
| 0.05 | 8.106 ± 0.037 | 8.001 |
| 0.07 | 7.954 ± 0.047 | 8.238 |
| 0.10 | 8.509 ± 0.031 | 8.590 |
| 0.30 | 10.79 ± 0.02 | 10.92 |
| 0.50 | 13.08 ± 0.026 | 13.25 |
| 0.70 | 15.04 ± 0.13 | 15.58 |
| 1.00 | 18.32 ± 0.13 | 19.07 |
| 1.20 | 20.38 ± 0.09 | 21.39 |
| 1.40 | 23.12 ± 0.20 | 23.72 |
| 1.50 | 25.11 ± 0.22 | 24.89 |
| 1.70 | 27.42 ± 0.20 | 27.21 |
| 1.80 | 28.56 ± 0.25 | 28.38 |
| 1.90 | 29.98 ± 0.24 | 29.54 |
| 2.00 | 31.44 ± 0.18 | 30.70 |

[a] $[Maleimide]_0 = 6.25 \times 10^{-4}$ M, 30°C. Unless otherwise stated the ionic strength was kept constant at 2.0 M; 5% 1,4-dioxane in the mixture. [b] Calculated from Eq. 2 with calculated values of $A_1$, $A_2$, and $A_3$ as mentioned in the text. [c] Error limits are standard deviations. [d] Calculated from pH values by: $[OH^-] = 10^{pH} \cdot K_w/\upsilon OH^-$. The activity coefficient ($\upsilon OH^-$) was calculated from: $\log \upsilon OH^- = -0.52Z^2[(\mu^{1/2}/1 + \mu^{1/2}) - 0.2\mu]$ (15) where $\mu$ is the ionic strength. The ionic strength was kept constant at 1.0 M for all mixtures containing buffer solutions of required pH.

[1] Aldrich Chemical Co., Milwaukee, Wis.
[2] BDH Chemicals Limited, Poole, England.
[3] Gallenkamp.
[4] Model 35 UV-VIS; Beckman Instruments International S.A., Geneva, Switzerland.
[5] The nonlinear and linear least-squares computer programs were developed in BASIC and the computations were carried out on VAX-11 and Commodore Professional 3016 computers.

**Table II—Effect of Water–1,4-Dioxane Mixed Solvent on the Aqueous Cleavage of Maleimide [a]**

| 1,4-Dioxane, % (v/v) | $10^3 k_{obs}$, $s^{-1}$ |
|---|---|
| 5 | 10.68 ± 0.030[b] |
| 10 | 9.219 ± 0.049 |
| 15 | 7.612 ± 0.017 |
| 20 | 6.572 ± 0.024 |
| 25 | 5.467 ± 0.012 |
| 30 | 4.580 ± 0.012 |
| 40 | 3.217 ± 0.010 |
| 50 | 2.223 ± 0.026 |
| 60 | 1.573 ± 0.004 |
| 70 | 1.199 ± 0.011 |

[a] Conditions: $[Maleimide]_0 = 6.25 \times 10^{-4}$ M, 30°C, $\mu$ = 0.1 M, $[NaOH]_0$ = 0.03 M. [b] Error limits are standard deviations.

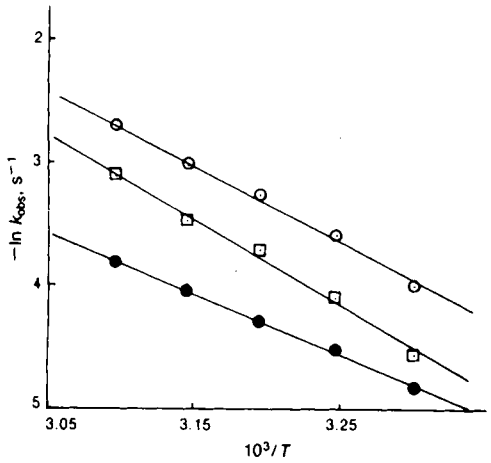



**Figure 1**—*Temperature dependence of* $k_{obs}$ *for* $k_1$ *step* (●), ($k_1 + k_2$) *step* (⊙), *and* $k_2$ *step* (⊡). *The solid lines are drawn through the least-squares calculated points using the Arrhenius equation.*

where $A_1$, $A_2$, and $A_3$ are unknown parameters. The values of $A_1$, $A_2$, and $A_3$ were calculated from Eq. 2 by the use of a nonlinear least-squares technique and the respective values thus obtained were: 72.2 ± 9.1 $M^{-1} s^{-1}$, 113.0 ± 15.6 $M^{-2} s^{-1}$, and 9709.5 ± 1299.2 $M^{-1}$. The fitting of observed data to Eq. 2 is evident from the standard deviations of calculated unknown parameters as well as from the calculated values of rate constants (Table I).

The effect of solvent on hydrolysis was studied at 30°C with organic cosolvent prepared by mixing 1,4-dioxane and water by volume. The hydroxide ion concentration and ionic strength were kept constant at 0.03 M and 0.1 M, respectively. The observed data are summarized in Table II. The increase in $k_{obs}$ with an increase in the dielectric constant (*i.e.*, increase of water content) of reaction medium cannot be explained by simple electrostatic theory (16) because under the experimental conditions employed, the proposed reaction mechanism involves a neutral and an anionic molecule. In the absence of any correct theoretical model which could be used to explain such rate dependence on mixed solvents and to assess, qualitatively, the effect of the solvating power of the mixed solvents on the rate of hydrolysis, we checked the fitting of the observed data with the empirical Grunwald-Winstein equation: $\log k_{obs} = \log k_0 + mY$ (18). Although the data were not in full agreement with the $mY$ equation, the value of m was ~0.29 (determined by drawing a straight line through the observed points obtained within the mixed solvent range of 30-50%[6]).

[6] The plot of $\log k_{obs}$ *versus* $Y$ was found to be a smooth nonlinear curve with initial and final slopes of ~0.17 and ~0.48, respectively.

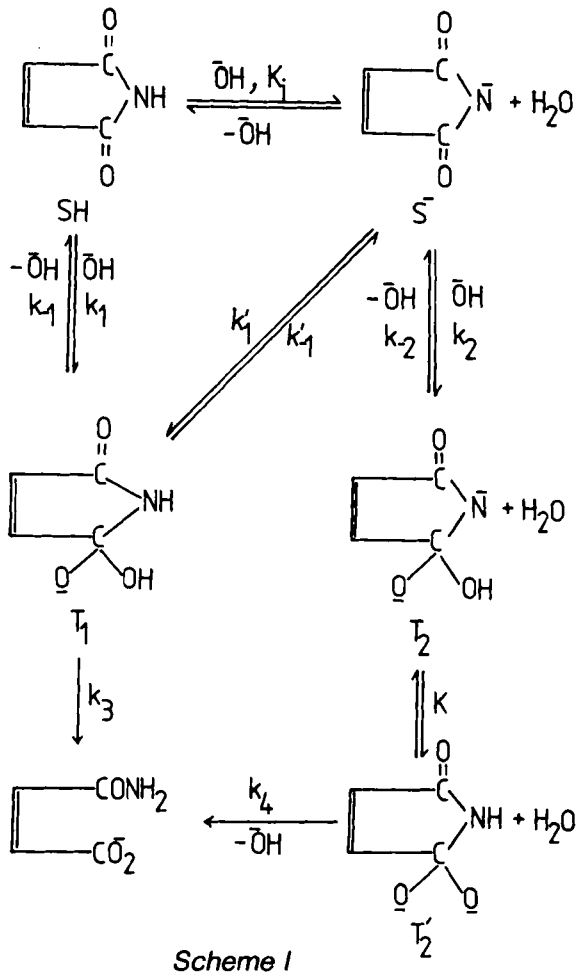
**Table IV—Effect of Ionic Strength on Hydrolytic Cleavage of Maleimide [a]**

| Ionic Strength, M | $[OH^-]$ = 0.03 M $10^3 k_{obs}$, $s^{-1}$ | $[OH]$ = 1.0 M $10^3 k_{obs}$, $s^{-1}$ |
|---|---|---|
| 1.0 | 8.882 ± 0.064 | 18.73 ± 0.70 |
| 1.5 | 8.932 ± 0.049 | 20.58 ± 0.24 |
| 2.0 | 7.989 ± 0.030 | 18.32 ± 0.13 |
| 3.0 | 8.226 ± 0.073 | 21.78 ± 0.21 |
| 3.5 | 7.958 ± 0.077 | — |
| 4.0 | — | 23.35 ± 0.23 |

[a] Conditions: $[Maleimide]_0 = 6.25 \times 10^{-4}$ M, 30°C.

The effect of temperature on rate of hydrolysis was studied at 30–50°C, at 0.03 M, and 1.0 M hydroxide ion concentrations, keeping ionic strength constant at 2.0 M. The observed data are shown graphically in Fig. 1. The observed pseudo-first-order rate constants were found to follow Eyring and Arrhenius equations (7) and the activation parameters calculated from these equations with linear and nonlinear least-squares techniques are summarized in Table III. The activation parameters obtained at 0.03 M NaOH are attributed to only the $k_1$ step because the $k_2$ step has negligible contribution at 0.03 M NaOH. Similarly, the activation parameters obtained at 1.0 M NaOH are attributed to both $k_1$ and $k_2$ steps.

The ionic strength effect of hydrolysis was studied at two different $[OH^-]$




*Scheme I*

**Table III—Activation Parameters of Hydrolytic Cleavage of Maleimide [a]**

| Reaction step | $\Delta F^*$ kcal/mole[b] | $\Delta H^*$, kcal/mol | $-\Delta S^*$, cal/deg.mol | $E_a$, kcal/mol | ln $A$, $s^{-1}$ | $R_{ms}$, $10^3$ $s^{-1}$ [c] |
|---|---|---|---|---|---|---|
| $k_1$[d] | 20.69 | 8.88 ± 0.22[e] | 38.8 ± 0.7[e] | 9.70 ± 0.25[e] | 11.31 ± 0.40 | 1.222 |
| ($k_1 + k_2$)[f] | 20.19 | 11.20 ± 0.47 | 29.4 ± 1.5 | 12.22 ± 0.54 | 16.34 ± 0.86 | 5.723 |
| $k'_2$[g] | 20.54 | 12.54 ± 0.73 | 26.1 ± 2.3 | 13.78 ± 0.81 | 18.37 ± 1.30 | 12.892 |

[a] Conditions: $[Maleimide]_0 = 6.25 \times 10^{-4}$ M, $\mu$ = 2.0 M. [b] $\Delta F^*$ was calculated from the relationship $k_{obs} = (K_B T/h) \exp(-\Delta F^*/RT)$ at 30°C. [c] $R_{ms} = [\Sigma_{i=1}(k_{obs_i} - k_{calcd_i})^2/(N-2)]^{1/2}$. [d] At 0.03 M NaOH. [e] Error limits are standard deviations. [f] At 1.0 M NaOH. [g] $k'_2$ ($s^{-1}$) was obtained from the relationship: $k'_2 = k_{obs}$ at 1.0 M NaOH $- k_{obs}$ at 0.03 M NaOH where $k'_2 = k_2[OH^-]$.

(0.03 and 1.0 M) within the ionic strength ranging from 1.0 to 4.0 M. The observed results are summarized in Table IV.

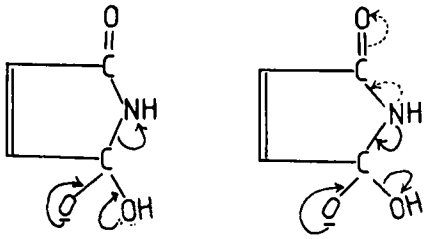
## DISCUSSION

The linear variation of $k_{obs}$ with $[OH^-]$ occurred at a pH much higher than the $pK_a$ of maleimide. This revealed that the alkaline hydrolysis of maleimide was not a simple second-order process, but followed a complex rate law. The simplest mechanism which could explain the observed results may be shown in Scheme I. The intermediates $T_1$, $T_2$, and $T_2'$ were considered short-lived chemical species and hence application of steady state approximation resulted in the kinetic equation:

$$k_{obs} = \frac{k_3(k_1 + k_1'K_i'[H_2O])[OH^-]}{(1 + K_i'[OH^-])(k_{-1} + k_{-1}' + k_3)} + \frac{k_4k_2KK_i'[OH^-]^2}{(1 + K_i'[OH^-])(k_{-2} + k_4K)} \quad \text{(Eq. 3)}$$

where $K_i' = K_i/[H_2O] = K_a/K_w$ with $K_a = [S^-]a_H/[SH]$.

Recently, Jencks *et al.* (19) demonstrated that in the nucleophilic substitution reactions, the rate of expulsion of the leaving group depends largely on the push provided by groups other than the leaving group attached to the same atom and the pull provided by the leaving group. Thus, in Scheme I, the



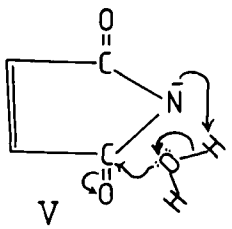
III IV

rate constant, $k_3$, should be considerably larger than $k_{-1}$ and $k_{-1}'$ because the push provided by the alcoholic oxygen atom to expel the amidic nitrogen atom would be larger than the push provided by the amidic nitrogen atom (since the nonbonded electrons on the nitrogen atom are not localized to the extent that they are localized on the alcoholic oxygen atom) to expel the alcoholic oxygen atom from $T_1$, as shown in III and IV. Furthermore, although the ionization constants of the conjugate acids of leaving groups involved in $k_{-1}$, $k_{-1}'$, and $k_3$ steps are almost the same[7] (20), the high carbon basicity of oxygen compared with that of nitrogen would make $k_3$ larger than $k_{-1}$ and $k_{-1}'$. These conclusions thus reveal that $k_3 \gg (k_{-1} + k_{-1}')$ and similarly $k_4K \gg k_{-2}$. Hence, application of these assumptions reduce Eq. 3 to:

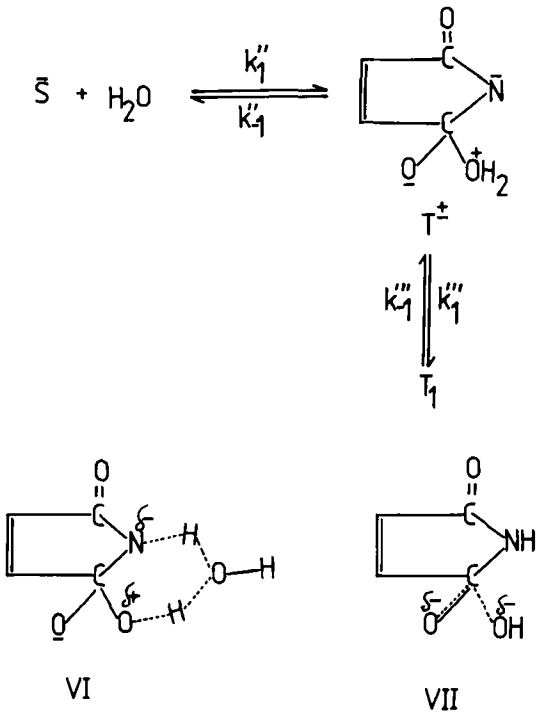
$$k_{obs} = \frac{(k_1 + k_1'K_i'[H_2O])[OH^-] + k_2K_i'[OH^-]^2}{1 + K_i'[OH^-]} \quad \text{(Eq. 4)}$$

Equation 4 is similar to Eq. 2 with $A_1 = (k_1 + k_1'K_i'[H_2O])$, $A_2 = k_2K_i'$, and $A_3 = K_i'$. The rate constant $k_2$ ($A_2/A_3$) was found to be 0.0116 $M^{-1}$ $s^{-1}$ and $K_a$ was calculated from $A_3$ with a known value of $K_w$ ($1.449 \times 10^{-14}$ $M^2$) (21). The value thus obtained ($1.41 \times 10^{-10}$ M) is comparable with the experimentally observed value of $3.3 \times 10^{-10}$ M. The values of $A_1/A_3$ ($7.44 \times 10^{-3}$ $s^{-1}$) and $A_2/A_3$ are considerably larger than the respective values of $6.64 \times 10^{-5}$ $s^{-1}$ and $25.68 \times 10^{-5}$ $M^{-1}$ $s^{-1}$ obtained at 80°C in the hydrolytic cleavage of succinimide (22) and $19.1 \times 10^{-5}$ $s^{-1}$ and $83.9 \times 10^{-5}$ $M^{-1}s^{-1}$ obtained at 80°C in the hydrolysis of 3,3-methylethylsuccinimide (23).

The present data are not sufficient to differentiate between a concerted process with transition state V and a stepwise process (Scheme II) involved



V



VI VII

*Scheme II*

in the conversion of $S^-$ to $T_1$. However, as Jencks (24) has pointed out, the concerted process should be expected to occur if the lifetime of an intermediate is shorter than that of a molecular vibration of $10^{-13}$ s. Classical one-step concerted $S_N2$ and $E_2$ mechanisms have been challenged by the proposal that such reactions occur through a stepwise mechanism (24); therefore, we prefer Scheme II for the conversion of $S^-$ to $T_1$. It has been concluded in the aminolysis of maleimide[8] that $k_{-1}''$ is larger than $k_1''$ even when the leaving group in $k_{-1}''$ step is a cationic amine. It is therefore obvious that in Scheme II, $k_{-1}''$ should be larger than $k_1''$ because the acidity of $H_2O^+$— is much larger than $>NH_2^+$. However, the high leaving ability of $H_2O^+$—, compared with $>NH_2^+$ from $T^\pm$—, caused by the difference in their respective acidity, could partially be offset by larger basicity toward carbon of oxygen nucleophiles than of amine nucleophiles, for a given basicity toward the proton (25). These conclusions lead to $k_1''$ as the rate-determining step. The proton transfer in the $k_1''$ step is presumably taking place through a proton switch mechanism (26).

In previous related studies (27), the formation of the oxydianionic tetrahedral intermediate, $T_2$, was assumed to occur by an equilibrium:

$$T_1 \overset{OH^-,\,K'}{\rightleftharpoons} T_2' \quad \text{(Eq. 5)}$$

Such an equilibrium is most likely to be significant if the nucleophilic attack to form $T_1$ is not the rate-determining step.

The significantly low value of the Grunwald-Winstein coefficient ($m \simeq 0.29$) indicates that the rate is not sensitive to the solvating power of the organic cosolvent. However, the increase in rate of hydrolysis with increase in water concentrations of the mixed solvents reveals that the transition state involved is more polar than the reactants (28). The solvent effect was studied at 0.03 M NaOH where the contribution of the $k_2$ step compared with the $k_1$ step was most likely negligible. It is therefore conceivable to assume that the $k_1'$ step should be dominant over the $k_1$ step in the formation of $T_1$ (Scheme I) because the transition state of the $k_1'$ step (VI) is apparently more polar than that of the $k_1$ step (VII) and because the ionic reactant of the $k_1$ step is presumably more strongly solvated than that of the $k_1'$ step in a polar solvent.

The sufficiently large negative value of $\Delta S^*$ for the $k_1'$ step must be attributed to the necessity for the proper orientation of more than one water molecule in the transition state (29); this could be expected if the transition state involved is highly polar. It is interesting to note that the $\Delta S^*$ for the $k_1'$ step is ~12.7 e.u. more negative compared with that for the $k_2$ step while the $\Delta H^*$ for the $k_2$ step is ~3.66 kcal/mol larger than that for the $k_1'$ step. These observations are consistent with the proposed transition states VI and VII. As expected from the proposed mechanism, the $k_1'$ step has been found to be

[7] The $pK_a$ of acetamide [15.4 (20a), 17.1 (20b)] and the value of $K_a/K_w$ of ~7 for succinamic acid (22) indicate that the acidity of the amide group is not much different from water.

[8] Unpublished observations.

insensitive to the ionic strength while a change in ionic strength from 1.0 to 4.0 M resulted in an increase of ~25% in $k_{obs}$ obtained at 1.0 M NaOH.

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# Dissolution at Porous Interfaces VI: Multiple Pore Systems


**H. GRIJSEELS *, D. J. A. CROMMELIN ˣ, and C. J. DE BLAEY ‡**



Received February 3, 1983, from the *Department of Pharmaceutics, University of Utrecht, 3511 GH Utrecht, The Netherlands.* Accepted for publication March 21, 1984. Present addresses: *Gist-brocades N.V., P.O. Box 43, 7940 AA Meppel, The Netherlands and ‡Royal Dutch Society for the Advancement of Pharmacy, 2514 JL The Hague, The Netherlands.



**Abstract** □ With the aid of rapidly dissolving sodium chloride particles, cubic pores were made in the surface of a theophylline tablet. The influence of the pores on the dissolution rate of the surface was investigated in a rotating disk apparatus. Like the drilled pores used in earlier studies, downstream on the surface they caused a turbulent flow regimen with the development of a trough due to enhanced erosion. The phenomenon of a critical pore diameter, discovered with single, drilled pores, seems to be applicable to the cubic pores investigated in this study, although a higher degree of surface coverage with pores caused complications, probably due to particles bordering one another and forming larger pores. The behavior of the porous surfaces at different rotation speeds was studied. Due to the presence of pores the laminar character of the boundary layer flow changes to turbulent, which induces locally an increased dissolution flux in the wake of a pore.



**Keyphrases** □ Dissolution rates—pore effects, theophylline □ Pore effects—influence on dissolution rate, theophylline


The promoting effect of pores on the dissolution rate of a tablet surface and the effects of individual pores drilled into a dissolving surface have been reported (1–5). The objective of this study was to investigate the changes in dissolution rate of a solid surface when several pores, which can not be considered to act individually, are present. The hydrodynamic conditions around each pore will be influenced by surrounding pores and, as a consequence of the interaction of the turbulent zones behind the pores, the erosion troughs will overlap.

Pores can be drilled into a tablet surface by a drilling technique (1–5), but this method is not feasible for a large number of pores, and an alternative procedure was followed in this study. Sodium chloride particles, characterized by an almost cubic shape, were embedded in the surface of a theophylline tablet. In the dissolution experiment, the sodium chloride particles rapidly dissolved leaving (cubic) pores in the slowly dissolving theophylline surface. In this way a surface was easily supplied with a large number of pores.


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