The Cyanolysis of Ethyl Thiolacetate

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Summary A re-investigation of the cyanolysis of ethyl thiolacetate has shown that the reaction pathway probably includes a protonation equilibrium possibly involving two forms of the tetrahedral intermediate.

HIBBERT and SATCHELL have recently shown[1] that the cyanolysis of ethyl thiolacetate (ETA) does not proceed *via* simple nucleophilic attack of cyanide. They conclude instead that both free cyanide (CN^-) and hydrogen cyanide catalyse the hydrolysis, with second-order rate constants $k_{CN^-} = 0{\cdot}2\ \text{M}^{-1}\ \text{min.}^{-1}$ and $k_{HCN} = 0{\cdot}07\ \text{M}^{-1}\ \text{min.}^{-1}$. The unusual nature of the mechanism suggested (concerted acid-catalysed nucleophilic catalysis) seemed to warrant further investigation of the system.

Titration of potassium cyanide (0·05—0·15M) gave pK_a values of 9·27 (25°, $\mu = 0{\cdot}15$) and 9·17 (30°, $\mu = 0{\cdot}15$). These values are in good agreement with literature values obtained under carefully controlled conditions.[‡]

The value of k_{HCN} determined by Hibbert and Satchell[1] predicts that in 0·15M-HCN (30°, 0·1M-acetate, pH 4·75, $\mu = 0{\cdot}25$), ester disappearance should have a half-life of approximately 70 min. However, no change in the optical density (233 nm.) of the solution ([Ester] = 10^{-4} M) was observed over a two-week period. Thus, if there is catalysis by HCN, the second-order rate constant must be vanishingly small.

The hydrolysis of ETA in cyanide buffers[§] at various pH's gave results similar to those of Hibbert and Satchell.[1] In Table 1 are listed the slopes (S) obtained from plots of k_{obs} against $[CN]_T$ at constant pH, with similar data calculated from ref. 1. When log S is plotted against pH, a titration curve is obtained for an apparent dissociation constant (pK_{app}) of 8·85 (30°) or 8·57 (25°). The data is in accord with the mechanism of the Scheme, which gives the rate equation:

$$k_{obs} = k_{OH^-}[OH^-] + \left[\frac{k_1k_3K_T/k_4 + k_1a_H}{(k_2+k_3)\,K_T/k_4 + a_H}\right]\left[\frac{K_a}{K_a + a_H}\right][CN]_T \qquad (1)$$

where a_H is the hydrogen ion activity measured at the glass electrode. S_{calc} in Table 1 gives the slopes calculated using the following constants (at 30° and 25°, respectively): $k_1k_3K_T/k_4 = 3$ or $12 \times 10^{-10}\ \text{M}^{-1}\text{min.}^{-1}$; $(k_2 + k_3)/k_4 = 9$ or $63{\cdot}3 \times 10^{-10}$; $k_1 = 0{\cdot}6$ or $1{\cdot}6\ \text{M}^{-1}\text{min.}^{-1}$; and $k_{OH^-} = 27$ or $13\ \text{M}^{-1}\text{min.}^{-1}$.

The slopes obtained in the cyanolysis of 2,2,2-trifluoroethyl thiolacetate (TETA) are listed in Table 2. In this case, S_{calc} is obtained from equation (2), which assumes simple nucleophilic catalysis. The values used in these calculations were (30°): pK_a = 9·17, $k_5 = 2{\cdot}14\ \text{M}^{-1}\text{min.}^{-1}$, and k_{OH^-} *ca* 200 $\text{M}^{-1}\text{min.}^{-1}$ (lit.[5] $k_5 = 2{\cdot}95\ \text{M}^{-1}\text{min.}^{-1}$ and $k_{OH^-} = 64{\cdot}5\ \text{M}^{-1}\text{min.}^{-1}$).

$$k_{obs} = k_{OH^-}[OH^-] + k_5\left[\frac{K_a}{K_a + a_H}\right][CN]_T \qquad (2)$$

TABLE 1

Cyanolysis of ethyl thiolacetate

pH	S[a]	S[b]calc	S[c]	S[b]calc
9·9	0·31	0·31		
9·64	0·277	0·291	0·177	0·178
9·24	0·248	0·239	0·156	0·156
8·94	0·197	0·182	0·135	0·135
8·64	0·121	0·122		
8·3	0·0631	0·0677		

[a] S = $k_{obs}/[CN]_T$, T = 30°, [ETA] *ca.* 10^{-4} M. [b] S_{calc} is the slope calculated from equation (1). See text. [c] Data from ref. 1, 25°.

A similar set of experiments showed that the hydrolysis of γ-thiobutyrolactone (TBL) is not catalysed by cyanide ($k_{OH^-} = 8{\cdot}4\ \text{M}^{-1}\text{min.}^{-1}$).

Several considerations reinforce the plausibility of the suggested mechanism. (i) A large number of possible schemes were evaluated, and no others were found which fit the data. (ii) Bruice and Schmir[6] have shown that a kinetically determined pK_a lower than the actual pK_a is generally associated with an equilibrium before the rate-determining step. Since no pre-equilibrium association of the buffer species, [¶] of the ester with itself, or of the ester with HCN can be observed, it appears reasonable that the equilibrium involves an intermediate. (iii) Equilibrium interconversions of tetrahedral intermediates in thioester hydrolyses are well documented.[8] (iv) It has previously been demonstrated[5] that CN^- is a nucleophile towards TETA. It is thus only a short step to the assumption that it is a nucleophile towards ETA. (v) The pK_a of ethanethiol is 10·5,[9] indicating that it is a rather poor

TABLE 2

Cyanolysis of 2,2,2-*trifluoroethyl thiolacetate*

pH	S[a]	S[b]calc
9·83	1·765	1·765
9·53	1·649	1·5
9·23	1·17	1·115
8·93	0·769	0·791
8·63	0·523	0·486

[a] S = $k_{obs}/[CN]_T$, T = 30°, [TETA] *ca.* 10^{-4} M. [b] S_{calc} is the slope calculated from equation (2). See text.

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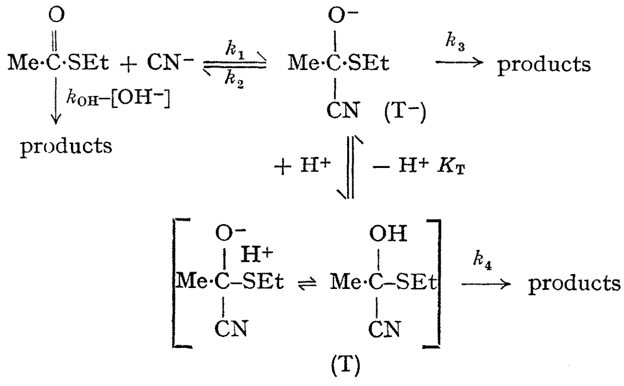
[‡] pK_a = 9·04 (33°, $\mu = 9{\cdot}86 \times 10^{-3}$),[2] 9·11 (30°, $\mu = 0$),[3] and 9·21 (25°, $\mu = 0$).[3] Compare with pK_a = 8·94, $\mu = 0{\cdot}13$, T = 25° used by Hibbert and Satchell.[1]

[§] Cyanolyses were performed in doubly-distilled, deoxygenated water, in Parafilm-sealed cuvettes. Ionic strength was maintained with potassium chloride. Reactions were followed by monitoring loss of thioester absorption at 233 nm. Pseudo-first-order rate constants (k_{obs}, $[CN^-] + [HCN] = [CN]_T \gg [ETA]$) were calculated by the method of Guggenheim.[4]

[¶] The kinetics of cyanide polymerization have previously been studied,[7] and results from this laboratory are in agreement. Under he experimental conditions, the self-condensation reaction is at least two powers of ten slower than the cyanolysis. The kinetics of he cyanolysis were observed to be first-order for at least three half-lives.

leaving group whose departure would be aided by prior protonation. 2,2,2-Trifluoroethanethiol, with a pK_a of 7·3,[5] is a much better leaving group, so that prior protonation is no longer important. (vi) At 30°, $k_3K_T/k_4 = 5 \times 10^{-11}$. Using a Taft $\sigma^*\rho^*$ plot for the ionization of substituted methanols,[10] we can make a good estimate of pK_T. If $\sigma^* = +1\cdot3$ for the cyano-group,[11] $-0\cdot1$ for the methyl,[11] and $+0\cdot33$ for the thioethyl,[12] then $\sigma^*\Sigma = 1\cdot53$. From the Taft plot, we then obtain $pK_T = 13\cdot72$. Thus, $k_3/k_4 = 2\cdot6 \times 10^3$, which is of the magnitude expected for this mechanism.



SCHEME

The non-susceptibility of TBL to cyanolysis may be readily explained. Thioanions have previously been demonstrated[13] to be good nucleophiles towards activated carbonyl-groups. The constrained anion should therefore be able to attack the acyl cyanide easily; since cyanide is at least as good a leaving group as the thio-anion, the net result would be regeneration of the ring, and no cyanolysis.

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