Intramolecular Catalysis in the Detritiation of 3-Carboxy-2-([^{3}H]acetyl)thiophene

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The kinetics of detritiation of 3-carboxy-2-([^{3}H]acetyl)thiophene have been studied at 50 °C in aqueous buffer systems as well as at 25 °C in sodium hydroxide solutions. The results, when compared with similar investigations on the corresponding 3-iodo- and 3-thiomethyl-2-([^{3}H]acetyl)thiophenes, serve to show the importance of intramolecular catalysis by the carboxylate group. Estimates of the efficiency of the catalysis have been obtained, these are similar in magnitude to the values previously reported for derivatives of 2′-carboxyacetophenones.

Rates of ionisation of compounds containing an acetyl group have frequently been measured in order to study various aspects of proton-transfer reactions. Initially rates of halogenation, particularly iodination, were studied [1,2] but in recent years the attractions of measuring rates of detritiation [3,4] have become appreciated by a wider audience.

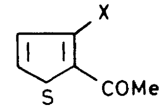
If the acetyl-containing compound also contains a basic group, such as carboxylate, there arises the possibility of intramolecular catalysis [5,6] of ionisation. Such catalysis is of interest as a model for enzyme reactions.[7] Previous investigations, mainly by Bell and co-workers,[8–11] have used various substituted acetophenones as substrates. The acetylthiophenes provide another interesting possibility, especially as there is more scope for varying the molecular geometry, a factor known to be important in intramolecular catalysis. The efficiency of the process can be ascertained by comparing the rates with those obtained for structurally similar compounds for which intramolecular catalysis is not possible; we have chosen the 3-iodo- and 3-thiomethyl-2-([^{3}H]acetyl)thiophenes to play this part and studied their detritiation in comparison with that of 3-carboxy-2-([^{3}H]acetyl)thiophene.

Experimental

Synthesis and Purification of Compounds.—Compounds (**I**)[12] and (**III**)[13] were prepared according to literature methods.

3-Methylthio-2-acetylthiophene (**II**).—A mixture of 3-methylthiothiophene (0.51 mol) and acetic anhydride (0.61 mol) is stirred and heated to 70 °C. Orthophosphoric acid (6.1 g) is added dropwise and the temperature kept below 90 °C by means of an ice-bath. The mixture is then refluxed for 2 h and, after cooling, diluted with 120 ml of water and stirred for a further 5 min. The mixture is steam distilled and the solid obtained is purified by crystallisation (m.p. 66—67 °C) from light petroleum.

Tritiation Procedure.—The tritiated 3-iodo and 3-thiomethyl compounds were prepared in essentially the same way as has been reported[14] for a series of 4- and 5-substituted 2-acetylthiophenes. In the case of the 3-carboxy compound the situation was slightly different in that at the end of the tritiation the solution was neutralised prior to solvent extraction of the substrate; further washing with small amounts of water served to remove any labile tritium associated with the carboxy group.



(I) X = I

(II) X = SMe

(III) X = CO_2H

Kinetic Measurements.—For the 3-carboxy compound it was possible to use the conventional detritiation procedure[3] in which the decrease in radioactivity of the substrate was followed, usually over 90% of the reaction; samples of the reaction mixture were periodically injected into tubes containing 10 ml of scintillator (diphenyloxazole in sulphur-free toluene) and 10 ml of aqueous hydrochloric acid. The first-order rate constants k^T were obtained from the plots of log (counts min^{-1}) against time; the second-order detritiation constants are given by $k^T_{OH^-} = k/[OH^-]$.

For the less reactive 3-iodo and 3-thiomethyl compounds the initial-rate method was adopted. This entails following the increase in the tritium content of the water over the first 3% of the reaction. Typically a drop of the dimethyl sulphoxide solution of the tritiated substrate was added to 50 ml of an aqueous buffer solution thermostatted at 50 °C. Samples (2 ml) were removed at intervals and added to small separating flasks containing toluene (10 ml) and water (5 ml). Most of the toluene layer was removed before carrying out a further extraction. Samples (1 ml) of the aqueous layer were then counted in a Nuclear Enterprises N.E. 250 scintillator (5 ml). Plots of counts min^{-1} against time were linear, and the first-order velocity constants k^T obtained by dividing the slopes of these lines by the number of counts per minute given by 1 ml of unseparated reaction mixture. Where necessary, allowance for differences in counting efficiency was made through the use of the internal-standard procedure.

In some cases the samples were taken over much longer time intervals. The value of C_∞ was determined from three samples taken after >10 half-lives, and the first-order rate constant obtained from a plot of log ($C_\infty - C_t$) against time. For all three compounds at least one check was made that these different procedures give the same results.

The results for detritiation in buffer solutions are collected in

Table 1. Rates of detritiation in buffer solutions ($10^7k^T/s^{-1}$ at 50.0 °C). Buffer ratio, r = [HA]/[A$^-$] = 1.0 throughout

[B$^-$]/M	(I)	(II)	(III)
Acetate buffers			
1.0			100
0.75			77.8
0.50		1.30	62.8
0.40	8.35	1.08	
0.30	6.76	0.90	
0.25			45.3
0.20	4.19	0.66	40.0
0.10	2.13	0.43	
Isobutyrate buffers			
0.50	12.7	1.09	60.3
0.40	9.83	0.89	51.7
0.30	7.30	0.69	49.0
0.20	5.08	0.57_7	38.4
0.10	2.76	0.27_8	30.8
Formate buffers			
0.50	4.57	0.55	100
0.40	3.75	0.46	85
0.30	2.79	0.39_2	69.6
0.20	1.85		55.0
0.10	1.24		39.5
Tartrate			
0.40	2.41		
0.30	2.05		31.0
0.25		0.24_9	29.8
0.20	1.30	0.22_7	29.3
0.15		0.20	28.1
0.10	0.95	0.19	27.0

Table 2. Rate constants ($k_o{}^T/s^{-1}$) for the 'spontaneous' detritiation of some acetylthiophenes and acetophenones at 50.0 °C

Compound	$10^8k_o{}^T/s^{-1}$	Reference
(II)	3.0	Present work
(II)	1.4	Present work
(III)	250	Present work
Acetophenone	0.2	15
p-Nitroacetophenone	1.8	15
p-Carboxyacetophenone	0.9[a]	8
o-Carboxyacetophenone	205[a]	8

[a] These results refer to $k_o{}^H$ at 25.0 °C.

Table 3. Summarised detritiation rate constants at 50.0 °C for the 3-substituted acetylthiophenes

Base	Rate constant	(I)	(II)	(III)
Water	$10^8k_o{}^T/s^{-1}$	3.0	1.4	250
Acetate	$10^7k^T_{B^-}/M^{-1}\ s^{-1}$	20.9	2.4_5	75.4
Isobutyrate	$10^7k^T_{B^-}/M^{-1}\ s^{-1}$	24.8	1.9_5	68.1
Formate	$10^7k^T_{B^-}/M^{-1}\ s^{-1}$	8.49	0.82	148
Tartrate	$10^7k^T_{B^-}/M^{-1}\ s^{-1}$	5.37	0.44	20.3
Hydroxide[a]	$10^3k^T_{OH^-}/M^{-1}\ s^{-1}$	14.4	2.3	1.9

[a] Data at 25.0 °C.

Table 4. Estimates of $C_i{}^T$ (M)

Base	$C_i{}^T$
Water	210—630
Acetate	28—37
Isobutyrate	21—43
Tartrate	28—56
Formate	130—210

Table 1. Unlike the situation experienced in other studies[10] all three compounds exhibited an increase of detritiation rate with increasing buffer concentration. Satisfactory extrapolation to zero buffer concentration was possible giving $k_o{}^T$ values (Table 2). The second-order hydroxide-catalysed rate constants ($k^T_{OH^-}$) are summarised in Table 3 as are also the buffer–base detritiation rate constants ($k^T_{B^-}$).

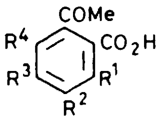
Results and Discussion

The 'spontaneous' or water-catalysed detritiation rate constants for both the 3-iodo- and 3-thiomethyl-substituted compounds (Table 2) are of the same order of magnitude as those obtained for acetophenone and *p*-nitroacetophenone.[14] However, they are some 80—180 times slower than for the 3-carboxy compound; a slightly greater factor (230) is obtained when the results of Bell *et al.*[8] for *p*-carboxy- and *o*-carboxyacetophenone are compared.

In the absence of buffer catalysis there are four reaction pathways available to a substrate AH, namely $AH_2{}^+ + OH^-$, $AH + OH^-$, $AH_2{}^+ + H_2O$, and $AH + H_2O$. For ketones such as the ones investigated here there are good reasons[16] for thinking that the last represents the more important pathway. This being the case the rate enhancement for the 3-carboxy compound can be rationalised on the basis that as well as a contribution due to intermolecular base catalysis by water there is further contribution arising from intramolecular catalysis by the carboxylate anion. The value of $k_o{}^T$ for the 3-carboxyacetylthiophene (2.5×10^{-6} s^{-1}) can be compared with a value of 2.05×10^{-6} s^{-1} for $k_o{}^H$ at 25.0 °C for the *o*-carboxyacetophenone;[8] the effect of a lower temperature is compensated for by the fact that the results refer to proton rather than tritium transfer.

Unlike some of the derivatives of 2′-carboxyacetophenone where no increase of rate with increasing base concentration was witnessed,[10] for the three compounds studied in the present investigation significant rate enhancements were observed (Table 1). For compounds (I) and (II) for which intramolecular catalysis is not an issue the second-order rate constants (Table 3) increase with increasing base strength, *viz.* acetate ≃ isobutyrate > formate > tartrate. The same trend applies for compound (III) with the difference that $k^T_{B^-}$ for the formate ion is much higher than expected. Clearly, intermolecular base catalysis makes an important contribution to the overall rate.

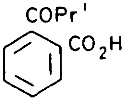
The relative importance of the inter- and intra-molecular processes is usually ascertained by measuring the latter's efficiency. This is customarily defined as an effective concentration C_i where $C_i = k_i/k^*$, k^* being the second-order constant for intermolecular catalysis by a hypothetical carboxylate ion having the same basic strength as the carboxylate group in the substrate. For this approach to be effective one needs to know the true dissociation constant of the keto acid; no such measurements have been made in this investigation. An alternative approach is to take advantage of the $k^T_{OH^-}$ values (available at 25 °C) and assume that the difference in the ratio $k^T_{OH^-}/k^T_{B^-}$ for compounds (I) and (II), and compound (III) reflects the importance of intramolecular catalysis. The estimates of $C_i{}^T$ obtained are given in Table 4. Not much quantitative significance can be attached to these values although it is clear that for acetate, isobutyrate, and tartrate they are very similar and close to those reported[10] for

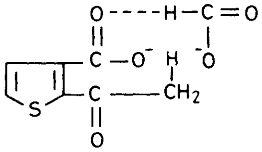


(IV) $R^1 - R^4 = H$

(V) $R^1 = R^4 = H$, $R^2 = R^3 = Me$

(VI)





(VII)

the 2′-carboxyacetophenones [(**IV**), (**V**), 39 and 66M, respectively] and [(**VI**), 890M] using a similar argument.

The results for water are subject to a large uncertainty which could in part arise from differences in solvation. The high C_i^T value for formate, *i.e.*, in the case where the nature of the 'internal' and 'external' catalyst is the same, leads us to speculate that hydrogen bonding such as is depicted in (**VII**) may be a contributing factor. The effect, if real, is likely to be more important for the formate anion than any of the other anions studied. The situation is analogous to that in which extra water molecules can be incorporated in a transition state *via* hydrogen bonding.

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