

Kinetics and determination of ethyl chloroacetate and ethyl bromoacetate with piperidine

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Manuscript received 4 January 2000, revised 24 August 2000, accepted 12 February 2001

A simple sensitive potentiometric method has been developed for determination of active haloester. It is based on the reaction of haloester with excess piperidine in ethanol at 40°. Under the optimum conditions the average recovery is 97%. The reaction proceeds kinetically as a pseudo-first order reaction. The reactivity of tested amines towards haloester follows the order : benzylamine < *n*-butylamine < ethylamine < piperidine. The activation parameters have been calculated and relevant reaction mechanism has been suggested.

Active haloesters have a physiological effect¹ and can be used in pharmaceutical preparation of antibiotics, enzymes, hormones and peptides². The rate of reaction of ethyl bromoacetate and phenacyl bromide with various substituted cinnamate, acrylate, benzoate and naphthoate ions have been kinetically studied³. The reaction of phenacyl bromide and *m*-nitrophenacyl bromide with different substituted aniline have also been studied⁴. The kinetics of the reaction of vinyl halide ester with amines and related nucleophile have been investigated^{4,5}. The present investigation reports an analytical method for determination of these haloesters.

Results and Discussion

Effect of different factors on the electrode response : Potentiometric measurements for the effect of various factors on the electrode response curves were carried out in the conventional manner. In every run, a certain volume (50 ml) of potassium chloride or potassium bromide solution was used as a source of chloride or bromide ions in the experiment to test the validity of Nernst equation⁶.

$$E = \text{Constant} - 2.303 \frac{RT}{ZF} \log [\text{Cl}^-] \quad (1)$$

The plot of potential of the electrode vs S.C.E. as a function of chloride ion concentration versus chloride concentration in the range 10^{-3} – 10^{-6} M was found to be a straight-line with slope 60 mV/log [Cl⁻] unit. The same experiment was carried out in presence of 0.1 M K₂SO₄ or KNO₃ as ionic strength adjustor. The values drifted with slopes 60 mV/log [Cl⁻] and 50 mV/log [Cl⁻] respectively, hence potassium nitrate was excluded as ionic strength adjustor. The effects of different substances, e.g. ethyl chloroacetate, ethyl bromoacetate, tested amines and sulfuric acid on the response of the chloride or bromide electrode were tested similarly. The results show drift in the observed values compared to

simple chloride or bromide calibration curve. The slopes of these lines have the same values as that calculated by eq. (1). This indicates that there is no interference of these substances on the sensitivity of the chloride or bromide electrode.

Determination of active haloester : Since the maximum rate of the reaction was obtained in case of piperidine as shown in Tables 1 and 2, therefore piperidine was selected as suitable reagent for determination of ethyl chloroacetate and ethyl bromoacetate.

Effect of piperidine concentration : The effect of piperidine concentration, ranging from 1 : 5 to 1 : 25 molar ratio haloester : piperidine on the maximum reading was investigated potentiometrically at 40°. The maximum reading was obtained at 1 : 15 molar ratio.

Effect of time and temperature : The reading reached the maximum after 90, 30 min at 40° due to the interaction of 1.6×10^{-3} M ethyl chloroacetate and ethyl bromoacetate with 0.04 M piperidine in ethanol, respectively.

Determination of ethyl chloroacetate and ethyl bromoacetate were carried out under the optimum conditions. Calibration graph data are shown in Table 1. Each point on the standard calibration curve represents the outcome of three determinations. From the relation, $A = a + bc$, where A is

Table 1. Statistical analysis of the calibration graphs for the determination of haloester by reaction with excess piperidine in absolute ethanol at 40°

Haloester	Slope	Intercept	Conc. µg/ml	Mean recovery %
Ethyl chloroacetate	0.006	0.03	8–53	97.0
Ethyl bromoacetate	0.040	–0.09	12–73	98.5

the reading (x) and a and b are intercept and slope, respectively and (c) is the concentration of haloester in the final solution. It is evident that as low as $8 \mu\text{g/ml}$ of the haloester can be determined.

Kinetic measurements : The relative reactivities of amines towards ethyl haloester (Cl, Br) have been kinetically investigated by individual rate measurements in ethanol as a solvent.

Order of reaction : The order of reaction between ethyl haloester (Cl, Br) with various tested amines (piperidine, ethylamine, benzylamine and butylamine) is determined. Each run is found to fit the kinetic eq. 2 of the first order,

$$k = \frac{2.303}{t} \log \frac{a}{a-x} \quad (2)$$

Thus, on plotting the values of $\log a/(a-x)$ vs time linear plots were obtained. The differential method⁷ was used to confirm the order of reaction with respect to ethyl chloroacetate whereas a linear plot of logarithmic relationship between the initial rates and initial concentrations were constructed. The slope of line was found to be 1.0, indicating that the reaction is first order with respect to ethyl haloester and the overall order of reaction is considered to be pseudo-first order due to excess amine used.

Structure versus reactivity : The kinetic data (Tables 2 and 3) indicate that the reactivity of amines towards ethyl haloester expressed in terms of k values increases in the following order : benzylamine < n -butylamine < ethylamine < piperidine. The change of halogen atom from chloro to bromo in ester for the same amine, showed an increase in the rate of reaction. The values of $k_{\text{Br}}/K_{\text{Cl}} = 12.46, 3.52, 3.67$ and 4.23 in case of piperidine, ethylamine, n -butylamine and benzylamine, respectively. These values are greater than those reported by Rappoport⁸ for the reactions to proceed by addition-elimination mechanism.

The rate of reaction can be examined through the Brönsted equation⁹. Thus upon plotting the values of the second order rate constant $\log k_2$ vs $\text{p}K_a$ for the reaction of the tested amines with ethyl chloroacetate and ethyl bromoacetate respectively in ethanol at 40° , linear relationships were obtained (Fig. 1) as required by Brönsted equation,

$$\log k_2 = \beta \text{p}K_a + \text{Constant} \quad (3)$$

the β values being 0.36, 1.75, respectively. A high Brönsted value appears due to the bond formation between the nucleophile and the reaction center at the transition state.

Activation parameters : Linear relationship was obtained between ΔH^\ddagger and ΔS^\ddagger values for the reaction of the tested amines with ethyl chloroacetate in ethanol. From the linear

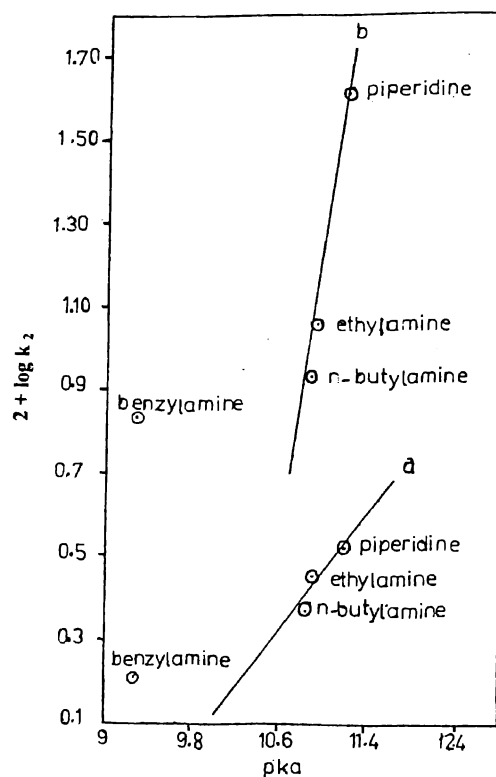


Fig. 1. Brönsted plot of $\log k_2$ vs $\text{p}K_a$ for the reaction of the tested amines with (a) ethyl chloroacetate and (b) ethyl bromoacetate at 40° .

plot, the value of the isokinetic temperature β is found to be 266 K which is lower than the experimental temperature by 47° , therefore, the amines-ethyl chloroacetate reaction is said to be governed by entropy of activation¹⁰. One of the useful features of the isokinetic relationship is that it can be expected to be applied only to a series of reactions in which a

Table 2. Rate constants and activation parameters for the reaction of $5 \times 10^{-3} M$ ethyl chloroacetate with $0.1 M$ of different amines in ethanol

Amine	T, K	$10^3 k$ min ⁻¹	ΔE^\ddagger kcal mol ⁻¹	ΔH^\ddagger kcal mol ⁻¹	ΔG^\ddagger kcal mol ⁻¹	$-\Delta S^\ddagger$ cal °K ⁻¹ mol ⁻¹
Piperidine	313	3.37	16.9	15.57	22.52	22.20
	318	5.18				
	323	7.83				
Ethylamine	313	290	15.75	15.13	22.61	23.90
	318	4.82				
	323	7.10				
<i>n</i> -Butylamine	313	2.36	12.22	11.60	22.74	35.60
	318	3.26				
	323	4.37				
Benzylamine	313	1.63	14.56	13.90	22.97	28.85
	318	2.36				
	323	3.35				

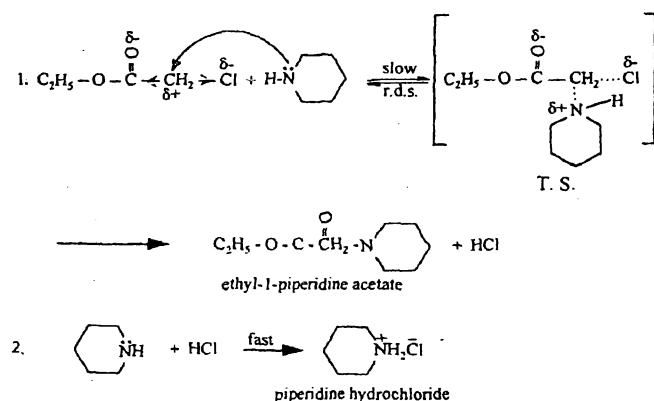
Table 3. Rate constants and activation parameters for the reaction of 5×10^{-3} M ethyl bromoacetate with 0.1 M of different amines in ethanol

Amine	T, K	$10^3 k$ min^{-1}	ΔE^\ddagger	ΔH^\ddagger	ΔG^\ddagger	$-\Delta S^\ddagger$
				kcal mol^{-1}		$\text{cal } ^\circ\text{K}^{-1} \text{mol}^{-1}$
Piperidine	313	42.0	2.93	2.30	20.95	59.56
	308	39.0				
	303	36.0				
Ethylamine	313	11.51	3.48	2.86	21.75	60.35
	308	10.46				
	303	9.54				
<i>n</i> -Butylamine	313	8.67	1.93	1.30	21.96	65.90
	308	8.24				
	303	7.83				
Benzylamine	313	6.90	6.33	5.71	22.07	52.26
	308	5.80				
	303	4.93				

structural change does not change the mechanism of the reaction or the nature of the transition state. Thus the existence of this relationship in the present series of reactions is considered to provide an evidence for the occurrence of one and the same mechanism. The large negative values of entropy of activation ΔS^\ddagger (Tables 2 and 3) appear to result from substantial losses in translational and rotational degrees of freedom in the transition state, and the transition state goes faster towards product formation. The small differences in the values of ΔG^\ddagger indicate the independence of the free energy of activation on the structure change of amines in the investigated reaction.

The structures of the products were established from b.p./m.p., m.m.p. with authentic sample, elemental analyses and IR spectra (Table 4).

Mechanism : In view of the kinetic data, the nature of the reaction products, and the application of the isokinetic relationship, the following mechanism is proposed :


Table 4. Nature of the reaction products

Reactants	Main product	Byproduct
I Ethyl chloroacetate or		
II ethyl bromoacetate with		
a Piperidine	Ia Ethyl-1-piperidine acetate oil, b.p. 109–111°/25 mm; ν_{max} 1757 cm^{-1} (C=O)	Ia' Piperidine hydrochloride, m.p. 245° IIa' Piperidine hydrobromide, m.p. 235°
b Benzylamine	Ib <i>N</i> -Benzylglycine ethylacetate, oil, b.p. 140–142°/10 mm; ν_{max} 1740 (C=O), 3050 cm^{-1} (NH)	Ib' Benzylamine hydrochloride, m.p. 262° IIb' Benzylamine hydrobromide, m.p. 216–118°
c Butylamine	Ic Ethyl- <i>N</i> -butyl glycinate, m.p. 205°; ν_{max} 1760 (C=O), 2940 cm^{-1} (NH)	Ic' <i>N</i> -Butylamine hydrochloride, m.p. 95° IIc' <i>N</i> -Butylamine hydrobromide, m.p. 175° Ia'-c', IIa'-c' : ν_{max} 2940–3050 cm^{-1} (NH ₂)

Experimental

All chemicals used were of A.R. grade unless otherwise specified.

A specific ion meter (407 A/L) was used along with chloride ion selective electrode (Orion, 941700), bromide ion selective electrode (Orion, 943500) and saturated calomel electrode (Orion, 900200). IR spectra were recorded on Pye-Unicam SP3-200 and Mahson 1000 FT-IR spectrophotometers.

Preparation of the reaction products. *Ethyl-1-piperidine acetate* : A mixture of ethyl chloroacetate (4 ml; 0.5 M) and piperidine (8 ml; 1 M) in ethanol was left for 24 h at room temperature to yield products ethyl 1-piperidineacetate and piperidine hydrochloride. The same procedure was used for the preparation of other reaction products of ethyl chloroacetate, and ethyl bromoacetate with the amines (Table 4).

Kinetic procedure : All runs were carried out in triplicate under pseudo-first order condition. The rate of reaction was followed up by determining the chloride ion liberated as a function of time potentiometrically using sample addition method.

Determination procedure : A calibration graph for each of ethyl chloroacetate and ethyl bromoacetate was obtained by transferring 0.5, 1.0, 1.5, 2.0, 2.5 and 3 ml aliquots of 8×10^{-3} M of tested haloester each containing 1 ml of 0.2 M

piperidine. The reaction mixtures were placed in a thermostat at 40° for 30 min in case of ethyl bromoacetate and for 90 min in case of ethyl chloroacetate. The content of each test tube was transferred after washing with the calculated volume of ethanol to attain the total volume of reaction mixture 5 to 50 ml of the blank. The halide ion concentration was determined using sample addition method. The calibration graphs thus constructed were used for subsequent determination of the concentration of the corresponding haloester in solution samples of unknown concentration.

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