# The Kinetics and Mechanism of a Highly Efficient Intramolecular Nucleophilic Reaction. The Cyclization of Ethyl *N*-[*o*-(*N*-Hydroxycarbamoyl)benzoyl]-carbamate to *N*-Hydroxyphthalimide

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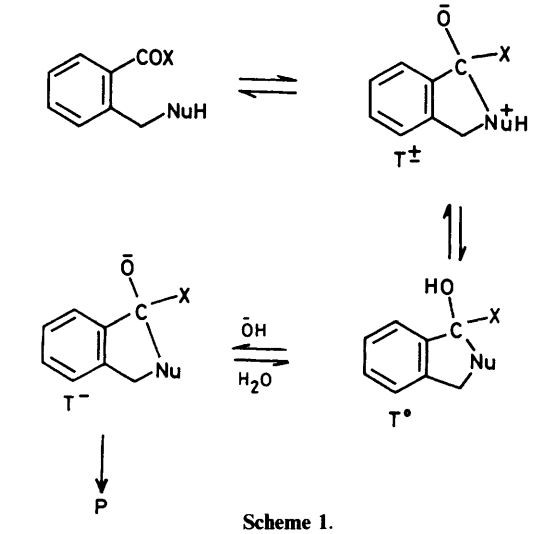
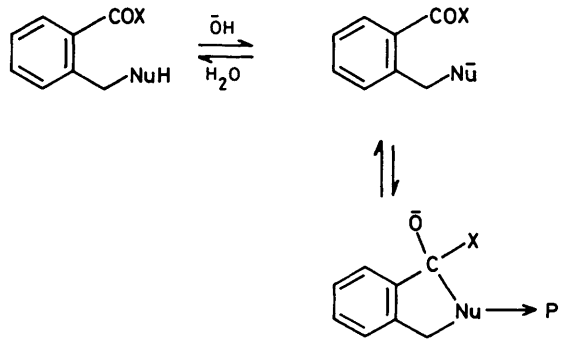
The cyclization of ethyl *N*-[*o*-(*N*-hydroxycarbamoyl)benzoyl]carbamate (SH) to *N*-hydroxyphthalimide (NHPH) has been studied within the pH range 5.18—7.84 at 30 °C. The observed first-order rate constants are linearly dependent on [$^-$OH]. Buffer catalysis could not be detected and the value of the second-order rate constant, $k_{OH}$, for the specific base-catalysed cyclization reaction is (4.06 ± 0.05) × $10^4$ l $mol^{-1}$ $s^{-1}$. The magnitude of $k_{OH}$ is *ca.* 3 × $10^5$-fold greater than $k_{OH}$ for hydroxide ion-catalysed hydrolysis of methyl benzoate. The suggested mechanism involves the pre-equilibrium formation of the anionic substrate which cyclizes to produce anionic tetrahedral intermediate followed by its breakdown as the rate-determining step. The cyclized product, NHPH, reacts rapidly and reversibly with hydroxylamine to produce *o*-(*N*-hydroxycarbamoyl)benzohydroxamic acid (P). The equilibrium constants for the processes NHPH + $NH_2OH \rightleftharpoons$ P and $\bar{N}$PH + $H^+$ + $NH_2OH \rightleftharpoons$ P, where $\bar{N}$PH is the ionized NHPH, calculated at different pH using authentic NHPH, reveal a non-linear dependence on total hydroxylamine buffer concentrations.

Interest in the factors that influence intramolecular reactions gained special impetus since the awareness of the fact that most enzyme-catalysed reactions are in actuality intramolecular.[1] Shafer and Morawetz[2] reported a very large rate enhancement for specific base-catalysed intramolecular nucleophilic attack by carbamoyl nitrogen on carbonyl carbon of amide and ester groups compared with that of the analogous intermolecular reactions. Efficient intramolecular nucleophilic reactivity could be detected in the cyclization of methyl and trifluoroethyl esters of 2-ureidobenzoic acid to quinazoline.[3] Exceptionally large nucleophilic rate constants have been found for the cyclization of the ethyl ester[4,5] and amide[6–8] of 2-hydroxymethylbenzoic acid to phthalide and methyl ester[9] and amide[10] of 2-aminomethylbenzoic acid to phthalimidine. The imidazoyl group is an excellent nucleophile in the cyclization of the trifluoroethyl and phenyl esters of the *o*-(2-imidazoyl)-benzoic acid.[11] But intramolecular nucleophilic attack by the imidazoyl group could not be detected in the cleavage of methyl *o*-(2-imidazoyl)benzoate.[11] Kirby *et al.*[12] have studied the cyclization of methyl 3-(2-aminophenyl)propionate which showed marked mechanistic difference when compared with the cyclization of methyl 2-aminomethylbenzoate.[9] In order to find out the effect of variable ring size on intramolecular nucleophilic attack, Fife and Duddy[13] have studied the cyclization of methyl and trifluoroethyl esters of (*o*-aminophenyl)acetic acid to 2-oxindole. External buffer catalysis has been detected in most of these cyclization reactions. Based on these studies, it is concluded that the efficiency of intramolecular nucleophilic participation depends largely on the acidity of the leaving group while it is essentially independent of the basicity of the nucleophile.[11]

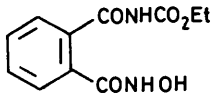
The mechanism of this thoroughly studied reaction may be explained by either of the kinetically indistinguishable mechanisms shown in Schemes 1 and 2. In Scheme 1 reaction is initiated by attack of un-ionized nucleophile upon the carbonyl group to yield the zwitterionic tetrahedral intermediate $T^{\pm}$ which can be expected to undergo a proton switch to form $T^0$:$T^0$ is then ionized to $T^-$ which expels the leaving group to form product. In Scheme 2 ionization of the nucleophile occurs before attack on the carbonyl group and $T^-$ is formed directly. No attempt seemed to be made in the earlier studies to differentiate between these alternative mechanisms (Schemes 1 and 2). We studied the cyclization of ethyl *N*-[*o*-(*N*-hydroxy-carbamonyl)benzoyl]carbamate (SH) to *N*-hydroxyphthal-imide and attempted to differentiate between the alternative mechanisms in Schemes 1 and 2.



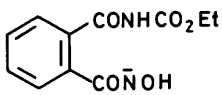

Scheme 1.



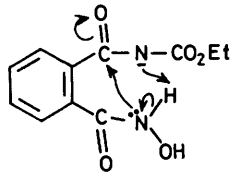

Scheme 2.




SH




$S_1^-$




$TS_1^-$

## Experimental

*Materials.*—Reagent grade chemicals such as sodium acetate, sodium dihydrogenphosphate, and hydroxylammonium hydrochloride were obtained from B.D.H. and *N*-ethoxycarbonylphthalimide and Tris were obtained from Aldrich. All other chemicals used were of reagent grade. Glass-distilled water was used throughout.

*Kinetic Measurements.*—The rates of cyclization of SH to *N*-hydroxyphthalimide (NHPH) were studied spectrophotometrically by monitoring the increase in absorbance ($A_{obs.}$) at 300 nm due to the formation of the cyclized product. In a typical experiment, the reaction mixture containing required amounts of hydroxylamine, buffer of desired pH, and potassium chloride (to maintain the ionic strength) was equilibrated at 30 °C for a few minutes. The reaction was then initiated by adding the appropriate amount of *N*-ethoxycarbonylphthalimide solution prepared in acetonitrile. The details of the kinetic procedure are the same as described elsewhere.[14] The constant concentration of $2 \times 10^{-3}$ or $2 \times 10^{-2}$M-hydroxylamine was maintained in all the kinetic runs where buffers other than hydroxylamine were used to keep the pH constant. The total volume of the reaction mixture in each kinetic run was 25 $cm^3$ which contained either 1% or 1.6% MeCN and the concentration of *N*-ethoxycarbonylphthalimide was kept constant at either $2 \times 10^{-4}$ or $2.8 \times 10^{-4}$M. The reaction conditions employed were such that the rate constants for the formation of SH from *N*-ethoxycarbonylphthalimide were ⩾ 270-fold larger than those for its cyclization to *N*-hydroxyphthalimide. A Hitachi 100-50 double beam u.v.–visible spectrophotometer was used. The pH values of reaction mixtures were determined with a Philips digital pH meter model PW 9409 and the pH was constant during the course of a reaction. Pseudo-first-order rate constants $k_{obs.}$ were calculated from equation (1) as described elsewhere.[14]

$$A_{obs.} = \varepsilon_{app}[X]_0[1 - \exp(-k_{obs.}t)] + A_0 \qquad (1)$$

The rates of hydrolysis of NHPH were studied by monitoring the decrease in absorbance ($A_{obs.}$) at 300 nm and 30 °C. The observed pseudo-first-order rate constants ($k_{obs.}$) were calculated from equation (2). In equations (1) and (2), $\varepsilon_{app}$ is the

$$A_{obs.} = \varepsilon_{app}[X]_0\exp(-k_{obs.}t) + A_\infty \qquad (2)$$

apparent molar extinction coefficient, $[X]_0$ is the initial concentration of substrate, and $A_0$ and $A_\infty$ are the absorbance at $t$ 0 and ∞, respectively.

The u.v.–visible spectra of the products of cyclization reactions obtained at different pH values were identical with those of *N*-hydroxyphthalimide obtained under similar experimental conditions.

*Hydroxamic Acid Assay.*—We used this assay to ascertain that the equilibrium product in the reaction of *N*-hydroxyphthalimide with $NH_2OH$ is *o*-(*N*-hydroxycarbamoyl)benzohydroxamic acid. It is known that the hydroxamic acid group forms a coloured complex with $FeCl_3$ in acidic medium which absorbs strongly at 540 nm. But no such complex formation could be detected with ionized or non-ionized *N*-hydroxyphthalimide.[15]

In a typical experiment, the reaction mixture (23 $cm^3$) containing appropriate amounts of hydroxylamine buffer of pH 5.29 and KCl (to maintain the ionic strength at 1.0M) was equilibrated for a few minutes at 30 °C. The reaction was then initiated by adding 0.02M-NHPH solution (2 $cm^3$; prepared in MeCN) to the reaction mixture. A portion (5 $cm^3$) was withdrawn at *ca.* 4 min and mixed with $FeCl_3$ solution prepared in 0.7M-HCl (5 $cm^3$). After 5 min, the absorbance ($A_{540}$) of the resulting mixture was measured at 540 nm. Similarly, iron(III) chloride reacting product was characterized at 540 nm for the second portion withdrawn at *ca.* 17 min. The values of $A_{540}$ obtained at *ca.* 4 and 17 min are essentially the same. This indicates that the hydroxylaminolysis of NHPH was completed within ⩽ 4 min under the experimental conditions employed.

The ionization constant $K_a$ of NHPH was found to be $(1.02 \pm 0.10) \times 10^{-6}$ mol $dm^{-3}$ at 30 °C as determined by spectrophotometry.[14] The $pK_a$ of 5.99 is comparable with the literature value of 6.1 at 25 °C.[15]

## Results

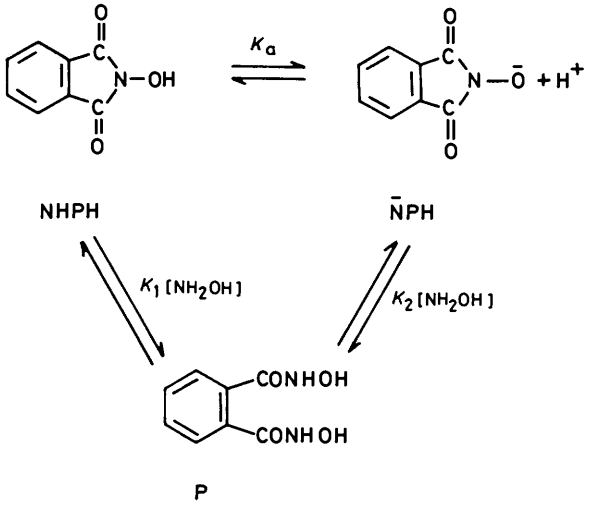
*Hydroxylaminolysis of* N-*Hydroxyphthalimide* (NHPH).—In the cyclization of SH to NHPH at different pH values, the reactant, SH, was generated by hydroxylaminolysis of *N*-ethoxycarbonylphthalimide. The rate constants for the formation of SH from *N*-ethoxycarbonylphthalimide were always ⩾ 270-fold larger than those for its cyclization to NHPH. In these reactions, it appeared that the product, NHPH, also reacted with hydroxylamine at a much faster rate compared with its formation from SH. In order to affirm it, we carried out experiments on hydroxylaminolysis of authentic NHPH. The hydroxylaminolysis of *N*-hydroxyphthalimide (NHPH) was studied, over the total hydroxylamine buffer concentration range 0.04—0.6M at various pH, by monitoring the disappearance of NHPH at 300 nm. The reaction is too fast to study by conventional spectrophotometry. The observed absorbance values were found to level off within <4 min even at the lowest total buffer concentration at pH 5.11. However, pseudo-first-order rate constants $k_{obs.}$ were calculated from equation (2) for a few kinetic runs at pH 5.11. The observed results are shown in the Table. Although these $k_{obs.}$ values are not very reliable because they are derived from the absorbance–time profiles where ⩾ 50% reaction was over before recording of the absorbance started, the kinetically estimated values of $A_0$ (absorbance at $t$ 0) are comparable with the expected $A_0$ values (Table).

The iron(III)–hydroxamate method was used to determine the equilibrium concentration of *o*-(*N*-hydroxycarbamoyl)benzohydroxamic acid at pH 5.29 for a total hydroxylamine buffer concentration ($[B]_T$) of 0.04—0.6M. The molar extinction coefficient ($\varepsilon_{540}$) of iron(III)–acetohydroxate complex at 540 nm has been reported to be 942 $dm^3$ $mol^{-1}$ $cm^{-1}$.[16] Using $\varepsilon_{540}$ 942 $dm^3$ $cm^{-1}$ and taking into account the fact that each molecule of *o*-(*N*-hydroxycarbamoyl)benzohydroxamic acid contains two CONHOH groups, the concentrations of *o*-(*N*-hydroxycarbamoyl)benzohydroxamic acid (P) at equilibrium, $[P]_e$, were determined.

**Table.** Pseudo-first-order rate constants for hydroxylaminolysis of *N*-hydroxyphthalimide[a]

| $[NH_2OH]_T$/M | $10^3 k_{obs.}$/s$^{-1}$ | $\varepsilon_{app}$/dm$^3$ mol$^{-1}$ cm$^{-1}$ | $A_\infty$ | $A_0^b$ | $A_0^c$ |
|---|---|---|---|---|---|
| 0.04 | 16.5 ± 4.4[d] | 356 ± 67[d] | 0.803 ± 0.004[d] | 0.903 | 0.880 |
| 0.12 | 36.0 ± 1.0 | 896 ± 19 | 0.670 ± 0.001 | 0.921 | 0.880 |
| 0.24 | 56.8 ± 1.8 | 1 175 ± 47 | 0.529 ± 0.001 | 0.858 | 0.880 |
| 0.36 | 77.3 ± 2.9 | 1 392 ± 86 | 0.450 ± 0.001 | 0.840 | 0.880 |

[a] $[X]_0$ 2.8 × 10$^{-4}$M, pH 5.11, ionic strength 1.0M and 30 °C. [b] Calculated from equation (2) at $t$ 0. [c] These expected values of $A_0$ were calculated at pH 5.11 from the relationship; $A_0 = (A_R^- K_a + a_H A_{RH})/(a_H + K_a)$ where $A_R^-$ (= 0.35) and $A_{RH}$ (= 0.95) represent the absorbance of ionized and non-ionized *N*-hydroxyphthalimide (NHPH), respectively, at 300 nm and $K_a$ (= 1.02 × 10$^{-6}$M) is the ionization constant of NHPH. [d] Error limits are standard deviations.




**Scheme 3.**

The complete reaction is shown in Scheme 3. It is evident from Scheme 3 that equations (3) and (4) hold. In equation (3),

$$\frac{K_1' K_2' a_H}{K_1' + K_2' a_H} = \frac{[P]_e}{[X]_e} \quad (3)$$

$$K_1'/K_2' = K_a \quad (4)$$

$[X]_e = [NHPH]_e + [\bar{N}PH]_e$ and $[P]_e$, $[NHPH]_e$, and $[\bar{N}PH]_e$ represent the equilibrium concentrations of P, NHPH, and N̄PH, respectively; $K_1' = K_1[NH_2OH]$ and $K_2' = K_2[NH_2OH]$. Equations (5) and (6) may be derived from equations

$$K_1' = \frac{[P]_e}{[X]_e} \times \frac{(a_H + K_a)}{a_H} \quad (5)$$

$$K_2' = \frac{[P]_e}{[X]_e} \times \frac{(a_H + K_a)}{a_H K_a} \quad (6)$$

(3) and (4). The values of $[P]_e/[X]_e$ at different total hydroxylamine buffer concentrations and pH were calculated as described in the Appendix. These values of $[P]_e/[X]_e$ were used to calculate $K_1'$ and $K_2'$ from equation (5) and (6), respectively, with known values of $a_H$ and $K_a$. The equilibrium constants $K_1'$ and $K_2'$ reveal a non-linear dependence on total hydroxylamine buffer concentrations. The values of $K_1'$ and $K_2'$ were also determined at pH 5.29 using the values of $[P]_e/[X]_e$ determined from iron(III)–hydroxamate method. These values are comparable with those calculated from $[P]_e/[X]_e$ values obtained from the alternative method as described in the Appendix. This shows that the assumption as described in the Appendix that P does not absorb significantly at 300 nm is most likely correct.

*Cyclization of Ethyl* N-[o-(N-*Hydroxycarbamoyl*)*benzoyl*]-*carbamate* (*SH*) *to NHPH.*—The cyclization of SH to NHPH was studied at three different pH for a total acetate buffer concentration, $[B]_T$, of 0.2—0.8M. The observed absorbance ($A_\infty^{obs.}$) at $t$ ∞ changed from 0.32 to 0.19 as $[B]_T$ changes from 0.2 to 0.8M at the lowest pH, 5.18. Such significant changes in $A_\infty^{obs.}$ could not be detected at higher pH (5.67 and 6.00). This could be attributed to the probably significant general base-catalysed hydrolysis of non-ionized cyclized product (NHPH) because the hydrolysed product, phthalhydroxamic acid, is expected to have essentially no absorption at 300 nm. In order to affirm this possibility we carried out a few experiments on hydrolysis of authentic NHPH under the same experimental conditions. The observed pseudo-first-order rate constants, $k_{obs.}$, obtained at pH 5.16 for $[B]_T$ 0.1—0.8M were found to obey equation (7) with

$$k_{obs.} = k_0 + k_B[B]_T \quad (7)$$

least-squares-calculated values of $k_0$ and $k_B$ as (7.68 ± 0.27) × 10$^{-4}$ min$^{-1}$ and (2.36 ± 0.06) × 10$^{-3}$ dm$^3$ mol$^{-1}$ min$^{-1}$, respectively. The observed significant contribution of $k_B$ term compared to $k_0$ term in equation (7) reveals the importance of general base catalysis in the hydrolysis of NHPH.

The cyclization of SH under the acetate buffer solutions of pH 5.18 is modelled by equation (8) where A—C represent SH,

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C \quad (8)$$

NHPH, and phthalhydroxamic acid, respectively. The observed absorbance ($A_{obs.}$) at any time $t$ during the course of the reaction is given by equation (9) where $A_0$ is the absorbance at $t$ 0, $[X]_0$ is

$$A_{obs.} = A_0 + \frac{\varepsilon'[X]_0 k_1}{(k_1 - k_2)}(e^{-k_2 t} - e^{-k_1 t}) \quad (9)$$

the initial concentration of the substrate, and $\varepsilon' = (\varepsilon_B' a_H + \varepsilon_{B^-}' - K_a)/(a_H + K_a)$ with $\varepsilon_B' = \varepsilon_B - \varepsilon_A$ and $\varepsilon_{B^-}' = \varepsilon_{B^-} - \varepsilon_A$. The notations $\varepsilon_A$, $\varepsilon_B$, and $\varepsilon_{B^-}$ represent the molar extinction coefficients of A, non-ionized and ionized NHPH, respectively. In the derivation of equation (9), the assumption introduced is $\varepsilon_A \simeq \varepsilon_C$ at 300 nm where $\varepsilon_C$ is the molar extinction coefficient of C. The unknown parameters $k_1$, $\varepsilon'$, and $A_0$ were calculated from equation (9) using the non-linear least squares technique with known values of $k_2$ and $[X]_0$. The fit of the observed data to equation (9) is evident from the plots shown in Figure 1. At higher pH (5.67 and 6.00), the consecutive nature of the reaction could not be detected simply because the increase of pH produces an increase in the value of $k_1$ and the concentrations of ionized NHPH which in turn decreases the rate hydrolysis of NHPH.

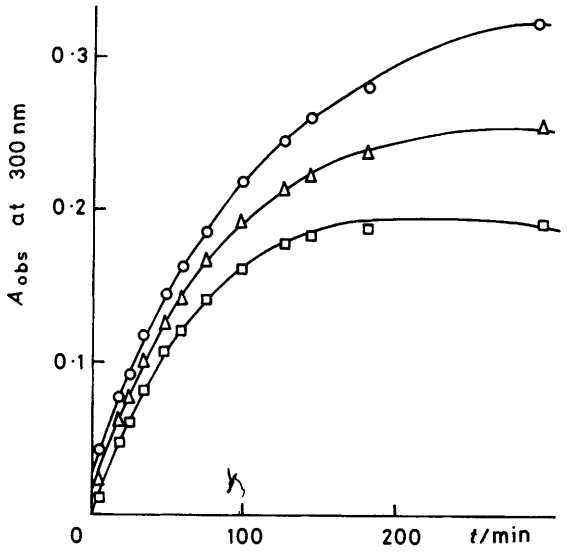



**Figure 1.** Plots of observed absorbance at 300 nm, $A_{obs.}$, against time for the cyclization reactions of ethyl *N*-[*o*-(*N*-hydroxycarbamoyl)benzoyl]-carbamate (SH) in acetate buffer solutions of pH 5.18 and $[X]_o$ = $2.0 \times 10^{-4}$ M {$[B]_T$ = 0.2 M (○), 0.5 M (△), and 0.8 M (□)}. Solid lines are drawn through the least-squares calculated points from equation (9) for (○), $10^3k_1$, = 6.16, $10^3k_2$ = 1.26 $min^{-1}$, ε′ = 2 155 l $mol^{-1}$ $cm^{-1}$, $A_0$ = 0.33; (△), $10^3k_1$ = 7.26, $10^3k_2$ = 1.90 $min^{-1}$, ε′ = 1 902 l $mol^{-1}$ $cm^{-1}$, $A_0$ = 0.016; (□), $10^3k_1$ = 7.79, $10^3k_2$ 2.68 $min^{-1}$, ε′ = 1 697 l $mol^{-1}$ $cm^{-1}$, $A_0$ 0.003

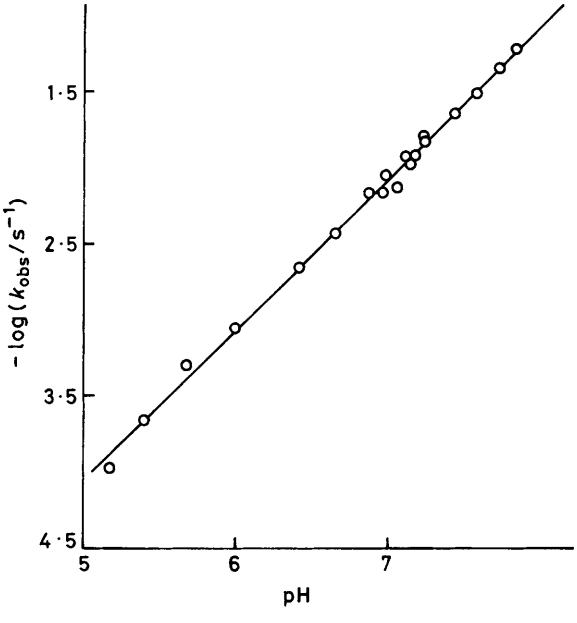
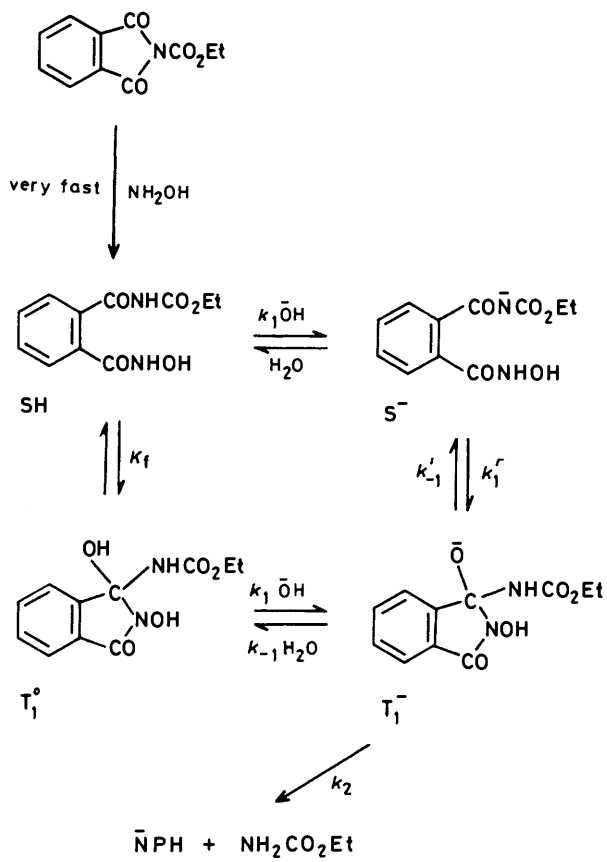



**Figure 2.** Effect of pH on first-order rate constants, $k_{obs.}$, for cyclization reactions of ethyl *N*-[*o*-(*N*-hydroxycarbamoyl)benzoyl]carbamate (SH).

The effect of the total hydroxylamine buffer concentrations $[B]_T$ on cyclization was studied at pH 5.40 and 6.96 for $[B]_T$ 0.05—0.40M. The observed first-order rate constants, $k_{obs.}$, were found to be independent of $[B]_T$. However, the observed absorbance values at $t \infty$ ($A_\infty^{obs.}$) were found to decrease significantly with increase in $[B]_T$. These $A_\infty^{obs.}$ values are comparable with those obtained in the hydroxylaminolysis of authentic NHPH under essentially similar experimental conditions. This shows that the cyclized product, NHPH, reacts rapidly with $NH_2OH$ and forms a fast equilibrium between




**Scheme 4.**

NHPH and P as shown in Scheme 3. The observed values of $A_\infty^{obs.}$ obtained at $t_\infty$ *ca.* 380 min, are significantly smaller than the corresponding values obtained at $t_\infty$ 4 min. This could be attributed to the slow hydrolysis of NHPA. An alternative possibility for the decrease of $A_\infty^{obs.}$ with increase of $[B]_T$ is the formation of P by the nucleophilic substitution reaction of $NH_2OH$ with SH. But this possibility could be ruled out for at least two reasons. (i) Such a parallel reaction along with cyclization reaction would yield $k_{obs.}$ which should increase with increase of $[B]_T$. But this dependence of $k_{obs.}$ on $[B]_T$ could not be observed. (ii) The values of $A_\infty^{obs.}$ observed at *t* 332 min at different $[B]_T$ values are comparable with the corresponding values obtained in the hydroxylaminolysis of authentic NHPH under essentially similar experimental conditions.

Cyclization of SH to NHPH was also studied under the buffer solutions of acetate ($[B]_T$ 0.2—0.8M), phosphate ($[B]_T$ 0.16—0.64M) and Tris($[B]_T$ 0.16—0.64M) at different pH. The observed first-order rate constants were found to be independent of $[B]_T$.

The buffer independent first-order rate constants, $k_{obs.}$, for the cyclization reactions were obtained at various pH ranging from 5.18 to 7.84. These rate constants give a good fit to equation (10). The value of $k_{OH}$ of $(4.06 \pm 0.05) \times 10^4$ $dm^3$ $mol^{-1}$ $s^{-1}$ was

$$k_{obs.} = k_{OH}[\bar{O}H] \qquad (10)$$

calculated from equation (10) using least-squares technique. The fit of the observed data to equation (10) is evident from the plot of Figure 2 where the solid line is drawn through the calculated points. The observed $k_{OH}$ value is *ca.* $3 \times 10^5$ times larger than $k_{OH}$ for hydroxide ion-catalysed hydrolysis of methyl benzoate ($k_{OH}$ 0.125 $dm^3$ $mol^{-1}$ $s^{-1}$).[3,17]

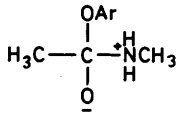
## Discussion

A reasonable reaction mechanism (Scheme 4) for the hydroxide ion-catalysed conversion of ethyl *N*-[*o*-(*N*-hydroxycarbamoyl)-benzoyl]carbamate (SH) into ionized *N*-hydroxyphthalimide ($\bar{N}$PH) involves either the pre-equilibrium formation of anionic substrate ($\bar{S}$) followed by intramolecular general base-catalysed cyclization of $S^-$ to $T_1^-$ ($k'_1$ step), or the initial attack of neutral carbamoyl nitrogen on the carbonyl carbon of SH to form $T_1^0$ followed by hydroxide ion-catalysed conversion of $T_1^0$ into $T_1^-$ ($k_1$ step). It is apparent that the nitrogen-bound proton of $CONHCO_2Et$ is more acidic than that of CONHOH because $\sigma^*$ for OH is smaller than that for $CO_2Et$.[18] $S^-$ can therefore be expected to be the predominant ionized form of the substrate. However, formation of $T_1^-$ from $S^-$ may be expected to involve the pre-equilibrium formation of $S_1^-$ from $\bar{S}$ followed by intramolecular nucleophilic attack at carbonyl carbon; although the occurrence of the transition state ($TS_1^-$) in the formation of $T_1^-$ from $S^-$ (Scheme 4) cannot be completely ruled out. It appears that the proton attached to nitrogen is more acidic than the one attached to oxygen in CONHOH group of $\bar{S}$ because $\sigma_I^{Ac} + \sigma_I^{OH}$ is larger than $\sigma_I^{NHAc}$.[19] Furthermore, the nucleophilic attack by the ionized group, $CONHO^-$, in which the charge resides on oxygen cannot lead to the formation of the observed product, NHPH.

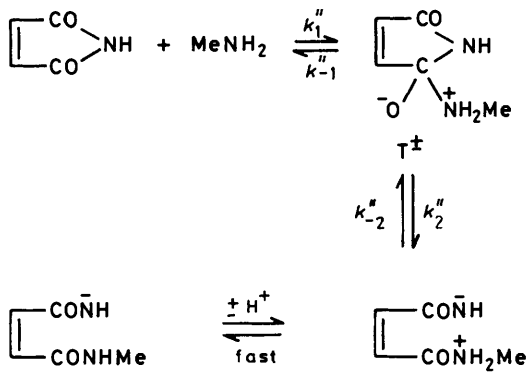
The reaction mechanism SH → $S^-$ → $T_1^-$ → $\bar{N}$PH is however kinetically indistinguishable from the mechanism SH → $T_1^0$ → $T_1^-$ → $\bar{N}$PH, especially where reaction of $T_1^-$ is rate determining. In most of the earlier related studies, the former mechanism was suggested. Fife and DeMark[10] have suggested both mechanisms in the intramolecular aminolysis of amides. In these and related reactions, it is of course not easy to assert with certainty that whether both the mechanisms are occurring simultaneously or one is dominating over the other under the changing structural features of the substrates. We present, although qualitative, evidence below to support the occurrence of SH → $S^-$ → $T_1^-$ → $\bar{N}$PH mechanism in the present system. The evidence is essentially based on the relative magnitudes of the rate constants $k'_{-1}$ and $k_{-1}[H_2O]$ which control the breakdown of $T_1^-$ towards the reactants.

The order of the magnitude of $k_{-1}[H_2O]$ was derived as follow. In $k_{-1}$ step, a thermodynamically unfavourable proton transfer takes place from $H_2O$ ($pK_a$ 15.7) to $T_1^-$ (the $pK_a$ of $T_1^0$ is estimated to be < 10.3 as described in the Appendix). Thus the magnitude of $k_{-1}[H_2O]$ could be estimated to be *ca.* $10^6$ $s^{-1}$ based on $[H_2O]$ 55M, and a β value of 1 (β 1 for acid–base reaction is the characteristic of the thermodynamically unfavourable proton transfer)[20] and the value of the second-order rate constant of $10^{10}$ $dm^3$ $mol$ $s^{-1}$ for the reaction between $H_2O$ and $\bar{O}H$ in which proton transfer takes place in presumably thermodynamically favourable direction. Alternatively, the value of $k_{-1}[H_2O]$ may be calculated as follows: from Scheme 4, $k_{-1}[H_2O] = k_1K_w/K_a$ and considering $k_1$ $10^{10}$ $dm^3$ $mol^{-1}$ $s^{-1}$, $K_w$ $10^{-14}$ $mol^2$ $dm^{-6}$, and $pK_a$ < 10.3, one gets $k_{-1}[H_2O]$ *ca.* $10^6$ $s^{-1}$.

The approximate value of $k'_{-1}$ was derived as follows. The $k'_{-1}$ step involves intramolecular general acid-catalysed conversion of $T_1^-$ into $S^-$. The estimated value of the rate constant for the expulsion of the nitrogen leaving group in (I) is



(I)



Scheme 5.

$3 \times 10^9$ $s^{-1}$.[21] Based on this value, the $k''_{-1}$ value in Scheme 5 may be assumed to be slightly less than *ca.* $10^9$ $s^{-1}$ because the push experienced by nitrogen leaving group in (I) is probably little more than that in $k''_{-1}$ step ($\sigma_I^{OAr}$ 0.38, $\sigma_R^{OAr}$ −0.34, $\sigma_I^{NHCOMe}$ 0.26, $\sigma_R^{NHCOMe}$ −0.25, $\sigma_I^{CH_3}$ −0.04, $\sigma_R^{CH_3}$ −0.11, $\sigma_I^{CH=CH}$ 0.05).[19] The value of $k''_1$ (for attack of $MeNH_2$ on maleimide) may be assumed to be *ca.* 10 $dm^3$ $mol^{-1}$ $s^{-1}$ for the reasons described as follows. The nucleophilic second-order rate constants for the reactions of highly basic amines with esters where nucleophilic attack was rate determining, were found to fall on a Brönsted plot of slope 0.2.[22] In these reactions, the second-order rate constants for $MeNH_2$ and $\bar{O}H$ were not significantly different from each other. Thus, assuming that $k''_1$ for $MeNH_2$ and $\bar{O}H$ fits the same Brönsted plot, a Brönsted slope of *ca.* 0.2 may be used to estimate qualitatively the value of $k''_1$ for $MeNH_2$ considering $k''_1$ 72 $dm^3$ $mol^{-1}$ $s^{-1}$ for $\bar{O}H$.[23] The reported rate constants for $\bar{O}H$-catalysed cleavages of maleimide and *N*-(2-bromoethyl)phthalimide are 72 and 20 $dm^3$ $mol^{-1}$ $s^{-1}$,[24] respectively, at 30 °C. These results reveal that the intrinsic reactivities of maleimide and phthalimide toward $\bar{O}H$ are only *ca.* 3—4-fold different from each other. The observed value of $k''_2k''_1/k''_{-1}$ of 3.8 $dm^3$ $mol^{-1}$ $s^{-1}$[25] gives the value of $k''_2$ of the order of $10^7$ $s^{-1}$ assuming $k''_{-1}$ and $k''_1$ of the order of $10^8$ $s^{-1}$ and 10 $dm^3$ $mol^{-1}$ $s^{-1}$, respectively. Comparing the tetrahedral intermediates $T_1^-$ (Scheme 4) and $T^{\pm}$ (Scheme 5), it appears that $k'_{-1}$ should be larger than $k''_2$ for at least two reasons. (i) The $pK_a$ of leaving group in $k''_2$ (Scheme 5) is expected to be larger than the $pK_a$ of leaving group in the $k'_{-1}$ step (Scheme 4).* (ii) The electronic push experienced by the leaving group in the $k'_{-1}$ step is apparently larger than that in the $k''_2$ step. Thus, this analysis reveals that $k'_{-1}$ is larger than *ca.* $10^7$ $s^{-1}$ because $k''_2$ is of the order of $10^7$ $s^{-1}$. The magnitude of the rate constant $k_2$ is presumably smaller than that of $k'_{-1}$ because the leaving group in $k'_{-1}$ step is more acidic than that in $k_2$ step† and this leads to $k_2$ step as the rate-limiting one.

* An approximate $pK_a$ range of 14—15[26] has been taken for maleamide on the basis of the reported values of $pK_a$ of benzamide, acetamide, and *N*-methylacetamide of 14—15,[27] 15.4,[27] and 17.1,[28] respectively. In the absence of any known reliable correlation of acidity constants of *N*-substituted benzamides with $\sigma^*$, we presume a reduction of *ca.* 3.8 $pK$ units in the $pK_a$ of benzamide due to the replacement of H by OH at nitrogen. This is based on the average of the difference of $pK_a$ of $\overset{+}{N}H_4$ and $\overset{+}{N}H_3OH$ (9.2—6.0) and that of $Me\overset{+}{N}H_3$ and $Me\overset{+}{N}H_2OH$ (10.66—6.25). The $pK_a$ of benzamide is also expected to be reduced by the replacement of *o*-H by *o*-$CONHCO_2Et$.

† The $pK_a$ of $H_2NCO_2Et$ is presumably similar to that of acetamide because $\sigma_I$ (0.28) and $\sigma_R$ (0.16) for Ac are not significantly different from $\sigma_I$ (0.30) and $\sigma_R$ (0.14 for $CO_2Et$.[21]

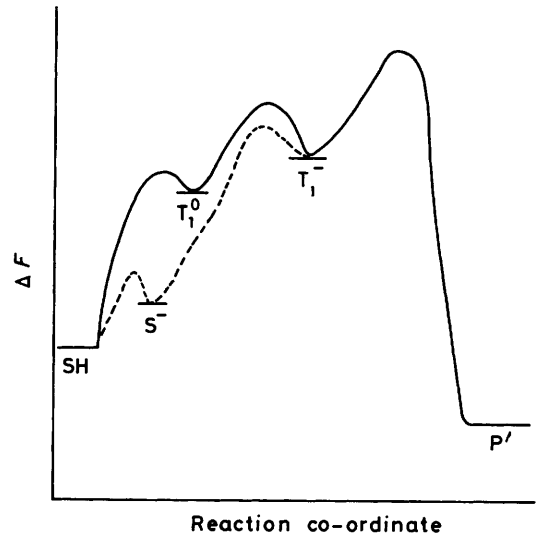



**Figure 3.** Free energy–reaction co-ordinate diagram for $OH^-$-catalysed cyclization of ethyl *N*-[*o*-(*N*-hydroxycarbamoyl)benzoyl]carbamate (SH) (based on mechanism shown in Scheme 4). Solid and broken lines represent the reaction path: SH → $T_I^0$ → $T_I^-$ and SH → $S^-$ → $T_I^-$, respectively

The conclusion that $k_{-1}[H_2O] \simeq 10^6$ s$^{-1}$ and $k'_{-1} > 10^7$ s$^{-1}$ reveals that the lowest-energy path for the breakdown of intermediate $T_I^-$ to reactant is $k'_{-1}$. According to the principle of microscopic reversibility, if $k'_{-1}$ step is the lowest-energy path (*i.e.* the most probable path) for breakdown of $T_I^-$, then the $k'_1$ step should be the lowest-energy path for its formation.[29] Thus, as illustrated by a qualitative free energy reaction co-ordinate diagram (Figure 3), the preferred (lower-energy) pathway of the reaction must be *via* $S^-$ → $T_I^-$. The preferred reaction path shown in Scheme 4 could lead to equation (11) on the presumption that reaction of $T^-(k_2)$ is rate determining. In equation (11) $K'_a$ =

$$k_{obs.} = k'_1k_2K'_a/(a_H + K'_a)k'_{-1} \quad (11)$$

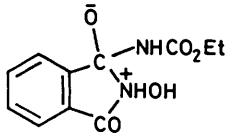
$[S^-]a_H/[SH]$. Within the observed pH range, it is appparent that $K'_a \ll a_H$ and application of this condition reduced equation (11) to (12). Comparing equation (12) with (10), we get equation (13). The p$K_a$ of diacetylamine is 12.9[30] at 25 °C.

$$k_{obs.} = k'_1k_2K'_a[\bar{O}H]/K_wk'_{-1} \quad (12)$$

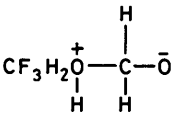
$$k_{OH} = k'_1k_2K'_a/K_wk'_{-1} \quad (13)$$

Assuming the $K'_a$ of the order of *ca.* $10^{-12}$, the value of $k'_1k_2/k'_{-1}$ of $4 \times 10^2$ s$^{-1}$ could be calculated from equation (13) using the observed value of $k_{OH}$. The observed values of $k_{OH}$ for cyclization of methyl 2-ureidobenzoate[3] and methyl *o*-carbamoylbenzoate[2] are 940 dm$^3$ mol s$^{-1}$ (30 °C) and $3.1 \times 10^3$ dm$^3$ mol$^{-1}$ s$^{-1}$ (25.9 °C), respectively. If we assume that p$K'_a \simeq$ p$K_w$ in these reactions then the calculated values of $k'_1k_2/k'_{-1}$ of 940 and $3.1 \times 10^3$ s$^{-1}$ may be compared with the corresponding value of $4 \times 10^2$ s$^{-1}$ obtained in the cyclization of SH.

The only sensible route to $T_I^0$ (Scheme 4) is *via* the dipolar intermediate (II). The approximate lifetime of (II) may be estimated as follows. Jencks[29] reported that the estimated lifetime of dipolar intermediate (III) is $\leqslant 10^{-13}$ s. The p$K_a$ of the conjugate acid of benzamide has been reported as −2.16 in aqueous $H_2SO_4$.[31] The p$K_a$ of nitrogen-bound proton in (II) is therefore expected to be less than −2.16. The carbon basicity of oxy anions is higher than that of nitrogen for a given proton basicity.[21] Thus, the driving force for breakdown of (II) to SH is more than that of (III) to $CF_3CH_2OH$ and HCHO which




(II)




(III)

reveals that the lifetime of (II) is even much smaller than $10^{-13}$ s (which is the period of a critical molecular vibration). The lifetime of (II) of *ca.* $< 10^{-13}$ s reveals that it does not exist in a potential-energy minimum. Nevertheless, it might be located at an inflection point on the potential-energy surface.*

Inspection of Scheme 4 reveals that for a given leaving group the increase in the basicity of the neutral nucleophile will decrease the value of $k'_{-1}$ and most likely increase the value of $k_{-1}[H_2O]$ by increasing the p$K_a$ of carbon-bound hydroxylic proton of $T_I^0$. The nature of the leaving group should also affect the relative magnitudes of $k'_{-1}$ and $k_{-1}[H_2O]$ (by affecting the p$K_a$ of $T_I^0$). An increase in the electron donating ability of the leaving group would increase both $k'_{-1}$ and p$K_a$ of $T_I^0$. Hence the polar effect of the leaving group is operating in the same direction while that of the neutral nucleophile is operating in the opposite direction to affect the magnitudes of both $k'_{-1}$ and $k_{-1}[H_2O]$. Thus an increase in the p$K_a$ of neutral nucleophile for a given leaving group might change the mechanism operating from SH → S → $T_I^-$ → P to SH → $T_I^0$ → $T_I^-$ → P (Scheme 4).

The observed rate constants, $k_{OH}$, for hydroxide ion-catalysed cyclization reactions of methyl *o*-carbamoylbenzoate, phthalamide, methyl *o*-aminomethylbenzoate, *o*-aminomethylbenzamide, ethyl *o*-hydroxymethylbenzoate, and *o*-hydroxymethylbenzamide are $3.1 \times 10^3$ (25.9 °C),[2] 4.9 (25.9 °C),[2] $7 \times 10^3$ (30 °C),[9] 0.16 (30 °C),[10] $10^4$ (30 °C)[4] and 0.154 (30 °C),[8] and 0.04 dm$^3$ mol$^{-1}$ s$^{-1}$ (25 °C),[6] respectively. It appears from these results that the basicity of the neutral nucleophile has essentially no effect on $k_{OH}$ values while the basicity of the leaving group has significant effect on $k_{OH}$ values. These results are consistent with reaction mechanism shown in Scheme 4. An increase in the basicity of the neutral nucleophile will increase the value $K_f$ and decrease the value of $k_1/k_{-1}$ and thus the multiple $K_fk_1/k_{-1}$ will remain essentially unchanged. The rate constant, $k_2$, for the presumed rate-determining step in Scheme 4 should be expected to depend significantly on the p$K_a$ of the leaving group. Thus the magnitudes of the observed rate constants essentially depend upon the p$K_a$ of the leaving groups.

The value of $k_{OH}$ of 4.9 dm$^3$ mol$^{-1}$ s$^{-1}$ for cyclization reaction of phthalamide[2] is nearly 30 times larger than that of *o*-hydroxymethylbenzamide ($k_{OH}$ 0.154[8] and 0.04 dm$^3$ mol$^{-1}$ s$^{-1}$ [6]). This shows that the hydroxide ion-catalysed cyclization reactions of phthalamide and *o*-hydroxymethylbenzamide follow different mechanisms. The cyclizations of phthalamide to phthalimide and *o*-hydroxymethylbenzamide to phthalide presumably follow reaction paths: SH → $S^-$ → $T_I^-$ → P and SH → $T_I^0$ → $T_I^-$ → P, respectively (Scheme 4). Although the p$K_a$ of neutral nucleophiles *o*-$CH_2OH$ and *o*-$CONH_2$ may not be very much different from each other, the larger basicity toward carbon of oxy anions than of amines for a given basicity toward the proton would make $k'_{-1}$ larger for phthalamide compared with that for *o*-hydroxymethylbenzamide. Gresser and Jencks[32] showed that, for an amine and aryl oxide with equal p*K*s of 5 and 10, the amine will be expelled faster by factors of $10^3$ and $10^5$, respectively. The values of $k_{-1}[H_2O]$ for both the system

* I thank a referee for suggesting this point.

should be nearly same and hence it might be possible that $k'_{-1} > k_{-1}[H_2O]$ for phthalamide and $k'_{-1} < k_{-1}[H_2O]$ for *o*-hydroxymethylbenzamide.

The $k_{OH}$ value for cyclization of SH to NHPH is only *ca.* 4 times larger compared with that for ethyl 2-hydroxymethylbenzoate which could be argued to be due to possibly slight difference in the acidity of $H_2NCO_2Et$ and ethanol. But the absence and presence of buffer catalysis in the cyclization reactions of SH and ethyl 2-hydroxymethylbenzoate, respectively, is an indication of the occurrence of different mechanisms in these two reactions. Buffer catalysis has been observed in the cyclization reactions of phenyl *o*-(2-imidazoyl)benzoate whereas no such catalysis could be detected in the cyclization reactions of trifluoroethyl *o*-(2-imidazoyl)benzoate.[11] The absence of the intermolecular general base catalysis in the present system is probably the consequence of the possible involvement of intramolecular general base catalysis in the $k'_1$ step (Scheme 4) where the $\bar{N}CO_2Et$ group is acting as the general base catalyst.

## Appendix

*Calculation of* $[P]_e/[X]_e$.—It has been observed that ethyl *N*-[*o*-(*N*-hydroxycarbamoyl)benzoyl]carbamate (SH) does not absorb at 300 nm. Therefore it may be safely assumed that the absorption of *o*-(*N*-hydroxycarbamoyl)benzohydroxamic acid (P) is nearly zero at 300 nm. Following this assumption, the observed absorbance at equilibrium ($A_\infty^{obs.}$) may be given by equation (ia or b) where $\varepsilon^-$ and $\varepsilon$ represent the molar extinction

$$A_\infty^{obs.} = \varepsilon^-[\bar{N}PH]_e + \varepsilon[NHPH]_e. \quad \text{(ia)}$$

$$A_\infty^{obs.} = \left(\frac{\varepsilon^- K_a + \varepsilon a_H}{a_H + K_a}\right)[X]_e \quad \text{(ib)}$$

coefficients of ionized ($\bar{N}PH$), and non-ionized (NHPH), *N*-hydroxyphthalimide. $[X]_e = [NPH]_e + [NHPH]_e$. Similarly, the observed absorbance ($A_0^{obs.}$) at *t* 0 may be given by (ii) where

$$A_0^{obs.} = \left(\frac{\varepsilon^- K_a + \varepsilon a_H}{a_H + K_a}\right)[X]_0 \quad \text{(ii)}$$

$[X]_0$ is the initial concentration of *N*-hydroxyphthalimide. At constant pH, equations (i) and (ii) lead to (iii) or (iv) where

$$[X]_e/[X]_0 = A_\infty^{obs.}/A_0^{obs.} \quad \text{(iii)}$$

$$[P]_e/[X]_0 = (A_0^{obs.} - A_\infty^{obs.})/A_0^{obs.} \quad \text{(iv)}$$

$[P]_e = [X]_0 - [X]_e$. Equations (iii) and (iv) can lead to equation (v).

$$[P]_e/[X]_e = (A_0^{obs.} - A_\infty^{obs.})/A_\infty^{obs.} \quad \text{(v)}$$

The values of $A_0^{obs.}$ were calculated from equation (ii) with known values of $\varepsilon^-$, $\varepsilon$, $a_H$, $[X]_0$, and $K_a$. Thus the known values of $A_0^{obs.}$ and $A_\infty^{obs.}$ were used to calculate $[P]_e/[X]_e$ from equation (v).

*Estimation of* $pK_a$ *of Carbon-bound Hydroxylic Proton of* $T_1^0$ (Scheme 4).—An approximate value of $pK_a$ of $T_1^0$ may be derived as follows. Fox and Jencks[33] reported that the acidities of the substituted alcohols $XCR^1R^2OH$ were satisfactorily correlated with a value of $\rho_I$ −8.2. The values of $\sigma_I$[19] for NHAc, Ac, and $CO_2R$ are 0.26, 0.28, and 0.30, respectively, and therefore $\sigma_I$ for $NHCO_2Et$ may be assumed to be *ca.* 0.28. Similarly, $\sigma_I$ for N(OH)CO may be considered to be larger than 0.26 ($\sigma_I$ for NHAc) because $\sigma_I^{OH} > \sigma_I^H$. The value of $\sigma_I$[19] for Ph is 0.1. The $pK_a$ of $CH_3OH$ is 15.5[34] and the substitution of $NHCO_2Et$, N(OH)CO, and Ph for H in the α-position gives the approximate $pK_a$ of *ca.* < 10.3 [= 15.5 − 8.2 × (0.28 + 0.26 + 0.1)] for $T_1^0$.

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## References

1 T. H. Fife, *Adv. Phys. Org. Chem.*, 1975, **11**, 1; A. J. Kirby, *ibid.*, 1980, **17**, 183.
2 J. A. Shafer and H. Morawetz, *J. Org. Chem.*, 1963, **28**, 1899.
3 A. F. Hegarty and T. C. Bruice, *J. Am. Chem. Soc.*, 1970, **92**, 6575.
4 T. H. Fife and B. M. Benjamin, *J. Am. Chem., Soc.*, 1973, **95**, 2059.
5 T. H. Fife, and B. M. Benjamin, *Bioorg. Chem.*, 1976, **5**, 37.
6 K. N. G. Chiong, S. D. Lewis, and J. A. Shafer, *J. Am. Chem. Soc.*, 1975, **97**, 418.
7 C. J. Belke, S. C. K. Su, and J. A. Shafer, *J. Am. Chem. Soc.*, 1971, **93**, 4552.
8 T. Okuyama and G. L. Schmir, *J. Am. Chem. Soc.*, 1972, **94**, 8805.
9 T. H. Fife and B. R. DeMark, *J. Am. Chem. Soc.*, 1976, **98**, 6978.
10 T. H. Fife and B. R. DeMark, *J. Am. Chem. Soc.*, 1977, **99**, 3075..
11 T. H. Fife, R. J. Bambery, and B. R. DeMark, *J. Am. Chem. Soc.*, 1978, **100**, 5500.
12 A. J. Kirby, T. G. Mujahid, and P. Camilleri, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1610.
13 T. H. Fife and N. W. Duddy, *J. Am. Chem. Soc.*, 1983, **105**, 74.
14 M. N. Khan, *J. Org. Chem.*, 1983, **48**, 2046.
15 W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 1960, **82**, 1778.
16 M. N. Khan, *J. Chem. Res.*, 1986, (*S*), 290; (*M*), 2384.
17 M. N. Khan, *Indian J. Chem.*, 1986, **25A**, 831.
18 J. Fastrez, *J. Am. Chem. Soc.*, 1977, **99**, 7004.
19 J. Hine, 'Structural Effects on Equilibria in Organic Chemistry,' Wiley, New York, 1975, ch. 3.
20 M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 1964, **3**, 1.
21 M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 6970.
22 W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, 1968, **90**, 2622.
23 M. N. Khan, *J. Pharm. Sci.*, 1984, **73**, 1767.
24 M. N. Khan, *Int. J. Chem. Kinet.*, 1987, **19**, 143.
25 M. N. Khan, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1977.
26 M. N. Khan, *J. Chem. Soc., Perkin Trans. 2*, 1985, 891.
27 G. B. Barlin and D. D. Perrin, *Quart. Rev. Chem. Soc.*, 1966, **20**, 75.
28 R. S. Molday and R. C. Kallen, *J. Am. Chem. Soc.*, 1972, **94**, 6739.
29 W. P. Jencks, *Chem. Soc. Rev.*, 1981, **10**, 345.
30 J. T. Edward and K. A. Terry, *J. Am. Chem. Soc.*, 1957, **79**, 3527.
31 J. T. Edward, H. S. Chang, K. Yates, and J. R. Stewart, *Can. J. Chem.*, 1960, **38**, 1518.
32 M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 6963.
33 J. P. Fox and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 1436.
34 D. J. Hupe and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 451.

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