

# Kinetics and mechanism of alkaline hydrolysis of hydroxamic acids

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Manuscript received 31 December 1997, revised 30 June 1998, accepted 20 July 1998

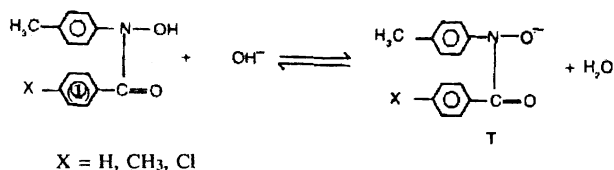
Kinetics and mechanism of the alkaline hydrolysis of *N-p*-tolylbenzohydroxamic acid ( $p$ -X-C<sub>6</sub>H<sub>4</sub>(C=O)N(OH)C<sub>6</sub>H<sub>4</sub>-CH<sub>3</sub>; X = H, CH<sub>3</sub>, Cl) and its *para*-substituted methyl and chloro derivatives have been studied in 10% (v/v) aqueous dioxane at 65°. Two cases of hydrolysis applicable to two different ranges of NaOH concentrations are recognized. The relative reactivity, temperature, salt, solvent and solvent isotope effects have also been examined.

In recent years, we have carried out investigations of acidic hydrolysis of hydroxamic acids<sup>1</sup>. Nevertheless, there appear to have been very few studies on alkaline hydrolysis of hydroxamic acid<sup>2</sup>. Owing to our interest in this subject, we have undertaken a detailed investigation on the alkaline hydrolysis of *N-p*-tolylbenzohydroxamic acid (*p*-TBHA) and two of its derivatives (1) to gain a better understanding of the mechanism.

A series of mechanistic probes have been employed, which include kinetic studies, temperature, salt, solvent and isotope effects.

## Results and Discussion

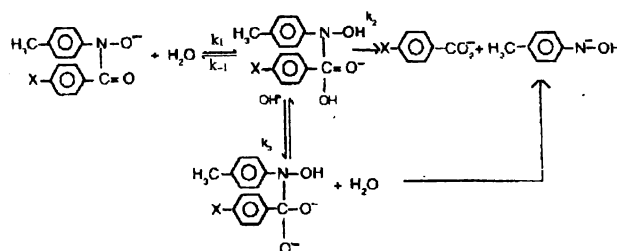
All systems showed first order dependence on hydroxide. The dependence of  $k_{\text{obs}}$  upon NaOH concentration for the hydrolysis of *p*-TBHA and its *para*-substituted derivatives are shown in Table 1 (rate constants were reproducible to within  $\pm 2\%$ ). The value of  $k_{\text{obs}}$  increases with increasing NaOH concentration upto 0.01 mol dm<sup>-3</sup> and then decreases gradually. The  $pK_a$  of *p*-TBHA is 9.38, thus the substrate is ionized to *p*-TBHA (Scheme 1) over the entire range of [OH<sup>-</sup>] used.



Scheme 1

The alkaline hydrolysis is believed to occur by following two mechanisms (Scheme 2), one catalysed by OH<sup>-</sup> and the other uncatalysed.

The reaction appears to involve a prior equilibrium addition of OH<sup>-</sup> to a carbonyl, the adduct then either cleaving or losing a proton from the hydroxyl in a second equilibrium step to give a dianion which undergoes cleavage. At high [OH<sup>-</sup>], this trapping of T<sub>0</sub> is the rate-determining. The T<sub>0</sub> (or its kinetic equivalent) is sufficiently reactive to break down to products without the assistance of OH<sup>-</sup>. The concentration of the undissociated substrate would



Scheme 2

decrease as the concentration of OH<sup>-</sup> increases. At low concentration of OH<sup>-</sup> very little of the substrate will be dissociated and the rate of the forward first step will be high. But because [OH<sup>-</sup>] is low, the specific base-catalysed second forward step is slow, and species T reverts to reactant faster than it proceeds to give the products. The first step, therefore, is a pre-equilibrium and the second step is rate-determining at high [OH<sup>-</sup>] however, substrate is extensively dissociated, so the reactive species (*p*-TBHA) is low which leads to a slow first forward step. But the second forward step from T<sub>0</sub>, being specific base-catalysed, has become faster at high [OH<sup>-</sup>] and effectively precludes reversal of the first step.

Table 1. Observed Pseudo-first order rate coefficients for the alkaline hydrolysis of X-C<sub>6</sub>H<sub>4</sub>(C=O)N(OH)C<sub>6</sub>H<sub>4</sub>-CH<sub>3</sub>

Temp. = 338 K, medium : 10% (v/v) dioxane-water		$k_y 10^6 \text{ s}^{-1}$		
[NaOH]		H	CH <sub>3</sub>	Cl
mol dm <sup>-3</sup>				
0.001	1.0	0.91	—	—
0.001 <sup>a</sup>	1.1	—	—	—
0.0025	1.5	1.4	—	—
0.0035	2.6	2.3	—	—
0.0050	3.2	3.1	—	—
0.0075	3.5	3.3	—	3.6
0.01	3.6	3.5	—	4.1
0.01 <sup>a</sup>	4.2	—	—	—
0.10	3.2	2.9	—	3.8
0.50	2.9	2.6	—	3.1
1.00	2.2	1.9	—	2.3
2.00	1.6	1.4	—	1.6
2.50	1.2	1.1	—	1.4
3.00	0.90	0.86	—	0.95
3.00 <sup>a</sup>	0.46	—	—	—
3.50	0.75	0.68	—	—
4.00	0.63	0.60	—	—

<sup>a</sup> In NaOD-D<sub>2</sub>O.

It has been observed that introduction of electron-attracting group increases the rate of hydrolysis whereas electron-repelling group decreases the hydrolysis. The products are substituted benzoic acids and *N-p*-tolyl-hydroxylamine.

**Correlation of reaction rates with the acidity function :** Little attention has been paid for correlation of the observed rate constant with the  $H_-$  acidity function<sup>3</sup>. Taking into consideration that the  $OH^-$  is strongly hydrated, the  $H_-$  function may be expressed in terms of concentrations of hydroxide ions and free water. Our results belong to the group, reactions expected to give a linear plot of  $\log k_\psi$  vs  $H_- + \log a_{H_2O}$  with about unit slope. The plot for our results is shown in Fig. 1 together with the Zucker-Hammett type plot,  $\log k_\psi$  vs  $H_-$ . Both plots indicate that in the range of NaOH concentration (Fig. 1) two linear parts can be obtained. By analogy with the Bunnett treatment of the acid-catalysed reactions,  $\log k_\psi - H_-$  was plotted against the  $\log a_{H_2O}$  and in concentrated NaOH solutions straight-line was observed with slope 1.9.

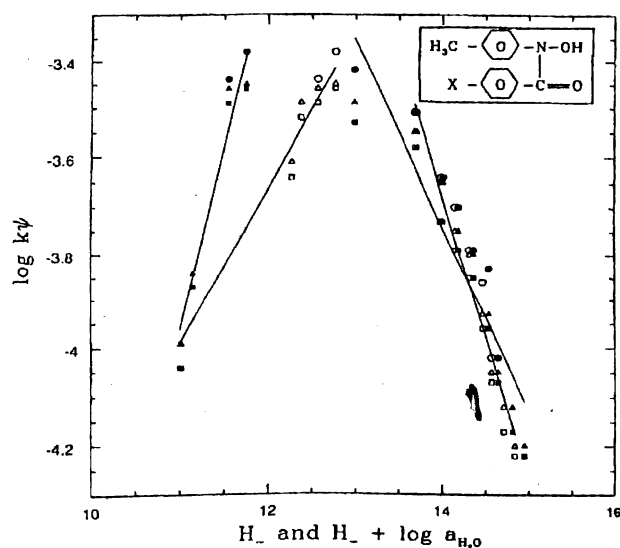


Fig. 1. Plots of  $\log k_\psi$  vs  $H_-$  and  $H_- + \log a_{H_2O}$  : ( $\Delta$ )  $X = H$ , ( $\blacksquare$ )  $X = CH_3$ , ( $\bullet$ )  $X = Cl$  for  $H_-$ ; ( $\Delta$ )  $X = H$ , ( $\square$ )  $X = CH_3$ , ( $\circ$ )  $X = Cl$  for  $H_- + \log a_{H_2O}$

Mashima and Ikeda<sup>4</sup> received such interpretations for hydrolysis of formhydrazide in alkaline solutions. The acidity function dependence of reaction rates will probably not only depend on the mechanism of the reaction and the hydration of the hydroxide ion but also on the hydration characteristics.

**Activation parameters :** Temperature effects were examined at 55, 65 and 75° for the reaction, solutions made with 0.001, 0.0075, 0.01, 1.0 and 3.0 mol dm<sup>-3</sup>. These concentrations lie in different ranges where the hydrolysis proceeds in different ways. The activation parameters are given in Table 2. Activation enthalpies ( $\Delta H^\ddagger$ ) and entropies ( $\Delta S^\ddagger$ ) were calculated by a linear least-square method,

using Eyring's equations. The  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  values continuously increase with increasing concentration of NaOH. Significantly large changes in  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  with negligible change in  $\Delta G^\ddagger$  with varying [NaOH] can normally be attributed to the enthalpy-entropy compensation effect. The negative values of  $\Delta S^\ddagger$  point to a transition state that is more ordered than the starting materials, as would be expected of a bimolecular reaction. The large  $\Delta S^\ddagger$  values are consistent with restriction of water of solvation in the transition states leading to or away from  $T_0$ .

Table 2. Activation parameters for alkaline hydrolysis of *p*-TBHA

Medium : 10% (v/v) dioxane-water

[NaOH] mol dm <sup>-3</sup>	X	=	H	CH <sub>3</sub>	Cl
0.001	$\Delta H^\ddagger$		81±0.65	83±0.88	—
	$\Delta S^\ddagger$		-85±0.39	-77±0.57	—
	$\Delta G^\ddagger$		106±1.15	106±1.23	—
	C.C.		0.999	0.999	—
0.0075	$\Delta H^\ddagger$		—	—	78±0.56
	$\Delta S^\ddagger$		—	—	-81±0.75
	$\Delta G^\ddagger$		—	—	102±1.51
	C.C.		—	—	0.999
0.01	$\Delta H^\ddagger$		84±0.60	85±0.82	82±1.30
	$\Delta S^\ddagger$		-64±1.31	-61±1.81	-69±2.00
	$\Delta G^\ddagger$		103±0.89	103±1.0	103±1.5
	C.C.		0.999	0.999	0.999
1.0	$\Delta H^\ddagger$		88±0.86	90±1.20	88±1.00
	$\Delta S^\ddagger$		-53±0.63	-50±1.01	-55±0.95
	$\Delta G^\ddagger$		105±0.58	105±0.92	104±0.80
	C.C.		0.999	0.999	0.999
3.0	$\Delta H^\ddagger$		93±1.22	95±1.53	92±1.39
	$\Delta S^\ddagger$		-48±0.91	-44±0.87	-49±0.72
	$\Delta G^\ddagger$		107±1.01	108±1.11	107±1.35
	C.C.		0.999	0.999	0.999

$\Delta H^\ddagger$  and  $\Delta G^\ddagger$  in kJ mol<sup>-1</sup>,  $\Delta S^\ddagger$  in JK<sup>-1</sup> mol<sup>-1</sup>.

**Solvent effect on rate :** In order to study the effect of the solvent on the rate of hydrolysis, experiments were carried out in different dioxane-water mixtures (Table 3). A large increase in rate was observed for increasing dioxane content in 0.01 mol dm<sup>-3</sup> NaOH, whereas in 3.0 mol dm<sup>-3</sup> NaOH a small increase in rate was observed for *p*-TBHA. Thus, those reactions with  $k_2$  in Scheme 2 as the rate-determining step show significantly greater increases in rate as the water content of the medium decreases than those with  $k_\psi$  in Scheme 2. This results from both the ability of dioxane to solvate charged dispersed structure and the greater need for protic solvation of localised charged structures.

**Kinetic isotope effect :** Kinetic solvent isotope effects have been used to investigate the mechanisms and mechanistic details of many reactions.

At low molarity an inverse isotope effect was found ( $k_{OD^-}/k_{OH^-} > 1$ ). The solvent isotope effect is a combination of three separate factors : solvation, the relative nucleophilicity of  $OD^-$  and  $OH^-$ , and a primary effect. Schowen<sup>5</sup> showed that  $k_{OD^-}/k_{OH^-}$  varies from 1 to 2 depending on the extent of bond formation in the transition

state. The magnitude of any primary isotope effect will depend on the extent of proton transfer from water, upto a maximum  $k_{\text{OH}}/k_{\text{OD}}$  of about 10, and it will offset the first two factors. The lack of an appreciable primary isotope effect appears to favour the mechanism (Scheme 2).

**Table 3.** Alkaline hydrolysis of *p*-TBHA in dioxane-water medium at 338 K in different concentrations of NaOH

Dioxane % (v/v)	$k_p \cdot 10^6 \text{ s}^{-1}$	
	0.001 mol dm <sup>-3</sup>	3.0 mol dm <sup>-3</sup>
10	3.6	0.9
20	4.6	1.1
30	5.8	1.6
40	8.7	1.9
50	11.4	—
60	12.1	—
70	12.9	—

The observed trend ( $k_{\text{OD}}/k_{\text{OH}} < 1$ ) in 3.0 mol dm<sup>-3</sup> NaOH suggests an increased, though small, extent of H transfer from water in the transition state.

**Salt effect:** The salt effects on the rate constants for *p*-TBHA in 10% (v/v) aqueous dioxane at 65° are shown in Table 4. A negative salt effect was observed in 0.01 mol dm<sup>-3</sup> NaOH and a positive salt effect in 3.0 mol dm<sup>-3</sup> NaOH.

**Table 4.** Alkaline hydrolysis of *p*-TBHA at 338 K with different concentrations of NaCl and NaClO<sub>4</sub>

Medium: 10% (v/v) dioxane-water

Salt mol dm <sup>-3</sup>	$k_p \cdot 10^6 \text{ s}^{-1}$			
	[NaOH] = 0.01 mol dm <sup>-3</sup>		3.0 mol dm <sup>-3</sup>	
	NaCl	NaClO <sub>4</sub>	NaCl	NaClO <sub>4</sub>
0.00	3.60	3.60	0.91	0.91
0.50	3.30	3.00	0.93	0.92
1.00	3.10	2.10	0.97	0.94
2.00	2.30	1.90	1.01	1.00
3.00	1.00	1.60	1.07	1.02

**Mechanism:** All the evidence discussed is in favour of the reaction presented in Scheme 2. Reactions may occur by two distinct mechanisms, one uncatalysed and the other catalysed by OH<sup>-</sup>. The substrate may be converted in a prior equilibrium to its conjugate base which then reacts, or the substrate may combine with OH<sup>-</sup>, proceeding through a transition state which contains the hydroxyl moiety. The analogous uncatalysed reactions corresponding to these mechanisms would be, respectively, reaction of the unionised substrate or reaction with water. This reaction appears to involve a prior equilibrium addition of hydroxide ion to a carbonyl, the adduct then either cleaving directly or losing a proton from the hydroxyl in a second equilibrium step to give a doubly charged anion which undergoes cleavage.

## Experimental

*p*-TBHA and its *para*-substituted derivatives were prepared by, benzoylating freshly prepared and purified *p*-tolylhydroxylamine<sup>6</sup>. Benzoyl chloride (Fluka), *p*-tolylbenzoyl chloride (Fluka) and *p*-chlorobenzoyl chloride (Merck) were used. Dioxane (GPR, B.D.H.), sodium chloride (AnalaR), sodium perchlorate (GR, Loba) were used as such. Heavy water (D<sub>2</sub>O, isotopic purity >99.8%) and sodium deuteroxide (NaOD, isotopic purity >95%) were procured from Bhabha Atomic Research Centre, Mumbai, India. Ferric chloride solution used in the colorimetric procedure was prepared by dissolution of anhydrous ferric chloride (SQ, Glaxo, 10 g) in distilled water (1 dm<sup>3</sup>) containing concentrated HCl (100 ml). Kinetic measurements were carried out by spectrophotometric method employing a Systronics 108 spectrophotometer. Rates of alkaline hydrolysis were determined spectrophotometrically by following the decrease in the characteristic absorption (520 nm) of the hydroxamic acid-ferric chloride complex. An aliquot (2 ml) of reaction mixture was periodically removed and added to ferric chloride solution (5 ml) on a spectrophotometer. Beer's law was obeyed by the system. The acidity of FeCl<sub>3</sub> solution was adjusted for the alkaline runs. The substrate concentration was  $6.6 \times 10^{-3}$  mol dm<sup>-3</sup>.

## Acknowledgement

The authors gratefully acknowledge for the financial assistance from U.G.C. and C.S.I.R., New Delhi. They are indebted to Dr. D. R. Mal, I.I.T., Kharagpur, for his help in synthetic work.

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