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Aminolysis of substituted phenyl thiolacetates by imidazole

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A series of *m*- and *p*-substituted phenyl thiolacetates have been prepared. The kinetics of aminolysis of these acetates by imidazole have been followed at 20°C and an ionic strength of 0.1 mol dm^{-3} at different *p*H in water containing traces of dioxan. The non-linear Hammett plot and the non-linear plot between $\log k_2$ and $\log k_{(OH)}$ indicate the possibility of two types of mechanism, viz., unassisted nucleophilic substitution for the compounds having electron-withdrawing groups in the leaving moiety and general acid-assisted nucleophilic substitution for the compounds having electron-releasing groups in the leaving moiety.

Although great deal of information is available on the aminolysis of oxyesters, only very little is known on the aminolysis of thiol esters and the catalysis involved therein. Even the reports on the intermolecular as well as the intramolecular aminolysis of alkyl thiolacetates[1] and aminolysis of aryl thiolacetates in aprotic solvents[2], on the aminolysis of *p*-nitrophenyl thiobenzoate[3], 2,2,2-trifluoroethyl thiolacetates[4] and thioimidates[5], on the aminolysis of phenyl thiolacetate and *p*-nitrophenyl thiolacetate with piperidine, morpholine and piperazine[6] and that on the aminolysis of 2,4-dinitrophenyl and 2,4,6-trinitrophenyl thiolacetates with alicyclic secondary amines and piperidines[7] have not brought to light the kind of catalysis that can be observed in such reactions as found in our present investigation. This may be due to limited number of substituents contained in the esters used in the earlier studies. Hence in the present investigation a large number of substituted phenyl thiolacetates have been prepared and the kinetics of their aminolysis with imidazole have been studied with a view to see the catalysis in the reaction.

Materials and Methods

All the *m*- and *p*-substituted phenyl thiolacetates were prepared from the corresponding thiophenols by reaction with acetyl chloride in pyridine according to reported procedures. Imidazole was recrystallized before use. Potassium chloride was reagent grade and used without purification. Water was doubly distilled and dioxan was purified by standard technique.

Determination of pK_a

The pK_a of imidazolium ion under kinetic conditions at 20 ± 0.01°C in aqueous solution, $\mu = 0.1$ mol dm^{-3} (maintained with KCl) was determined from *p*H by half-neutralization method.

Imidazole buffer

This was prepared shortly before use, by mixing standard hydrochloric acid and imidazole[8]. This solution was suitably diluted with water to prepare five different solutions of same *p*H with different concentrations of imidazole by maintaining the ionic strength with potassium chloride so that $[Im]_T + [KCl] = 0.1$ mol dm^{-3} in buffer.

At a desired *p*H the concentration of free imidazole ($[Im]_F$) in the buffer was evaluated using Eq. (1).

$$[Im]_F = \frac{[Im]_T \cdot K_a}{K_a + a_{H^+}} \qquad \ldots (1)$$

where $[Im]_T$ is the total concentration of imidazole buffer ($[Im]_F + [Im\ H^+]$), K_a is the dissociation constant of $Im\ H^+$ and a_H^+ is the hydrogen ion activity.

Kinetic measurements

The reaction of imidazole with substituted phenyl thiolacetates were followed using a JASCO UVIDEC 340 UV/Vis spectrophotometer equipped with a thermostated cell holder. The reactions were initiated by adding a solution of (30 μl) ester in dioxan to 3 ml of thermally equilibrated (temp. $= 20.0 \pm 0.01$°C) buffer taken in a quartz cell. The optical density of the liberated

thiophenolate ions was recorded at regular time intervals, the wavelengths of maximum absorption λ_{max} (nm) for the substituted esters are as follows: H, 260; *m*-CH_3, 263; *p*-CH_3, 261; *m*-OCH_3, 264; *p*-OCH_3, 261; *m*-Cl, 267; *p*-Cl, 270; *m*-Br, 267; *p*-Br, 271; *p*-NO_2, 410. In all the solutions the dioxan content was 1.0%. The initial [ester] was 5 to 6×10^{-4} mol dm^{-3} and [amine] was at least ten-fold in excess of the ester. For each compound the aminolysis was studied at five different [imidazole] in buffers of fixed *p*H at each of the four different *p*H values. The pseudo-first order rate constants (k_{obs}) were determined by the method of Guggenheim employing least squares technique. The pseudo-first order rate constants and the experimental conditions of the reactions are presented in Table 1.

The hydrolysis of the esters using potassium hydroxide was also followed spectrophotometrically at 20°C and ionic strength 0.1 mol dm^{-3} (KCl). The rate constants are shown in Table 2.

Results and Discussion

The electron-withdrawing groups increase the

Table 1—The rate constants for the aminolysis of substituted phenyl thiolacetates in dioxan (1% v/v)-water by imidazole at 20°C, $\mu = 0.1$ mol dm^{-3} (maintained with KCl)

$10^3 \times [Im]_T$ (mol dm^{-3})	$10^3 \times k_{obs}$ (s^{-1})				k'_2 (dm^3 mol^{-1} s^{-1})			
	*p*H				*p*H			
	7.11	7.28	7.49	7.69	7.11	7.28	7.49	7.69
	Phenyl thiolacetate							
2.5	1.78	1.16	1.12	1.07	1.05	0.84	0.68	0.59
5.0	1.94	1.91	1.94	1.86	0.86	0.70	0.59	0.51
7.5	2.67	2.64	2.62	2.56	0.79	0.64	0.53	0.47
10.0	3.24	3.30	3.31	3.32	0.72	0.60	0.50	0.46
12.5	3.63	3.87	3.97	4.01	0.65	0.57	0.48	0.44
	m-Methylphenyl thiolacetate							
7.5	2.38	2.29	2.20	2.43	0.71	0.56	0.44	0.45
10.0	2.93	2.86	2.90	3.00	0.65	0.52	0.44	0.42
12.5	3.36	3.36	3.21	3.67	0.59	0.49	0.38	0.41
15.0	3.93	3.81	3.74	4.35	0.58	0.46	0.38	0.40
17.5	4.42	4.22	4.30	4.88	0.56	0.44	0.37	0.38
	p-Methylphenyl thiolacetate							
4.5	2.48	2.04	1.88	1.71	0.99	0.81	0.63	0.53
7.0	3.86	3.18	2.81	2.37	0.89	0.71	0.61	0.47
9.5	5.24	4.31	3.14	2.92	0.80	0.67	0.50	0.43
12.0	6.62	5.45	3.79	3.54	0.73	0.61	0.48	0.41
14.5	7.99	6.58	4.34	4.18	0.70	0.57	0.45	0.40
	m-Methoxyphenyl thiolacetate							
4.5	1.70	1.70	1.71	1.77	0.84	0.69	0.57	0.54
7.0	2.45	2.43	2.42	2.47	0.78	0.63	0.52	0.49
9.5	2.93	3.07	2.97	3.23	0.69	0.59	0.47	0.47
12.0	3.81	3.90	4.13	4.19	0.71	0.59	0.52	0.48
14.5	4.55	4.65	4.85	4.77	0.70	0.58	0.50	0.45
	p-Methoxyphenyl thiolacetate							
2.5	2.01	1.86	1.68	1.45	1.79	1.36	1.02	0.80
5.0	3.06	2.93	2.61	2.30	1.36	1.07	0.79	0.63
7.5	4.15	3.88	3.34	2.81	1.23	0.94	0.67	0.52
10.0	4.65	4.63	4.15	3.65	1.03	0.84	0.63	0.51
12.5	5.50	5.42	4.89	4.36	0.98	0.79	0.59	0.48

(*contd*)

Table 1—The rate constants for the aminolysis of substituted phenyl thiolacetates in dioxan (1% v/v)-water by imidazole at 20°C, $\mu = 0.1$ mol dm^{-3} (maintained with KCl)—*Contd.*

$10^3 \times [Im]_T$ (mol dm^{-3})	$10^3 \times k_{obs}$ (s^{-1})				k'_2 (dm^3 mol^{-1} s^{-1})			
	*p*H				*p*H			
	7.11	7.28	7.49	7.69	7.11	7.28	7.49	7.69
				m-Chlorophenyl thiolacetate				
10.0	3.34	3.76	4.23	4.57	0.74	0.68	0.64	0.63
12.0	3.91	4.47	5.10	5.53	0.73	0.68	0.64	0.63
14.0	4.22	4.79	5.47	5.87	0.73	0.63	0.60	0.60
16.0	5.17	5.85	6.77	7.34	0.72	0.68	0.64	0.63
18.0	5.68	6.62	7.55	8.40	0.70	0.67	0.64	0.64
				p-Chlorophenyl thiolacetate				
10.0	3.37	3.40	3.72	3.91	0.72	0.62	0.56	0.54
12.0	3.91	3.94	4.36	4.71	0.72	0.60	0.60	0.54
14.0	4.17	4.22	4.60	5.10	0.72	0.59	0.55	0.50
16.0	4.99	5.08	5.53	6.16	0.69	0.60	0.57	0.54
18.0	5.48	5.59	6.25	7.09	0.70	0.60	0.57	0.54
				m-Bromophenyl thiolacetate				
6.0	2.40	2.47	2.80	3.19	0.90	0.73	0.69	0.70
8.0	3.00	3.17	3.46	3.94	0.91	0.73	0.65	0.68
10.0	3.39	3.82	4.07	4.59	0.89	0.70	0.65	0.64
12.0	3.96	4.31	4.57	5.18	0.88	0.70	0.60	0.64
14.0	4.31	4.81	5.37	6.24	0.89	0.70	0.60	0.64
				p-Bromophenyl thiolacetate				
10.0	2.93	3.49	3.65	3.73	0.60	0.62	0.55	0.53
12.0	3.55	3.98	4.67	—	0.66	0.60	0.61	—
14.0	3.86	4.20	4.84	—	0.60	0.60	0.55	—
16.0	4.30	5.12	5.37	6.14	0.60	0.60	0.55	0.53
18.0	5.14	5.79	5.83	6.44	0.63	0.60	0.54	0.50
				p-Nitrophenyl thiolacetate				
6.0	3.27	3.73	4.60	5.23	1.23	1.14	1.20	1.28
8.0	4.42	5.18	6.15	7.50	1.23	1.20	1.20	1.30
10.0	5.54	6.27	8.29	9.31	1.23	1.14	1.25	1.28
12.0	6.72	7.79	9.93	10.74	1.24	1.20	1.25	1.28
14.0	7.81	9.18	11.35	12.38	1.24	1.20	1.25	1.28

second order rate constants for the hydrolysis of phenyl thiolacetates while electron-releasing groups decrease them (Table 2).

The logarithms of the second order rate constants for the hydrolysis of phenyl thiolacetates were plotted against Hammett σ constants (Fig. 1). The plot is linear with slope of 0.705 ($r \doteq 0.986$; $s = 0.040$). The plot of the hydrolysis rate constants of the phenyl thiolacetates against the pK_a of the conjugate acids[9] of the leaving groups is linear (Fig. 2) with Brönsted slope, $\beta = -0.341$ ($r = 0.996$, $s = 0.020$). The linearity of the Brönsted plot indicates that the substituent effect of all the groups is similar in the dissociation of thiophenols and in the hydrolysis of the corresponding thiolacetates.

The pseudo-first order rate constants calculated for the aminolysis of phenyl thiolacetates are converted to the apparent second order rate constants k'_2; $\{k'_2 = (k_{obs} - k_H)/[Im]_F\}$. The term k_H is the product of $k_{(OH)}$, the second order rate constants for the hydrolysis, and the concentration of the hydroxide ion. At constant *p*H the k_{obs} values for all the compounds increase with increase in total [buffer].

The second order rate constants for the nucleophilic attack of imidazole on the substituted thio-

Table 2—Second order rate constants in the aminolysis and alkaline hydrolysis of substituted thiolacetates

No.	Substituent	$10^4 \times k_0$ (s^{-1})	k_2 ($dm^3\ mol^{-1}\ s^{-1}$)	$k_{(OH)}$ ($dm^3\ mol^{-1}\ s^{-1}$)
1	H	5.10	0.47	0.77
2	*m*-CH_3	7.61	0.36	0.62
3	*p*-CH_3	8.60	0.43	0.58
4	*m*-OCH_3	3.22	0.52	0.83
5	*p*-OCH_3	9.70	0.59	0.56
6	*m*-Cl	2.60	0.65	1.32
7	*p*-Cl	4.51	0.55	1.01
8	*m*-Br	3.90	0.49	1.36
9	*p*-Br	3.79	0.56	1.05
10	*p*-NO_2	2.41	1.26	3.03

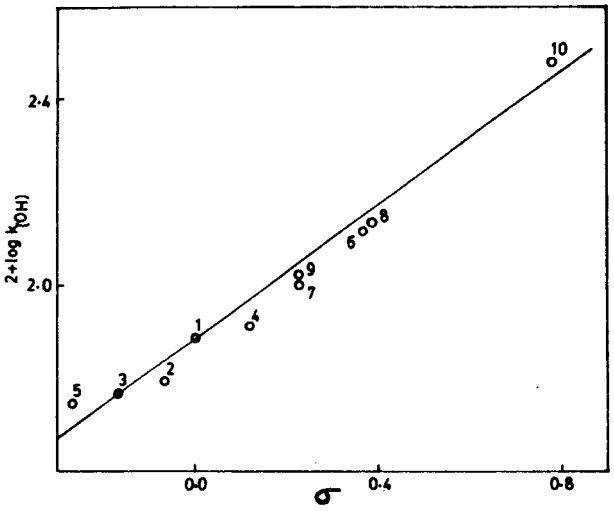


Fig. 1—Hammett plot for the hydrolysis of substituted phenyl thiolacetates. Numbering used in the graph is as in Table 2.

lacetates were obtained from the slope of the linear plots of $(k_{obs} - k_H)$ versus $[Im]_F$ at constant *p*H. The general rate law obeyed by the reactions under consideration is given by Eq. (2).

$$k_{obs} - k_H = k_0 + k_2 F_N [Im]_T \quad \ldots (2)$$

where k_0 is the rate constant in the absence of amine, F_N is the free amine fraction $([Im]_F/[Im]_T)$. The k_2 values obtained from the slopes and k_0 values obtained from the intercepts are given in Table 2.

The logarithms of the second order rate constants evaluated by Eq. 2 were plotted against the Hammett substituent constants σ (Fig. 3). The plot is non-linear in which the electron-withdrawing groups exhibit a positive slope of 0.6 while

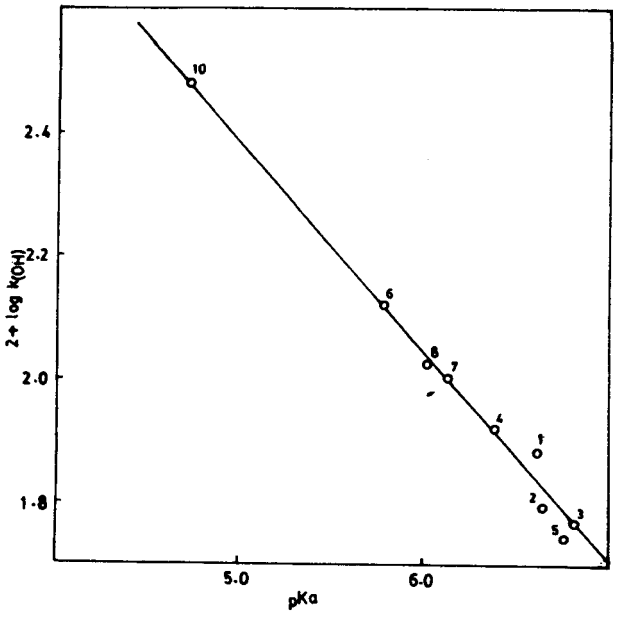


Fig. 2—Brönsted plot for the hydrolysis of substituted phenyl thiolacetates. Numbering used in the graph is as in Table 2.

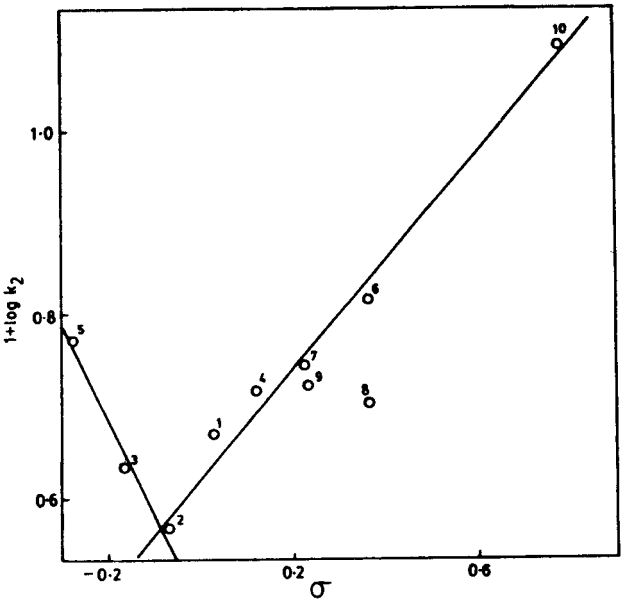


Fig. 3—Hammett plot for the aminolysis of substituted phenyl thiolacetates by imidazole. Numbering used in the graph is as in Table 2.

the electron-releasing groups display a negative slope of −1.02. This type of non-linear Hammett plot suggests a change in the mechanism with the nature of the substituents on the leaving group. The plot of log k_2 against log $k_{(OH)}$ (Fig. 4) exhibits a similar break, indicating a change in the mechanism of the reaction.

In the reactions of imidazole with substituted

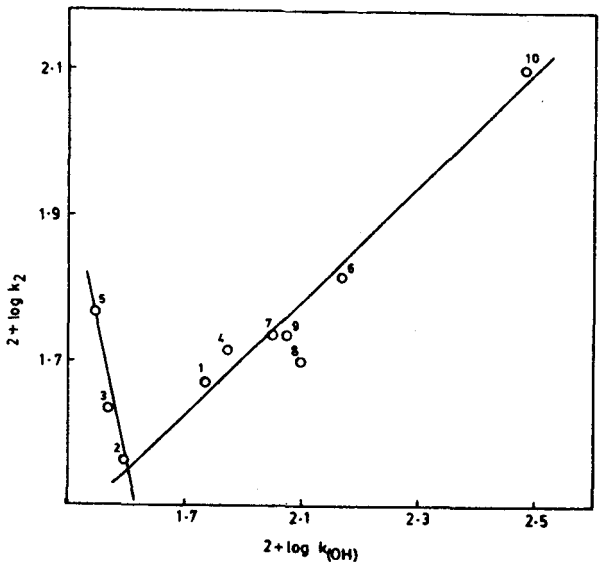


Fig. 4—Plot of $\log k_2$ versus $\log k_{(OH)}$. Numbering used in the graph is as in Table 2.

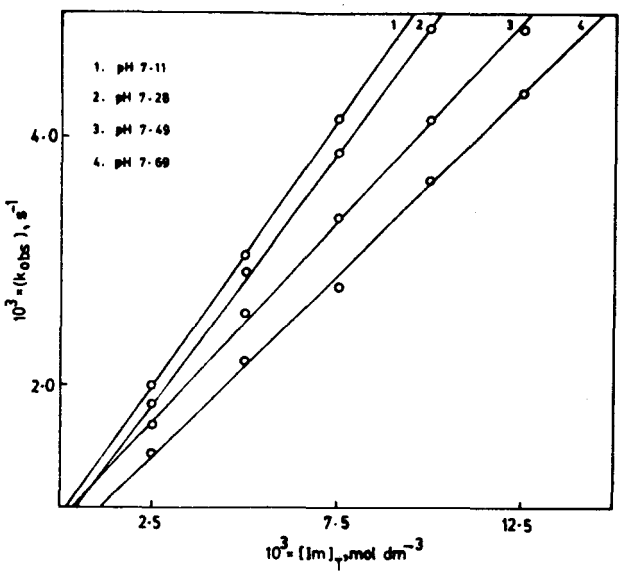
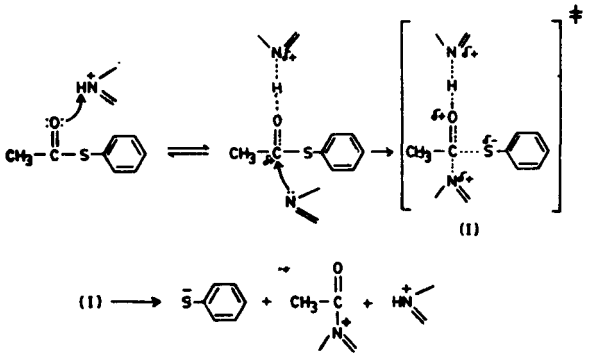


Fig. 5—Plot of (k_{obs}) versus $[Im]_T$ for the aminolysis of *p*-OCH_3phenyl thiolacetate by imidazole.

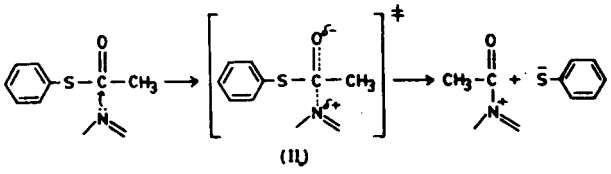
phenyl acetates, Bruice *et al.*[10] observed that the reactions were first order in imidazole for *p*-nitro, *m*-nitro, *p*-chloro and unsubstituted phenyl acetates while for *p*-methyl and *p*-methoxyphenyl acetates the reactions were found to be dependent on a higher than the first power of [imidazole] This observation was taken to mean that in the reactions with unsubstituted, *p*-nitro, *m*-nitro and *p*-chlorophenyl acetates there was nucleophilic catalysis while in the case of *p*-methyl and *p*-methoxyphenyl acetates there was general base catalysis. Nevertheless, Castro *et al.*[6] could not observe either the general base or the general acid catalysis in the aminolysis of phenyl thiolacetate and *p*-nitrophenyl thiolacetate by piperidine, piperazine and morpholine.

The values of k_2' observed in the present study are constant (Table 1) for thiolacetates with electron-withdrawing groups at a given *p*H although the concentration of free imidazole in the buffers was varied. The plots of log k_{obs} against log $[Im]_F$ for the above acetates are linear with unit slope.

However, the values of k_2' are not constant at any given *p*H for the thiolacetates with electron-releasing substituents such as *p*-methyl, *p*-methoxy and *m*-methyl and they decrease with increase in [free imidazole] in the buffers (Table 1). Jencks *et al.*[11] observed an opposite trend in the base catalyzed reaction of oxyesters containing electron-releasing groups with imidazole as discussed earlier. It is evident from the data in Table 1, that the order of the reaction is not one with respect to free imidazole in the reaction of thiolacetates having



Scheme 1



Scheme 2

electron releasing groups. The plots of log k_{obs} against log $[Im]_F$ for the above esters are linear, with the slope close to 0.8. The k_2 values obtained from the plots of k_{obs} versus $[Im]_F$ at constant free amine fraction are found to decrease with increase in *p*H.

The k_{obs} values increase linearly with increase in total [buffer] and they decrease with increase in *p*H. This implies that the reaction rate is dependent on the concentration of the conjugate acid of imidazole in the buffer[12]. Jencks *et al.*[13] utilised a similar behaviour observed in their study to esta-

blish general acid catalysis in the hydrolysis of several alcohol adducts formed from N,O-trimethylenephthalimidium cation. Hence it is reasonable to assume that in the present investigation general acid catalysis is dominent in esters having electron-releasing groups such as *m*-methyl, *p*-methyl and *p*-methoxy.

Figure 5 shows a typical plot of k_{obs} for *p*-methoxyphenyl thiolacetate at different buffer ratio against the total [buffer]. In Fig. 5 the slopes of the plots decrease with increase in *p*H. This observation may also be considered as an evidence for the existence of general acid catalysis in esters having electron-releasing groups.

The dependence of the concentration of the conjugate acid of imidazole (NH^+) on the reaction rate in the esters possessing electron-releasing groups suggests the involvement of Im and ImH^+ in the transition state (I) as indicated in Scheme 1.

In the case of thiolesters with electron-withdrawing groups the transition state resembles the structure (II) and is formed by the nucleophilic attack of imidazole on the esters (Scheme 2). The feasibility of this direct attack may possibly be due to the better leaving nature of the leaving group.

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