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Comparative kinetic studies on the alkaline hydrolysis of halogen substituted isocoumarins

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Kinetics of the hydrolysis of 3-(2′-chloro-6′-fluorobenzyl)isocoumarin (**1**), 3-(4′-fluorophenyl)isocoumarin (**3**), 3-(2′-fluorophenyl)isocoumarin (**5**), 3-(2′-chlorophenyl)isocoumarin (**7**), and 3-(4′-chlorophenyl)isocoumarin (**9**) were studied spectrophotometrically in the presence of aqueous solution of potassium hydroxide. The rates of hydrolyses for these isocoumarins were compared. The data for isocoumarin (**1**) were further investigated to probe the reaction mechanism. 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.

Key Words: Hydrolysis, isocoumarin, kinetics.

Introduction

Isocoumarins are hydrolyzed to ketoacids by treating them with aqueous potassium hydroxide solution.[1] The mechanism of such a reaction 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 continuation of our previous studies,[6] kinetics of hydrolysis of 3-(2′-chloro-6′-fluorobenzyl)isocoumarin (**1**), 3-(4′-fluorophenyl)isocoumarin (**3**), 3-(2′-fluorophenyl)isocoumarin (**5**), 3-(2′-chlorophenyl)isocoumarin (**7**), and 3-(4′-chlorophenyl)isocoumarin (**9**) to respective keto acids were observed to probe the reaction mechanism and to compare the rates of reactions of isocoumarins.

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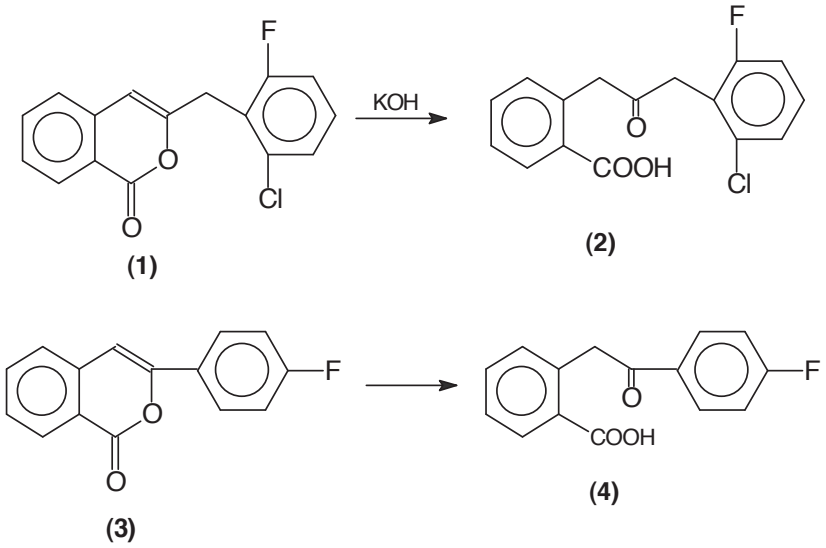
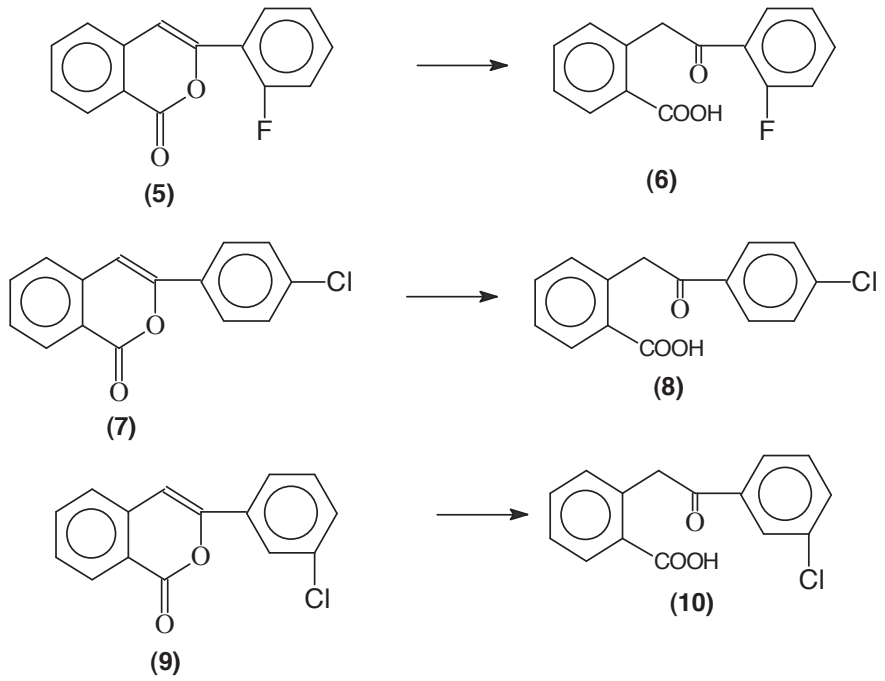
Experimental

Kinetics of the hydrolyses of the 3-(2′-chloro-6′-fluorobenzyl)isocoumarin (**1**), 3-(4′-fluorophenyl)isocoumarin (**3**) 3-(2′-fluorophenyl)isocoumarin (**5**) 3-(2′-chlorophenyl)isocoumarin (**7**) 3-(4′-chlorophenyl)isocoumarin (**9**) were studied in the presence of various concentrations (0.2-1.0 M) of aqueous potassium hydroxide solution at 25 °C. The substrates (0.1g) were dissolved in ethanol (10cm^3). The reactions were initiated by injecting 0.1 cm^3 of the substrate solution to 3 cm^3 potassium hydroxide solution. Initial concentration of the substrate were usually of the order 10^{-4} mol dm^{-3} and were kept at least 20-fold less than the concentration of the most dilute potassium hydroxide solution to maintain the pseudo-first order conditions. Rate measurements were made, by using UV-Visible Spectrophotometer. Reactions were followed at a single wavelength as a trace of absorbance versus time (or a printout of absorbance readings against time). In some cases, the change in absorbance with time was followed by scanning over an appropriate wavelength range at suitable time intervals. Rate coefficients were obtained as the slope of plots of ln(A∞-At) versus time where A∞ and At are the absorbances at the completion of reaction and that at any time (t) respectively.

Results and Discussion

The compounds, 3-(2′-chloro-6′-fluorobenzyl)isocoumarin (**1**), 3-(2′-fluorophenyl)isocoumarin (**3**), 3-(4′-fluorophenyl)isocoumarin (**5**), 3-(4′-chlorophenyl)isocoumarin (**7**), and 3-(3′-chlorophenyl)isocoumarin (**9**) were synthesized by a literature procedure.[7] On hydrolysis of these compounds with potassium hydroxide, they afford 2-[2′-oxo-3′-(2′′-chloro-6′′-fluorophenyl)propyl]benzoic acid (**2**), 2-(4′-fluorobenzoyl)methylbenzoic acid (**4**), 2-(2′-fluorobenzoyl)methylbenzoic acid (**6**), 2-(4′-chlorobenzoyl)methylbenzoic acid (**8**), and 2-(3′-chlorobenzoyl) methylbenzoic acid (**10**). The products were confirmed by their NMR and mass spectrometric studies.





Kinetic studies of these reactions were carried out spectrophotometrically. The data were obtained for at least three half lives to calculate rate constants (k_{obs}). Measurements were made at the wavelengths where the changes in absorbances were maximum. The absorbances decrease with time. Plots of ln(A∞-At) versus time, gave a straight line showing the reactions are of first order in the substrate. The rates of reactions for the hydrolyses of compounds (**1**), (**3**), (**5**), (**7**), and (**9**) are compared in the Table.

Table. Comparison of rates for the hydrolysis of isocoumarins.

S No.	Name of isocoumarin	2^{nd} order rate constants in $dm^3\ mol^{-1}\ min^{-1}$
1	3-(2′-Chloro-6′-fluorobenzyl)isocoumarin (**1**)	0.0272
2	3-(4′-fluorophenyl)isocoumarin (**3**)	0.0217
3	3-(2′-fluorophenyl)isocoumarin (**5**)	0.0264
4	3-(2′-chlorophenyl)isocoumarin (**7**)	0.0252
5	3-(3′-chlorophenyl)isocoumarin (**9**)	0.0237

It is obvious from the Table that rate of reaction for compound **1** is maximum and that of compound **3** is minimum. This may be interpreted as due to the presence of anionic intermediate. In the case of compound **1**, 2 halogen atoms are attached to the benzene ring. Due to their strong withdrawing inductive effect, the anionic intermediate is stabilized, hence facilitating the reaction, and the rate of reaction is faster. Based on comparison of the rates of reaction of compounds **5** and **7**, fluorine has a stronger electron withdrawing effect than chlorine**.** On comparing the rates for the hydrolyses of compounds **3** and **5** a fluorine atom is attached at position 4 in compound **3** and on position 2 in compound **5**. Hence the latter has a faster rate than the former. The hydrolysis of 3-(2″-choloro-6″-fluorobenzyl)isocoumarin was further investigated to determine the

reaction mechanism. The intercept (k_o = 0.0186 per min) of the plot of pseudo-first order rate constant k_{obs} against hydroxide ion concentration indicates the occurrence of significant spontaneous hydrolysis. The value of second order rate constant k (0.0272 $dm^3 mol^{-1} min^{-1}$) was calculated as a slope of this plot (Figure 1).

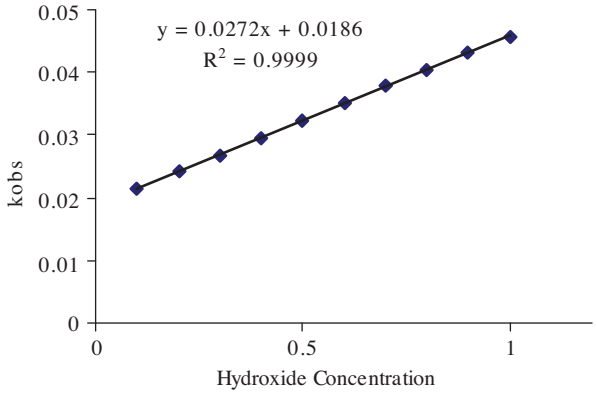
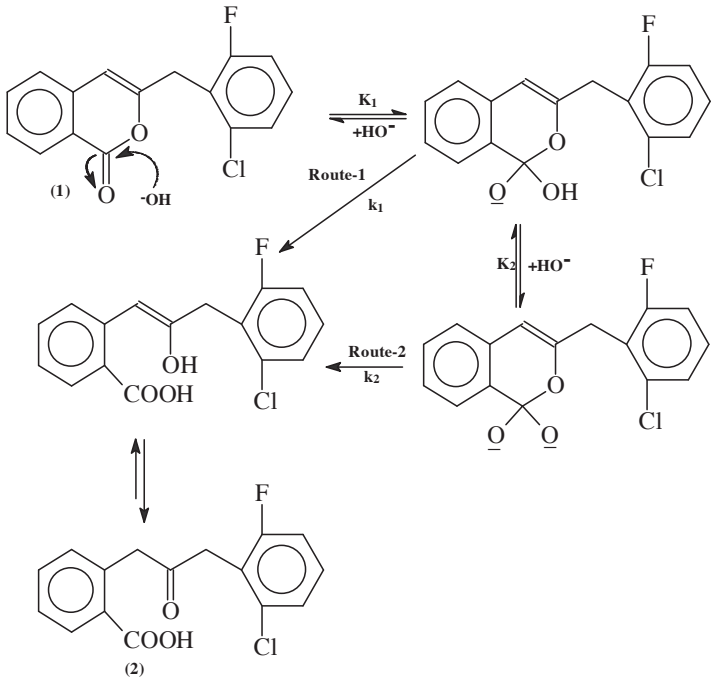


Figure 1. Plot of pseudo-first order rate constant k_{obs} against hydroxide ion concentration.

One possible mechanism for this reaction is given in the Scheme, which is in line with previous studies.[9]



Scheme

While discussing the presence of monoanionic or dianionic intermediate 2 equations are proposed:

$$k_{obs} = k_o + k_1[OH] \tag{1}$$

$$k_{obs} = k_o + k_1[OH] + k_2[OH]^2 \tag{2}$$

If the dianionic intermediate is formed then the second order equation should follow experimental data. If it is true then Eq. (2) can be rearranged as follows:

$$k_{obs} - k_o/[OH] = k_1 + k_2[OH] \tag{3}$$

The plot of k_{obs} – $k_o/[OH]$ for different concentrations of hydroxide ions gives a straight line. This indicates the presence of a dianionic tetrahedral intermediate (Figure 2).

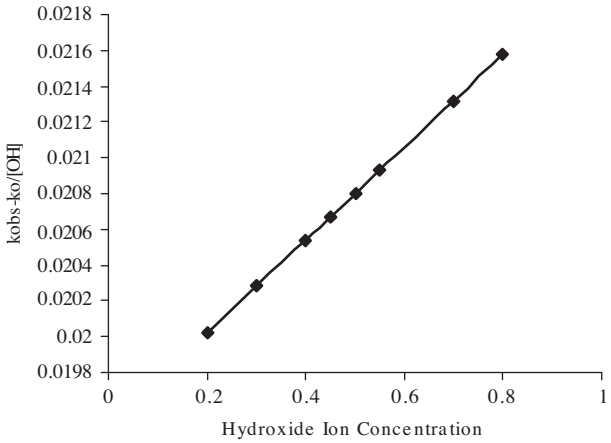


Figure 2. Plot of kobs-ko/[HO^-] versus [HO^-] for the hydrolysis of 3-(2′-chloro-6′-fluorobenzyl)isocoumarin in the presence of aqueous solution of KOH.

Taking the values of k_2 and k_1 as intercept and slope, respectively, k_{obs} was calculated by using Eq. (2). The values of kobs and kcal are in good agreement with each other for the alkaline hydrolysis of compound **1.** The overlaid data of kcal and kobs at various hydroxide ion concentrations is shown in Figure 3, where the solid line is a plot of kcal versus hydroxide ion concentrations and the points represent the experimental values.

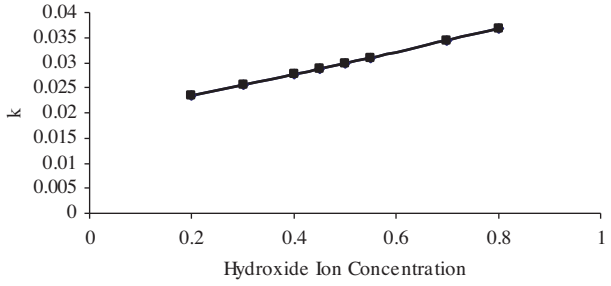


Figure 3. Comparison of the pseudo-first order rate constant kobs with kcal for the hydrolysis of 3-(2′-chloro-6′-fluorobenzyl)isocoumarin in the presence of aqueous solution of KOH.

If a graph is plotted between k_{obs} / [HO^-] and hydroxide ion concentrations, ignoring the term k_o, the plot is not linear (Figure 4). This shows the significant contribution of k_o in the reaction.

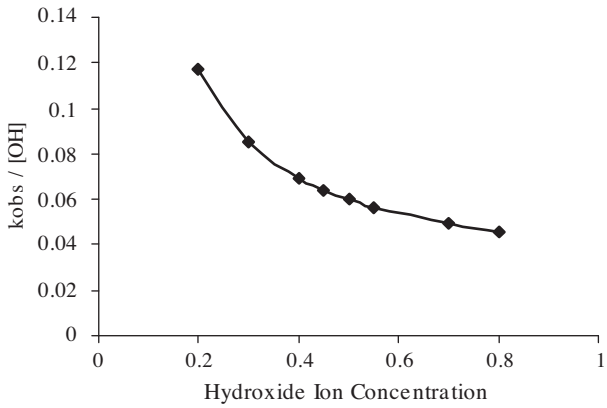


Figure 4. Plot of $k_{obs}/[HO^-]$ vs $[HO^-]$ ignoring k_o for the hydrolysis of 3-(2′-chloro-6′-fluorobenzyl)isocoumarin in the presence of aqueous solution of KOH.

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