Kinetic Studies of Alkaline Hydrolysis of Methyl-2-[2′-oxo-3′-(2″-chloro-6″-fluorophenyl)propyl]benzoate and Methyl-2-benzoylmethylbenzoate in Aqueous and EtOH-H_2O Media

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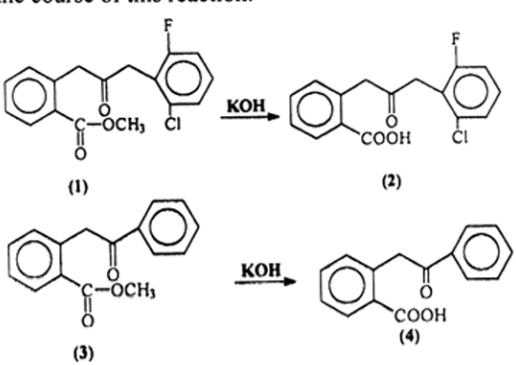
Summary: The hydrolysis of the compound, methyl-2-[2′-oxo-3′-(2″-chloro-6″-fluorophenyl)propyl]benzoate has been studied spectrophotometrically in the presence of hydroxide ions in aqueous, 25 % and 50 % (V/V) EtOH-H_2O mixtures. The dependence of pseudo-first order rate constant k_{obs} on hydroxide ion concentration is fitted by the expression $k_{obs} = k_o + k_1[OH] + k_2[OH]^2$, showing the formation of monoanionic and dianionic tetrahedral intermediates during the course of reaction. The magnitude of k_o shows significant participation of solvent in the reaction mechanism which goes on decreasing with increasing concentration of ethanol in the solvent mixture. The hydrolysis of methyl-2-benzoylmethylbenzoate has also been studied in aqueous medium in the presence of different hydroxide ion concentrations and results were compared with the former ester.

Introduction

Methyl-2-[2′-oxo-3′-(2″-chloro-6″-fluorophenyl)propyl]benzoate and methyl-2-benzoylmethylbenzoate have been synthesized from isocoumarins via the formation of keto acids [1]. The mechanism of reactions of such compounds with hydroxide ions has not yet been studied. Various pathways have been proposed for the hydrolysis of esters and amides [2-4]. Some exceptional cases [5] of such reactions involve the formation of dianionic tetrahedral intermediates. In the present investigations, kinetics of the alkaline hydrolysis of methyl-2-[2′-oxo-3′-(2″-chloro-6″-fluorophenyl)propyl] benzoate (**1**) and methyl-2-benzoylmethylbenzoate (**3**) are studied to see whether any dianionic intermediate are formed in the course of this reaction.



Results and Discussion

i) Hydrolysis of Methyl-2-[2′-oxo-3′-(2″-chloro-6″-fluorophenyl)propyl]benzoate

The compound, methyl-2-[2′-oxo-3′-(2″-chloro-6″-fluorophenyl)propyl]benzoate was hydrolyzed with aqueous KOH solution to produce 2-[2′-Oxo-3′- (2″-chloro-6″-fluorophenyl) propyl] benzoic acid. The product gave a broad singlet at 11.2 ppm exchangeable with D_2O in NMR spectra, which indicates the presence of –COOH group. After characterization of the product kinetics of hydrolysis of the compound (**1**) was studied spectrophotometrically. Change in absorbance with time for the hydrolysis of the compound (**1**) was observed; it was first increased and then decreased. The increase in absorbance may be interpreted in terms of charge redistribution. Such effects have also been observed in reaction of indole-1, 3-dione with hydroxide ion [6]. Plots of $\ln(A_\infty - A_t)$ against time are straight lines which indicates that the reaction is accurately of first order in the substrate. Large value of intercept (k_o= 0.031 per min.) shows significant role of solvent in the hydrolysis reaction. Second order rate constant k (91.11 dm^3 $mole^{-1}$ min^{-1}) was calculated as a slope of the plot (Fig 2). A reaction mechanism compatible to these results is shown in Scheme-1.

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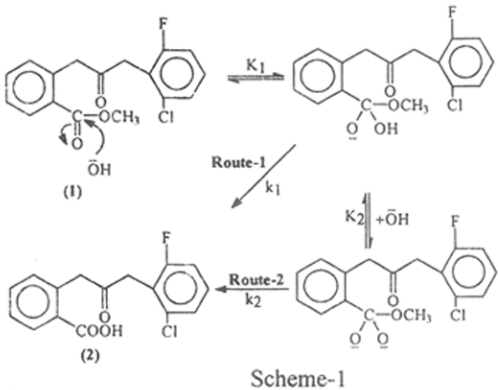


Scheme-1

Rate equations for Scheme-1 are given in equation (1) and (2).

$$k_{obs} = k_o + k_1 [^-OH] + k_2[^-OH]^2 \quad (1)$$

$$k_{obs}-k_o/ [^-OH] = k_1 + k_2 [OH] \quad (2)$$

Plot of $k_{obs}-k_o/[^-OH]$ versus $[^-OH]$ (0.002M-0.009M) gave a straight line. The values of k_2 and k_1 (88.263 dm^6 mol^{-2} min^2, 90.655 dm^3mol^{-1} min^{-1}) as slope and intercept respectively are obtained from the plot (Fig 1).

Putting the values of k_1 and k_2 in equation (1), pseudo first order rate constants were calculated. The experimental data (represented as points in Fig 2) showed excellent agreement with the calculated values of pseudo first order rate constant (k_{cal}) shown as solid line in the same figure. Assuming k_o is insignificant, the equation (2) became equation (3).

$$k_{obs}/ [^-OH] = k_1 + k_2[^-OH] \quad (3)$$

The plot between $k_{obs}/[^-OH]$ against hydroxide ion concentration is not linear which is indicative that the term k_o can not be ignored (Fig 3).

Hydrolysis of the compound (**1**) with potassium hydroxide was also studied in 25 % and 50 % (v/v) ethanol-water mixtures. The values of k_o obtained as intercepts of the plots of k_{obs} versus hydroxide ion concentrations in 25 % and 50 % (v/v) ethanol-water system decreased with increase in alcoholic contents. The values of the second order rate constants (k) increase with increase in the water contents. This may be attributed due to more basic strength of KOH in water (pKa = 14.0) as compared to ethanol (pka = 19.1) [7].

ii) Hydrolysis of Methyl-2-benzoylmethylbenzoate

The compound, methyl 2-benzoylmethylbenzoate, an unsubstituted analogue of the keto ester (**1**), was also hydrolyzed with aqueous KOH solution. The product was identified by comparing its extinction coefficient with that of separately prepared 2-benzoylmethylbenzoic acid. This comparison verified that the hydrolysis of the keto ester (**3**) afforded keto acid (**4**). The kinetic studies were made by observing the change in absorbance with time spectrophometerically. The change in absorbance at 280 n.m; first increased and then decreased which may be explained on the same reasons [6]. Pseudo first order rate constants were plotted against different hydroxide ion concentrations (0.002M-0.01M). The slope of this plot gave second order rate constant. The value of second order rate constant (k = 126.69 dm^3 mol^{-1} min^{-1}) for the hydrolysis of methyl-2-benzoylmethylbenzoate (Fig 4) is greater than the value (k = 91.11 dm^3 mol^{-1} min^{-1}) for the alkaline hydrolysis of methyl-2-[2′-oxo-3′-(2″-chloro-6″-fluorophenyl)propyl]benzoate. This may be interpreted in terms of field effect of chloro and fluoro groups in the ester (**1**). The hydrolytic reaction of methyl-2-benzoylmethylbenzoate with hydroxide ion follows a path-way similar to that shown for the reaction of hydrolysis of methyl-2-[2′-oxo-3′-(2″-chloro-6″-fluorophenyl) propyl]benzoate with hydroxide ion in Scheme-1.

iii) Identification of Reaction Product

The product of the alkaline hydrolysis of methyl-2-benzoylmethylbenzoate was identified to be 2-benzoylmethylbenzoic acid.

Table-1: Comparison of Extinction Coefficient of Ketoacid Present in the Reaction Mixture with that of the Ketoacid Prepared Separately

Wavelengths	Extinction Coefficients of Keto-Acid in the Reaction Mixture	Extinction Coefficients of Keto-Acid Separately Prepared
280	40.91644	40.57971
290	31.37466	30.55072
300	24.42049	23.47826
310	22.04852	21.33333
320	21.64420	21.82609
330	22.23720	23.30435
340	23.50404	24.43478
350	24.31267	24.43478
360	18.14016	18. 28986
370	13.01887	12.92754
380	8.787062	8.492754
390	4.932615	4.405797

The product of reaction of the compound (**3**) with hydroxide ion in aqueous medium was identified as follows. After mixing the reactants, the reaction was left overnight for its completion. An appropriate quantity of 2-benzoylmethylbenzoic acid (separately

prepared) was added to aqueous KOH solution to get exactly the same concentration, as of the reaction product in the mixture. UV-Visible spectra of both the keto acids were compared by calculating the values of molar extinction coefficients at different wavelengths. These values (Table-1) are very close to each other. This confirms that the reaction product obtained as a result of alkaline hydrolysis of methyl-2-benzoylmethylbenzoate is 2-benzoylmethyl benzoic acid.

Experimental

Water used in preparation of all the solutions was doubly distilled. KOH solutions were freshly prepared for all measurements. The reactions were initiated by injecting 0.1cm^3 of the substrate solution to 3 cm^3 of KOH solution. Initial concentrations of the substrate were usually of the order of 10^{-4} mol dm^{-3}. These concentrations were kept at least 20-fold less than the concentration of the most dilute buffer solution or KOH solution to maintain the pseudo first order conditions. All the measurements were made at 25 °C. Hitachi (Model U-200) and Cecil (Model 3041) UV-Visible spectrophotometers were used for kinetic measurements. The temperature of the cell housing was kept constant with water circulating from an external thermostat bath. Quartz cells with path length of 10 mm and equipped with Teflon stopper were used throughout. Reactions were followed at a single wavelength as a trace of absorbance versus time. Methyl-2-[2′-oxo-3′-(2″-chloro-6″-fluorophenyl)propyl]benzoate and methyl-2-benzoylmethylbenzoate were prepared by the methods given in literature [8].

i) Kinetics of Hydrolysis of Methyl-2-[2′-oxo-3′-(2″-chloro-6″-fluorophenyl)propyl]benzoate in KOH solution

The compound (**1**) (0.1g, 3.12x10^{-4} mol) was dissolved in ethanol (10 cm^3). The reaction of ester with aqueous solution of KOH (0.001M-0.01M) was monitored by observing the change in absorbance with time at 280 n.m. where the change was significant. Pseudo first order rate constants (k_{obs}) for each concentration of hydroxide was calculated as gradients of the plots of ln(A∞-At) against time. Kinetics of the same reaction was observed by using 25 % (v/v) EtOH-Water mixture and 50% (v/v) EtOH-Water mixture as solvents.

ii) Kinetics of Hydrolysis of Methyl-2-benzoylmethylbenzoate

Hydrolysis of methyl-2-benzoylmethylbenzoate was studied in aqueous solution of KOH. The initial concentration of the ester (**3**) in the reaction solution was 1.27x10^{-3} M. Absorbance readings were recorded at suitable intervals. Pseudo first order rate coefficients (k_{obs}) were calculated in the same manner as described earlier.

Key Words: Hydrolysis, Esters

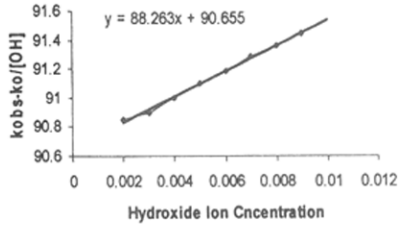
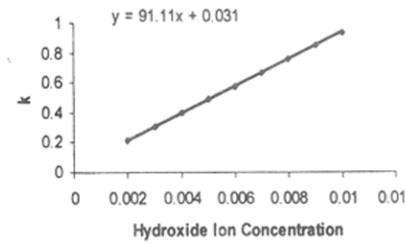


Fig.1: Plot of k_{obs}-k_o/[$^-$OH] versus [$^-$OH] for the hydrolysis of Methyl 2-[2′-oxo-3′-(2″-chloro-6″-fluorophenyl)propyl]benzoate in the presence of Aqueous Solution of KOH



Fig,2: Plot of pseudo-first order rate constant, k_{obs} against hydroxide ion concentration for the hydrolysisof Methyl 2-[2′-oxo-3′-(2″-chloro-6″-fluoro-phenyl) propyl]benzoate in the presence of Aqueous Solution of KOH

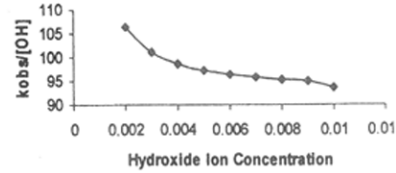


Fig. 3: Plot of k_{obs}/[OH$^-$] vs [OH$^-$] ignoring k_o for the hydrolysis of Methyl 2-[2′-oxo-3′-(2″-chloro-6″-fluorophenyl)propyl]benzoate in the presence of Aqueous Solution of KOH

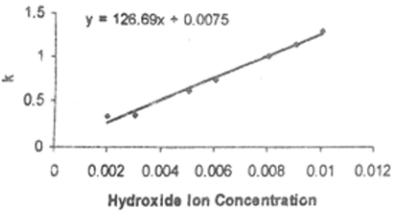


Fig. 4: Plot of pseudo-first order rate constant, k_{obs} against hydroxide ion concentration for the hydrolysis of Methyl-2-benzoylmethylbenzoate

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