# Acid-catalysed Hydrolysis of N-Phenyl-*n*-butyrohydroxamic Acid*

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The acid-catalysed hydrolysis of N-phenyl-*n*-butyrohydroxamic acid has been studied in hydrochloric and perchloric acids. The effect of different variables such as [catalyst], temperature, ionic strength and dielectric constant of the medium have been investigated. It is concluded that the hydrolysis occurs by $A_{AC}2$ mechanism with the cleavage of N-acyl bond giving *n*-butyric acid and phenylhydroxylamine as the products, though the latter could not be detected under the reaction conditions due to its instability.

EXCEPT for two reports on the kinetics and hydrolysis of benzohydroxamic acid and some *para*-substituted benzohydroxamic acids[1,2], not much data are available on this subject. In this paper a detailed study on the acid-catalysed hydrolysis of N-phenyl-*n*-butyrohydroxamic acid is described. A mechanism consistent with the results has also been proposed.

## Materials and Methods

N-Phenyl-*n*-butyrohydroxamic acid was prepared according to literature procedure[3]. The stock solutions of 8M hydrochloric acid (BDH, AR) and perchloric acid (S. Merck, GR) were prepared and standardized by titration against alkali. A stock solution of 0·02M ammonium metavanadate (Hopkin & Williams, AR) was prepared in water. Ferric chloride hexahydrate (BDH, AR) solution (1%, w/v) was prepared in water containing a little HCl. Ethanol-free chloroform was obtained by the recommended procedure[4]. Dioxane (BDH, AR) was purified[5] before use. $D_2O$ (isotopic purity 99·4%) was procured from BARC, Trombay. All other chemicals used were of AR grade.

The optical density measurements were carried out on a Bausch & Lomb spectronic-20 colorimeter. NMR spectra of the hydrolysis products were recorded on a Varian 60 MHz spectrometer either in $CCl_4$ or $CDCl_3$ solution.

*Determination of hydrolysis rates* — The hydrolysis rates were determined from the rate of disappearance of the hydroxamic acid. Aliquots of the reaction mixture were withdrawn at regular time intervals and the concentration of N-phenyl-*n*-butyrohydroxamic acid was determined colorimetrically. The new method recently reported for the colorimetric determination[4] of N-phenyl-*n*-butyrohydroxamic acid was adopted for measuring the rate constants in hydrochloric acid. Perchloric acid and dioxane were found to interfere in the determination, and,

therefore, the usual colour reaction with Fe(III) was used for studying the hydrolysis rates in these media. While studying the kinetics in aq. dioxane medium, requisite volumes of dioxane and water were mixed.

## Results and Discussion

The hydrolysis was found to be first order with respect to both substrate and HCl; but as the hydrolysis was carried out in the presence of excess hydronium ions pseudo-first order rates were ensured and the rate constants, in all the experiments, were calculated using the integrated rate equation for first order reactions.

*Kinetics in dil. HCl* — When the observed rate constants were plotted against [HCl] in the range 0·1 to 0·8M (Table 1), a linear plot was obtained indicating that the rate of hydrolysis increased proportionately with the [HCl]. From the intercept it could be inferred that N-phenyl-*n*-butyrohydroxamic acid did not react with water (in the absence of catalyst) to a measurable extent at ~40°. The Arrhenius parameters were calculated by studying the hydrolysis at different temperatures keeping

TABLE 1 — VARIATION OF RATE CONSTANT ($k$) IN HCl AT DIFFERENT IONIC STRENGTHS

(Ionic strength maintained by adding KCl; temp. = 40·2°)

| [HCl] M | μ not adjusted | $k$ (hr$^{-1}$) at | | |
|---|---|---|---|---|
| | | μ=0·5M | μ=0·8M | μ=1·2M |
| 0·1 | 0·0257 | 0·0355 | 0·0394 | — |
| 0·2 | 0·0545 | 0·0659 | 0·0701 | 0·0817 |
| 0·3 | 0·0945 | 0·103 | 0·104 | — |
| 0·4 | 0·125 | 0·130 | 0·142 | 0·155 |
| 0·5 | 0·166 | — | 0·176 | — |
| 0·6 | 0·198 | — | 0·213 | 0·230 |
| — | 0·343* | — | — | — |
| 0·7 | 0·237 | — | 0·243 | — |
| 0·8 | 0·275 | — | — | 0·305 |
| 1·0 | 0·364 | — | — | 0·370 |
| 1·2 | 0·449 | — | — | — |

*In $D_2O$ medium.

TABLE 2 — EFFECT OF TEMPERATURE ON THE RATE
CONSTANT AT $\mu=0\cdot8M$ (KCl)

| [HCl] M | $k$ (hr$^{-1}$) at | | | |
|---|---|---|---|---|
| | 30·2° | 40° | 50·2° | 60·2° |
| 0·4 | — | 0·142 | 0·311 | — |
| 0·5 | 0·0746 | 0·176 | 0·392 | 0·821 |
| 0·6 | — | 0·213 | 0·467 | — |
| 0·7 | — | 0·243 | 0·539 | — |

TABLE 3 — EFFECT OF VARYING [ACID] ON THE
RATE CONSTANT

| [Acid] M | $k$ (hr$^{-1}$)* | | |
|---|---|---|---|
| | HCl at 40·2° | HCl at 35° | HClO$_4$ at 35° |
| 1·0 | 0·364 | 0·236 | 0·203 |
| 1·2 | 0·449 | — | — |
| 1·5 | 0·552 | — | — |
| 2·0 | 0·734 | 0·476 | 0·339 |
| 3·0 | 1·11 | 0·702 | 0·419 |
| 4·0 | 1·45 | 0·937 | 0·433 |
| 4·5 | — | — | 0·405 |
| 5·0 | 1·82 | 1·18 | 0·350 |

*Rate constants were computed from the energy of
activation.

the ionic strength at $0\cdot8M$ (KCl) (Table 2). The values obtained for the energy of activation $(E_a)$, frequency factor $(A)$ and entropy of activation $(\Delta S^{\ddagger})$ are $15\cdot96\pm0\cdot23$ kcal mole$^{-1}$, $6\cdot76\times10^6$ sec$^{-1}$ and $-27\cdot34\pm0\cdot71$ e.u. respectively. The values of activation parameters fall in the range typical of reactions proceeding by $A2$ mechanism. The entropy of activation is negative and falls in the range of $-15$ to $-30$ e.u. characteristic of bimolecular mechanism[6].
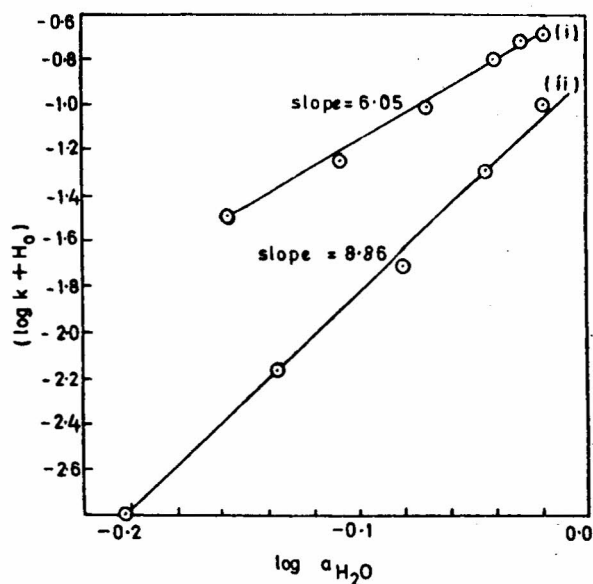
*Kinetics in moderately conc. HCl solutions* — The hydrolysis rates were studied in HCl at 40·2° and in HClO$_4$ at 35° in the range of 1 to $5M$ acid concentrations (Table 3). In HCl the rates increased proportionately with the [HCl] up to $5M$ without any rate maximum. The rate maximum may be obtained at a higher [HCl], but could not be experimentally verified because the reaction became very fast (half-life in $5M$ HCl is about 23 min). In HClO$_4$, the rates increased steadily with increasing [HClO$_4$], attained a maximum at $3\cdot75M$ HClO$_4$ and then decreased. It can be presumed, in an analogy with amides[7,8], that the protonation of N-phenyl-$n$-butyrohydroxamic acid is complete at $3\cdot75M$ HClO$_4$. A possible explanation for this behaviour is that below the rate maximum increasing acidity raises the concentration of the conjugate acid whereas beyond the rate maximum the increase in concentration of the protonated species by a given increase in [HClO$_4$] is proportionately smaller than the accompanying decrease in the activity of water so that the hydrolysis goes more slowly as the acidity is increased. With solutions of lower acidity the increase in [conjugate acid] outweighs the decrease in the activity of water and so the rate of hydrolysis increases with the acid concentration.

On applying the Zucker-Hammett treatment[9], we observed that the plot of log $k$ against $-H_0$ was not linear. However, the plot of log $k$ versus log [HX] was linear up to $5M$ HCl with a slope of unity. In HClO$_4$ the plot was linear up to $3M$ [HClO$_4$] with a slope of 0·7, beyond which a curvature was noticed, which can be attributed to the observed rate maximum. It is now believed that this hypothesis is not generally valid but the linearity may be taken as a rough indication of an $A1$ $(-H_0)$ or an $A2$ (log $C_{\text{acid}}$) mechanism. Thus, the linear plot of log $k$ versus log [HX] is indicative of a bimolecular mechanism and needs further confirmatory evidence.

Application of Bunnett's treatment[10] to the present data gave values of 6·1 (in HCl) and 8·9 (in HClO$_4$) for $w$ parameter from the plots of (log $k+H_0$) versus log $a_{\text{H}_2\text{O}}$ (Fig. 1). These values suggested that water played the role of a proton-transfer agent $(w>3\cdot3)$. On the basis of Bunnett's argument, which takes into account the difference in the degree of hydration of hydrated state and the reactants, we can say that the transition state is more polar than the substrate. The value of $w$ in HClO$_4$ is greater by about three units than that in HCl. Such differences in $w$ parameter have also been observed for reactions catalysed by different acids especially when $w$ is positive[11].

Treatment of the data in accordance with Bunnett and Olsen[12], which does not involve any water activity data, gave linear plots with slopes of 1·0 and 1·3 in HCl and HClO$_4$ respectively when (log $k+H_0$) was plotted against (log [HX]$+H_0$) (Fig. 2). These values of $\phi$ parameter fall clearly in the third category of their classification and support the conclusion that water acts as a proton transfer agent $(\phi>0\cdot58)$. This implies that water plays some additional role in the rate-determining step besides behaving as a nucleophile.

Though the hydrolysis in HCl was studied at 40·2°, the values of $k$ could be computed for 35°



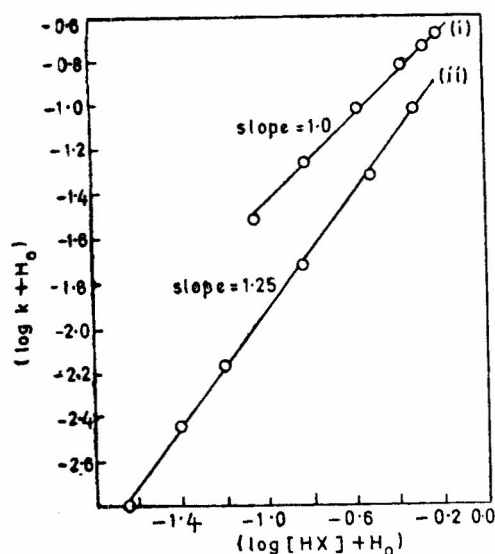Fig. 1 — Plots of (log $k+H_0$) versus log $a_{\text{H}_2\text{O}}$ in (i) HCl and (ii) HClO$_4$

Fig. 2 — Plots of $(\log [HX] + H_0)$ versus $(\log k + H_0)$ in (i) HCl and (ii) HClO$_4$

TABLE 4 — EFFECT OF VARYING [HClO$_4$] AT $\mu = 5 \cdot 0M$ (NaClO$_4$) AND TEMPERATURE 35°C

| [HClO$_4$] $M$ | $k$ (hr$^{-1}$) |
|---|---|
| 1·0 | 0·195 |
| 2·0 | 0·296 |
| 3·0 | 0·320 |
| 4·0 | 0·334 |
| 5·0 | 0·350 |

TABLE 5 — EFFECT OF VARYING [DIOXANE] ON THE RATE CONSTANT {[HCl] = 0·6$M$; [KCl] = 0·2$M$}

| % dioxane (v/v) | Molal conc. of water | $k$ (hr$^{-1}$) at 40·2° | $k$ (hr$^{-1}$) at 50·2° | $E_a$ kcal mole$^{-1}$ |
|---|---|---|---|---|
| 0·0 | 1·745 | 0·213 | 0·467 | 15·79 |
| 10·0 | 1·700 | 0·196 | 0·447 | 16·59 |
| 20·0 | 1·645 | 0·176 | 0·403 | 16·66 |
| 30·0 | 1·595 | 0·149 | 0·363 | 17·92 |
| 40·0 | 1·520 | 0·123 | 0·317 | 19·04 |
| 50·0 | 1·435 | 0·090 | 0·255 | 20·95 |

from a knowledge of the activation energy (Table 3). A comparison of the $k$ values reveals that the rate of hydrolysis is faster in HCl than in HClO$_4$. Bunton and coworkers[13] have suggested that for reactions involving $A1$ mechanism the catalytic effects of the added acids lie in the order HClO$_4$>HCl~H$_2$SO$_4$ while for $A2$ reactions the order is reversed. Thus, a higher rate in HCl in comparison to HClO$_4$ also provides support for a bimolecular mechanism.

*Isolation and identification of the products* — After measuring the hydrolysis rate, the reaction in remaining solution was allowed to go to completion. The solution was vigorously shaken with ether, the ethereal layer separated and the solvent evaporated at room temperature, when a colourless liquid, identified as *n*-butyric acid, was obtained. The formation of *n*-butyric acid showed that hydrolysis occurs with the cleavage of C—N bond. The identification of the other reaction product, viz. phenylhydroxylamine, could not be made in view of its instability under the reaction conditions.

*Effect of varying ionic strength* — The hydrolysis of N-phenyl-*n*-butyrohydroxamic acid, studied at varying [HCl] and ionic strengths [0·5, 0·8 and 1·2$M$ (KCl)] (Table 1), showed only a slight increase in the rate constant with increasing ionic strength. The change in ionic strength from 0·5 to 1·2$M$ increased the observed rate constant by only 20-24%. When the observed rate constants were plotted against [HCl] at different ionic strengths, linear plots were obtained. The linear plots meet at a point on the rate axis very close to zero corresponding to a value of 0·005. This indicates that the hydrolysis via neutral species is negligible and is independent of ionic strength. Therefore, it follows that conjugate acid is the reactive species. This information is equally consistent with a mechanism in which H$_3$O$^+$ donates a proton in the rate-determining step. The linearity of the plots with positive slopes indicates an acid-catalysed reaction[14].

The hydrolysis via the conjugate acid species exhibited a positive salt effect since the slope of the linear plots increased with increasing ionic strength. The gradients of the plots gave the specific rate constants, $k_\mu$, for the acid-catalysed reaction at a particular ionic strength. The values of $k_\mu$ at $\mu = 0 \cdot 5$, 0·8 and 1·2$M$ are 0·33, 0·35 and 0·37 respectively. With the limited data available in a narrow range of ionic strength studied, an attempt was made to observe the trend of the plot of log $k_\mu$ versus $\mu$. A linear plot indicated an ion-dipole type of reaction[15].

A comparison of the results obtained in HClO$_4$ at $\mu = 5M$ (NaClO$_4$) (Table 4) with those in Table 3 reveals that the rate decreases in the presence of sodium perchlorate. Normally the addition of NaClO$_4$ should increase the acidity of HClO$_4$ as measured by Hammett acidity function[16], and as a result the hydrolysis rate should also increase if an $A1$ mechanism is operating. The absence of such an acceleration pointed out to a bimolecular mechanism[17].

*Solvent isotope effect* — Experiments carried out for the hydrolysis in H$_2$O and D$_2$O using 0·6$M$ HCl at 40·2° (Table 1) show that the hydrolysis occurs 1·7 times faster in D$_2$O than in H$_2$O. The higher rate in D$_2$O suggests that a rapid transfer of protons to the substrate occurs in the reaction, and the pre-equilibrium step, therefore, is not the rate-determining step[18]. Considering the structural similarity with amides, the seat of protonation in hydroxamic acids may also be assumed to be the oxygen atom[19-21]. However, both O-protonated and N-protonated forms lead to kinetically indistinguishable results.

*Effect of dielectric constant* — In order to study the effect of dielectric constant of the medium on the rate of hydrolysis, experiments were carried out in different dioxane-water mixtures (Table 5). A change-over from water to aq. dioxane as solvent decreased the rate of hydrolysis indicating a more

polar character for the transition state as compared to reactants[22]. As a result, the complex formed tends to bind solvent molecules more strongly than do the reactant molecules and this results in a considerable negative entropy of activation and a corresponding low frequency factor[23].

When log $k$ was plotted against Grunwald's $Y$-values linear plots were obtained with slopes of 0·144 and 0·107 at 40·2° and 50·2° respectively. The small value of the sensitivity constant $(m)$ (slope) also supports a bimolecular mechanism[24].

Laidler-Landskroener treatment[25] yielded a value of 3·2 for the $b$ function which is similar in magnitude to those reported for the acid-catalysed hydrolysis of esters (3·0), amides (2·8) and anilides (3·4). This shows that like the acid-catalysed hydrolysis of these carboxylic acid derivatives, the hydrolysis of N-phenyl-$n$-butyrohydroxamic acid is also an ion-dipole reaction and involves the formation of a transition complex containing more than one water molecule.

The plots of log $k$ versus log $[H_2O]$ at 40·2° and 50·2° were linear having slope values of 1·1 and 0·8 respectively up to 50% (v/v) dioxane. From the results it can be presumed that the hydrolysis is first order with respect to solvent, and occurs throughout the range of the solvent composition studied by $A_{AC}2$ mechanism[26].

*Suggested mechanism* — The above observations prove beyond doubt the involvement of water in the rate-determining step. The number of water molecules actually involved in the formation of the transition complex cannot be ascertained with the present data because it is now well recognized that no single acidity function is generally applicable to the protonation behaviour of different neutral bases. Thus, for the amide hydrolysis the rate data have been correlated with the amide acidity function, $H_A$, by Yates and Stevens[19] who concluded that in all three water molecules were involved in the formation of the transition complex; one water molecule attacking the conjugate acid as a nucleophile assisted by two more water molecules by hydrogen bonding. In the absence of a suitable acidity function for the hydroxamic acids, it is worth while to examine the applicability of the method proposed by Yates and McClelland[27]. The new acidity function, $H_s$, can be obtained from the results reported by Tillet and coworkers[2] for the protonation of some *para*-substituted benzohydroxamic acids. The value of $M$ (a measure of the protonation behaviour of the substrate relative to Hammett bases) was in the range 0·58 to 0·68. If the average value of $M$ for the four hydroxamic acids falling in a close range is taken as 0·60, the new acidity function, $H_s$, can be calculated by relationship (1).

$$H_s = MH_0 \qquad \qquad \dots(1)$$

The plot of (log $k + H_s$) versus log $a_{H_2O}$ was linear with a slope of 1·85, indicating that two water molecules are involved in the formation of the transition complex during the hydrolysis of N-phenyl-$n$-butyrohydroxamic acid.

Thus, on the basis of the above results the plausible mechanism (Scheme 1) appears to involve a rapid
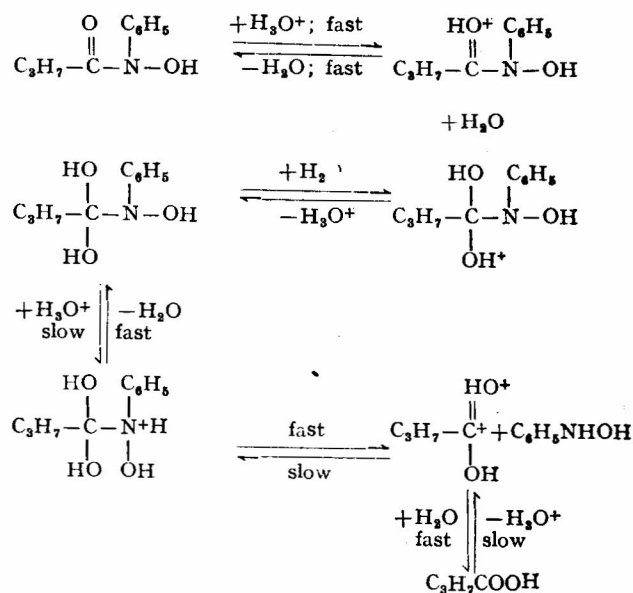


Scheme 1

protonation equilibrium of N-phenyl-$n$-butyrohydroxamic acid followed by a slow reaction of water with the protonated form, leading to the transition complex and subsequent hydrolysis resulting in the fission of N-acyl bond giving $n$-butyric acid and phenylhydroxylamine as the products.

The formation of a tetrahedral addition intermediate can be presumed by analogy with the hydrolysis of other carboxyl derivatives[28,29]. In fact Bunnett suggested a general acid catalysis for the breakdown of the tetrahedral intermediate as an explanation for the observed high value of $w$ in the case of ester hydrolysis by $A_{AC}2$ mechanism[10].

## Acknowledgement

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