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KINETICS AND MECHANISM OF ACID HYDROLYSIS OF 2-CARBOETHOXYPYRIDINE *N*-OXIDES

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Rate constants and activation parameters have been measured for the acid hydrolysis of six 2-carboethoxypyridine *N*-oxides. The correlations of log $k_{obs.}$ vs Hammett's constants and chemical shifts of intramolecular hydrogen-bonded protons in parent acids are analysed. Evidence was found for the participation of intramolecular hydrogen bonding in the hydrolysis of the esters.

INTRODUCTION

The kinetics and mechanisms of acid and base hydrolyses of esters are now well recognized. These reactions have been shown to proceed by six of the eight possible mechanistic pathways, which are essentially the S_N1, S_N2 or tetrahedral type mechanism.[1,2] Acid-catalysed hydrolysis of esters usually occurs by a bimolecular mechanism with acyl—oxygen fission, designated $A_{AC}2$. In very strongly acidic solutions, a unimolecular mechanism, $A_{AC}1$, involving acyl—oxygen cleavage of the conjugate acid can operate.[3] This mechanism is the result of the decreased nucleophilicity of water molecules in the strongly acidic medium. When the ester is derived from a tertiary alcohol, acid-catalysed hydrolysis often occurs by a mechanism involving alkyl—oxygen fission, referred to as $A_{AL}1$. The change in mechanism is due to the stability of the carbonium ion that can be formed by C—O heterolysis, and probably also to a decrease in the rate of nucleophilic attack at the carbonyl group because of the steric factors.[4] Much study has been devoted to establishing substituent effects and proton transfers during the formation and breakdown of the tetrahedral intermediates.[5] These studies have been undertaken in part because of the fundamental importance of hydrolytic reactions in biological systems.[6,7]

Substituents play different roles in the base- and acid-catalysed hydrolysis of esters. With esters without special structural features, the base-catalysed reaction is facilitated by electron-withdrawing substituents in either the acyl or the alkoxy group. Since the rate-determining tetrahedral intermediate is negatively charged, the transition state leading to it will be stabilized by electron withdrawal. This stabilization is primarily an inductive effect, which is reduced as the substituent becomes further removed from the carbonyl group. The reaction constants, ρ, for the base-catalysed hydrolysis of esters vary from $1\cdot129$ to $2\cdot849$.[8] The substituent effects in acid-catalysed hydrolysis of esters are more complex. On the one hand, electron-releasing substituents increase the proton affinity of the carbonyl oxygen atom, but on the other hand, these substituents reduce the electrophilicity of the carbonyl carbon atom. Hence the acid-catalysed hydrolysis of esters is much less sensitive to substituents. The reaction constants, ρ, for acid-catalysed hydrolysis of esters range from $-0\cdot299$ to $0\cdot555$,[8] including those of picolinic and nicotinic esters.[9–11] The ratio of the reaction constants for the acid-catalysed hydrolysis of picolinic and benzoic esters is $0\cdot89$, indicating a similar sensitivity of aromatic and heteroaromatic rings to substituents.[12]

We have recently found that ability of carboethoxy groups in carboethoxypyridine *N*-oxides to undergo acid hydrolysis is significantly different for those in position 2 and for those in positions 4 and 5.[13] Product analysis for the acid-catalysed hydrolysis of 2,4- and 2,5-dicarboethoxypyridine *N*-oxides in $0\cdot1$ mol l^{-1} hydrochloric acid at 50–80 °C showed that only one carboethoxy group, that in position 2, hydrolyses to give the corresponding monoacids. This different reactivity can be of value, in practical synthetic terms, since it allows certain types of esters to be converted to the corresponding acids very selectively. To understand better the mechanism of this reaction, we have undertaken detailed kinetic studies of the acid hydrolysis of substituted 2-carboethoxypyridine *N*-oxides in $0\cdot1$ mol l^{-1} hydrochloric acid.

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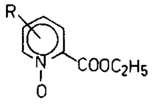


1-6

1 R = 4-NO$_2$

2 R = 4-COOEt

3 R = 5-COOEt

4 R = 4-Br

5 R = H

6 R = 4-OEt

RESULTS AND DISCUSSION

Acid hydrolysis of the 2-carboethoxypyridine *N*-oxides **1–6** was found to occur at convenient rates at 50–80 °C and was followed spectrophotometrically. In spite of the fact that pH–log $k_{obs.}$ profiles have not been precisely established, the reduced values of $k_{obs.}$ at 80 °C at lower acid concentrations (0.05 and 0.001 mol l^{-1}) in comparison with those at 0·1 mol l^{-1} at the same temperature demonstrate the catalytic effect of acid on the hydrolysis of 2-carboethoxypyridine *N*-oxides. Rate constants (k_{obs}) at 60 °C and activation parameters are given in Table 1.

The data obtained reveal an influence of the substituent on the hydrolysis rate; a factor of 15 is found between the fastest reaction for R = 4-OEt and the slowest reaction for R = 4-NO$_2$. A plot of log k_{obs}. against Hammett's constant, $\sigma_{p,m}$ for the *N*-oxide group (σ_{NO}), shows that the data are distributed about straight line given by the equation (Figure 1, solid line)

$$\log k_{obs.} = -1 \cdot 120\sigma_{NO} - 3 \cdot 455 \quad (1)$$

The relatively low correlation coefficient, $r = 0 \cdot 9820$, indicates that substituents simultaneously influence the electron density of the NO group ($\sigma_{p,m} = \sigma_{NO}$) and carboethoxy group. Taking into account the substituent effect on the carboethoxy group ($\sigma_{p,m} = \sigma_{COOEt}$), the following equation is obtained by computer fitting of data:

$$\log k_{obs.} = -1 \cdot 095\sigma_{NO} + 0 \cdot 030\sigma_{COOEt} - 3 \cdot 490 \quad (2)$$

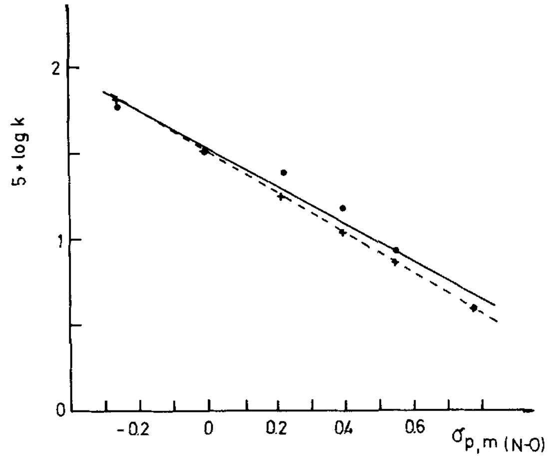


Figure 1. Plots of log k_{obs}. vs Hammett's constants: solid line, equation (1); dashed line, equation (2)

In this case the correlation coefficient is 1·0 (Figure 1, dashed line). As can be seen from equation (2), the NO group is more sensitive to a substituent (by a factor of ca 30) than the carboethoxy group. The sign and value of the reaction constant, $\rho = -1 \cdot 095$, are significantly different from those previously published.[8] It clearly indicates that a different mechanism to classical tetrahedral $A_{AC}2$ must be involved in the acid hydrolysis of 2-carboethoxypyridine *N*-oxides. We believe that the proton-donor ability of the NO group plays a dominant role in this mechanism.

The plot of the logarithms of the observed rate constants, log $k_{obs.}$, for the acid hydrolysis of 2-carboethoxypyridine *N*-oxides against the chemical shifts of parent acids was a straight line (Figure 2). Straight lines were also obtained for correlation of the chemical shifts (δ) of the intramolecular hydrogen-bonded protons in 2-pyridinecarboxylic acid *N*-oxides and their derivatives (**7**) against Hammett's constants, σ_p.[14–17] The highest chemical shifts, which correspond to the strongest hydrogen bonds, were found for acids with electron-releasing substituents.

Table 1. Hydrolysis of 2-carboethoxypyridine *N*-oxides in 0·1 mol l^{-1} hydrochloric acid at 60 °C.[a]

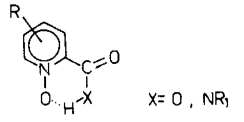
Compound	R	σ_p^b NO	σ_m^b CO$_2$Et	$\lambda_{kin.}$ (nm)	$10^4 k_{obs.}$ (s^{-1})	Error (%)	Correlation coefficient	RXN[c] (%)	$\tau_{0 \cdot 5}$ (min)	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$-\Delta S^{\ddagger}_{333}$ (J mol^{-1} K^{-1})	δ^d (ppm)
1	4-NO$_2$	0·778	0·710	330	0·383 ± 0·002	0·64	0·9999	81	301·9	68·91 ± 2·50	123·43 ± 7·53	16·20
2	4-CO$_2$Et	0·552	0·398	290	0·839 ± 0·008	1·02	0·9999	79	137·6	66·07 ± 4·73	125·52 ± 14·24	17·01
3	5-CO$_2$Et	0·398	0·552	275	1·560 ± 0·017	1·07	0·9999	89	74·0	61·71 ± 0·67	133·47 ± 2·09	17·66
4	4-Br	0·232	0·391	275	2·438 ± 0·025	1·03	0·9999	92	47·4	66·19 ± 1·30	115·90 ± 3·77	18·49
5	H	0	0	270	3·147 ± 0·018	0·58	1·0000	89	36·7	64·52 ± 1·42	119·24 ± 4·18	18·89
6	4-OEt	−0·250	0·150	275	5·951 ± 0·031	0·52	1·0000	93	19·4	59·87 ± 0·63	128·03 ± 2·09	19·92

[a] concentration of esters 2·5 × 10^{-5} mol l^{-1}.

[b] Ref. 8.

[c] Precentage to which the reaction was followed.

[d] Chemical shift of intramolecular hydrogen-bonded protons in 2-pyridinecarboxylic acid *N*-oxides (acetonitrile solution, 0·3 mol l^{-1}).



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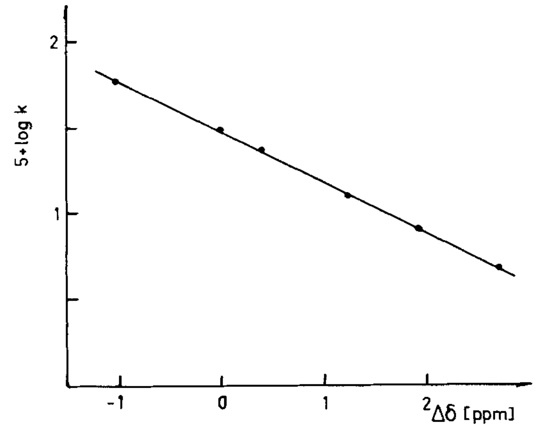
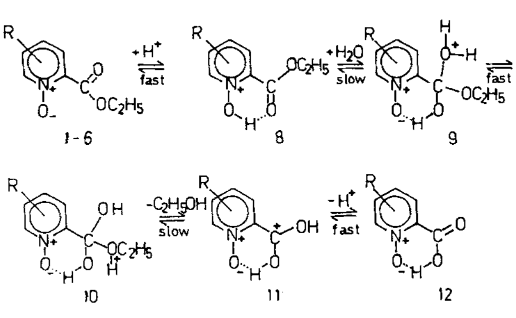


Figure 2. Plot of log k_{obs}. for the acid hydrolysis of 2-carboethoxypyridine *N*-oxides vs chemical shift of intramolecular hydrogen-bonded protons in parent acids ($\Delta\delta = \delta_H - \delta_R$)

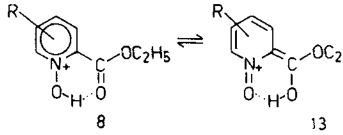
The above findings suggest that the acid hydrolysis of 2-carboethoxypyridine *N*-oxides occurs via an intermediate intramolecular hydrogen bonds. The pK_a values of substituted pyridine *N*-oxides vary from −1·7 to 4·0 and the protonation of the *N*-oxide group in acidic media is almost quantitative.[18,19] Hence the direct protonation of a carboethoxy group, which would lead to the classical tetrahedral intermediate, is precluded since the carboethoxy group is not only much less basic but additionally is involved in strong intramolecular hydrogen bonds.

The strong intramolecular hydrogen bond increases the electrophilicity of the carbonyl group, which in turn facilitates the nucleophilic attack of molecule of water, i.e. the rate-determining step (**8** → **9**) (Scheme 1). Hence the stronger the intramolecular hydrogen bond, the more easily hydrolysis occurs. The first step of the mechanism (Scheme 1), involving protonation of the *N*-oxide group (**1–6** → **8**), and the last step (**11** → **12**), diffusion-controlled deprotonation, are not considered to be rate determining because proton transfers are known to occur much faster than the hydrolysis process.[20]



Scheme 1

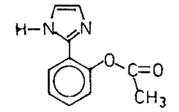
IR studies of the protonated compounds **1–6** in acetonitrile showed, that the esters **1–6** may easily undergo proton transfers to give a tautomeric form **13** (Scheme 2).[13] According to this equilibrium, the electron-releasing substituents cause an increase in the hydrogen bond strength, i.e. they can accelerate the hydrolysis reaction.



Scheme 2

Intramolecular hydrogen bond participation in ester hydrolysis has been extensively studied. These investigations are important to the understanding of biological mechanisms because enzymes are believed to act as exceedingly efficient catalysts, at least in part, by bringing together at the 'active site' the various basic, nucleophilic or acidic groups in a very favourable orientation of particular reactions.[6]

A study of a number of derivatives of compound **14** showed that at low pH the general acid catalysis mechanism dominates and comparison with analogous systems where the intramolecular proton transfer process is not available suggest that the intramolecular catalysis result in a 25–100-fold rate enhancement.[21]



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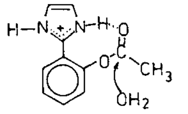

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Similarly, the intramolecular participation of the *o*-hydroxy group in the aminolysis of phenyl salicylate has been established, showing that such compounds are more reactive than analogues lacking the hydroxyl substituent.[22]

Compounds **2** and **3** possess two ester groups but only one of them can form intramolecular hydrogen bonds. Therefore, the reactivities of these groups are expected to be very different and indeed only one, that at position 2, hydrolyses under the investigated conditions.

The proposed mechanism is strongly supported by thermodynamic parameters of activation. As can be seen from Table 1, the entropies of activation for the hydrolysis of **1–6** are ca $-124\ \mathrm{J\,mol^{-1}\,K^{-1}}$, and are about $20\ \mathrm{J\,mol^{-1}\,K^{-1}}$ lower than those for aliphatic and aromatic esters where intramolecular hydrogen bond participation in the hydrolysis process is not possible.[23–25] The reactions that take place by way of cyclic transition states typically have negative entropies of activation because of the loss of rotational degrees of freedom with the introduction of a high degree of order in the activated complex. Hence the more negative entropy of activation for the acid-catalysed hydrolysis of 2-carboethoxypyridine *N*-oxides in relation to reactions proceeding via a classical $A_{AC}2$ mechanism forces the conclusion that the transition state has a higher degree of order, which is undoubtedly introduced by intramolecular hydrogen bonding.

The calculated free energies of activation, $\Delta G^{\ddagger}$, for the acid hydrolysis of **1–6** decrease from $110{\cdot}01\ \mathrm{kJ\,mol^{-1}}$ for R = 4-NO$_2$ to $102{\cdot}50\ \mathrm{kJ\,mol^{-1}}$ for R = 4-OEt. For the acid hydrolysis of ethyl benzoate, where intramolecular hydrogen bond participation does not occur, this value is $117{\cdot}0\ \mathrm{kJ\,mol^{-1}}$.[23] Therefore the decreased values of the free energy of activation, $\Delta G^{\ddagger}$, again demonstrate the participation of intramolecular hydrogen bonding in the acid hydrolysis of 2-carboethoxypyridine *N*-oxides.

CONCLUSIONS

Analysis of the measured rate constants for the acid hydrolysis of 2-carboethoxypyridine *N*-oxides by linear free energy relationships shows that the reaction undoubtedly proceeds via intermediates with intramolecular hydrogen bonds. An increase in the hydrogen bond strength by electron-releasing substituents causes an increase in reaction rate. The reduced value of the free energy of activation for the transition state formed by a carboethoxy group at position 2 compared with those at position 3 or 4 allows the diesters to be converted to monoacids very selectively.

EXPERIMENTAL

The ethyl esters **1–6** and the parent acids were prepared according to the literature procedures.[26–28]

^{1}H NMR spectra were measured at 60 MHz on a Varian 360 spectrometer in acetonitrile solution ($0{\cdot}3\ \mathrm{mol\,l^{-1}}$). All chemical shifts were reported to a sharp solvent resonance signal and then converted to δ values. All preparations and transfers for NMR measurements were carried out in a carefully dried glove-box.

UV spectra of reactants and products were measured on a Pye Unicam PU 8800 spectrophotometer.

Kinetics were followed by UV spectrophotometry by monitoring the decrease in ester absorbance at fixed wavelengths. Tightly stoppered UV cells ($l = 1$ cm) used as the reaction vessel were controlled to $\pm 0{\cdot}4\ ^{\circ}\mathrm{C}$ in a cell basket inside the UV spectrophotometer by a Pye Unicam Cell Temperature Controller. Pseudo-first-order rate constants were calculated from the slopes of conventional plots of $\ln(\varepsilon_1 - \varepsilon_2)/(\varepsilon - \varepsilon_2)$ vs time.[29] Such plots were linear to at least 80% completion and the k_{obs} values were reproducible to ca. 1%.

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