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Chlorination of acetylpyridines by N-chlorosaccharin

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Abstract. The kinetics of chlorination of 2,3 and 4-acetyl-pyridines by N-chlorosaccharin have been studied in aqueous acetic acid medium both in the absence and in the presence of sulphuric acid. The solvent effect on these reactions has also been studied. The results have been rationalised on the basis of a suitable mechanism.

Keywords. N-chlorosaccharin ; acetylpyridines ; acid-base catalysis ; intramolecular general base catalysis ; chlorination.

1. Introduction

The importance of N-halo compounds as halogenating and oxidising agents for a variety of organic substrates arises because they are potential sources of positive halogens in acidic solutions (Filler 1963; Mathur and Narang 1975; Brown and Soper 1953; Carr and England 1958). N-chlorosaccharin (NCSA) is one such compound first prepared by Chattaway (1905) and has been used for allylic and benzylic chlorinations as well as for the oxidation of primary and secondary alcohols (Bacchawat *et al* 1973). The present work deals with the kinetic and mechanistic aspects of the chlorination of 2,3 and 4-acetylpyridines by NCSA.

2. Experimental

N-chlorosaccharin was prepared by methods described in literature (Chattaway 1905). The NCSA obtained was recrystallised from chloroform-hexane mixture m.p. 150–152° C). The substrates 2,3 and 4-acetylpyridines used in the present study were of extra pure variety and were used without further purification.

The rate of reaction was followed by titrimetric methods, the disappearance of NCSA being monitored iodometrically. The reactions were carried out in binary solvent mixtures of acetic acid and water. The rate coefficients were evaluated by using the corresponding integrated rate expression.

3. Results and discussion

3.1. *Dependence on [NCSA]*

The reaction of acetylpyridine with NCSA was found to be smooth both in the absence and in the presence of sulphuric acid when conducted in aqueous acetic acid medium. The order dependence on [NCSA] was found to be zero as evidenced by the neat and linear zero order plots of the concentration of the reacted NCSA versus time.

3.2. *Dependence on [substrate]*

The effect of variation of the concentration of 2-acetylpyridine has been studied both in the absence and in the presence of sulphuric acid and it was observed that the order dependence on the ketone was unity (table 1). But in the case of 3- and 4-acetyl-pyridines, this dependence was greater than one but less than two in the absence of acid and it was unity in the presence of acid (table 2), other conditions being the same.

3.3. *Effect of acidity*

The dependence of the rate on $[H^+]$ has been studied by varying the concentration of sulphuric acid and it was noted that the addition of acid decreases the rate of chlorination upto a certain range of $[H^+]$ beyond which the rate increases with increasing concentration of acid with all the three acetyl pyridines (table 3).

3.4. *Effect of solvent polarity*

The effect of solvent polarity on the rate of chlorination has been studied in binary solvent mixtures of acetic acid and water with the composition ranging between 30% HOAc–70% H_2O (v/v) and 70% HOAc–30% H_2O (v/v) (table 4).

Table 1. Order dependence on [substrate] : (2-acetylpyridine) [NCSA] : $1{\cdot}80 \times 10^{-3}$ M. 40° C. 50% HOAc–50% H_2O (v/v).

10^2 [ketone] M	$[H_2SO_4]$ M	$10^7 k_0$ moles/lit/sec	$10^5 k_1$ sec^{-1}
1·01	..	14·3	14·2
2·07	..	29·4	14·2
3·10	..	44·9	14·5
6·20	..	89·6	14·4
1·01	0·2	2·10	2·08
2·02	0·2	4·00	1·98
3·03	0·2	5·78	1·91
6·04	0·2	11·5	1·90

Table 2. Order dependence on [substrate] : (3- and 4-acetylpyridine) [NCSA] : $1{\cdot}80 \times 10^{-3}$ M. 40° C. 50% HOAc–50% H_2O (v/v)

10^2 [ketone] M	$[H_2SO_4]$ M	$10^8 k_0$ moles/lit/sec	$10^6 k_1$ sec^{-1}
3-Acetylpyridine			
1·01	..	24·9	24·6
2·03	..	56·5	27·8
3·04	..	95·6	31·4
6·31	..	245	38·8
1·25	0·2	6·07	4·85
2·03	0·2	10·0	4·93
3·00	0·2	13·8	4·64
6·34	0·2	29·4	4·64
4-Acetylpyridine			
1·00	..	62·1	62·1
2·00	..	149	74·5
3·01	..	254	84·4
6·06	..	603	99·5
1·25	0·2	9·23	7·38
2·21	0·2	15·9	7·20
3·01	0·2	21·9	7·28
5·95	0·2	42·5	7·15

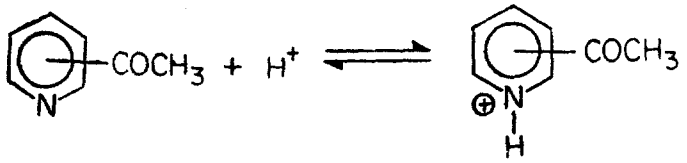
3.5. *Mechanism of chlorination of acetylpyridines*

The chlorination of acetyl pyridines under investigation obeys the following rate law:

$$\frac{-d\,[\mathrm{NCSA}]}{dt} = k\,[\mathrm{ketone}]\,[\mathrm{NCSA}]^{\circ}\,[\mathrm{H^+}]^{e} \tag{1}$$

in the presence of acid, where $+1 > x > -1$ and

$$\frac{-d(\mathrm{NCSA})}{dt} = k\,[\mathrm{ketone}]^{y}\,[\mathrm{NCSA}]^{\circ} \tag{2}$$



(3)

in the absence of acid, where $y = 1$ in the case of 2-acetylpyridine but $1 < y < 2$ in the case of 3- and 4-acetylpyridines. The zero order dependence on [NCSA] indicates that the rate-determining step is probably the enolisation of the ketone. Enolisation of ketones is known to be a general acid-base catalysed reaction. The

Table 3. Effect of acidity :
[NCSA] : $1 \cdot 80 \times 10^{-3}$ M. 40° C. 50% HOAc–50% H_2O (v/v)

[Ketone]	$[H_2SO_4]$ M	$10^8 k_0$ moles $lit^{-1} sec^{-1}$
2-Acetylpyridine		
$1 \cdot 01 \times 10^{-2}$ M	0·04	45·7
	0·08	33·5
	0·1	28·9
	0·2	21·0
	0·4	20·2
	0·6	20·8
	0·8	21·6
	1·0	23·0
	1·52	25·2
	1·9	27·6
3-Acetylpyridine		
$1 \cdot 25 \times 10^{-2}$ M	0·04	6·50
	0·08	5·10
	0·1	4·55
	0·2	6·07
	0·4	8·58
	0·8	15·4
	1·0	19·5
4-Acetylpyridine		
$1 \cdot 25 \times 10^{-2}$ M	0·04	13·0
	0·08	9·31
	0·1	9·06
	0·2	9·23
	0·4	12·1
	0·8	19·3
	1·0	23·2

halogenation of ketones can thus be catalysed by pyridines also (Feather and Gold 1965). Acetylpyridines used as substrates for chlorination in the present study are capable of functioning as general base catalysts. This is only to be expected in view of the pK_a values of these substrates (the pK_a values of 2,3 and 4-acetylpyridines are 2·64, 3·18 and 3·5 respectively (Cox 1974). Under the conditions of the experiment, viz., in aqueous acetic acid in the absence of mineral acid, acetylpyridines may exist in equilibrium with their conjugate acids.

Assuming general base catalysis by pyridines, the common rate law for the chlorination of all the acetylpyridines studied, may be given as

$$\frac{-d[\text{NCSA}]}{dt} = \{k_{H_2O}[H_2O] + k_{H^+}[H^+] + k_{OH^-}[OH^-] + k_{HOAc}[HOAc] + k_{OAc^-}[OAc^-] + k_{AcPy}[AcPy]\}[AcPy],$$

(AcPy: acetylpyridine).

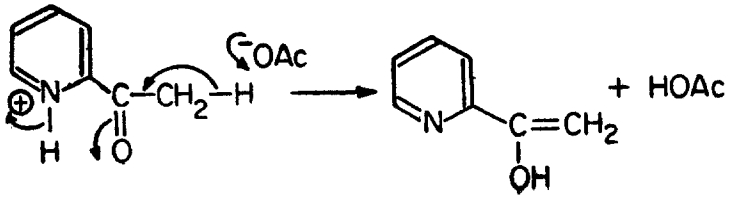
Table 4. Effect of solvent polarity.
[NCSA] : $1{\cdot}80 \times 10^{-3}$ M. 40° C

[Ketone]	$[H_2SO_4]$ M	Solvent composition % HOAc–% H_2O (v/v)	$10^8 k_0$ moles/lit/sec
2-Acetylpyridine			
($1{\cdot}01 \times 10^{-2}$ M)	..	30–70	138
	..	50–50	143
	..	70–30	152
	0·2	30–70	25·2
	0·2	50–50	21·0
	0·2	70–30	15·2
3-Acetylpyridine			
($1{\cdot}01 \times 10^{-2}$ M)	..	30–70	29·7
	..	50–50	24·9
	..	70–30	20·8
($1{\cdot}25 \times 10^{-2}$ M)	0·2	30–70	6·67
	0·2	50–50	6·07
	0·2	70–30	5·38
4-Acetylpyridine			
($1{\cdot}00 \times 10^{-2}$ M)	..	30–70	65·9
	..	50–50	62·1
	..	70–30	53·5
($1{\cdot}25 \times 10^{-2}$ M)	0·2	30–70	11·2
	0·2	50–50	9·23
	0·2	70–30	7·25

It follows from the above rate expression that the order on acetylpyridines would vary between one and two depending on the relative efficiency of the acetylpyridine as a general base catalyst as against that of acetate.

In the case of 2-acetylpyridine, the order on the substrate is unity and this suggests that there is probably very little catalysis by 2-acetylpyridine. For 3- and 4-acetylpyridines, the order on substrate is more than one (1·3) indicative of a greater involvement of these general base catalysts. Such a fact is borne out by an earlier observation (Cox 1974) in the iodination of acetylpyridines. However, one cannot rule out the probability of an intra-molecular general base catalysis in 2-acetylpyridine and such catalysis would result in a rate acceleration without affecting the rate picture. The rate gain observed on change of substrate from 4-acetylpyridine to 2-acetylpyridine is of the order of five.

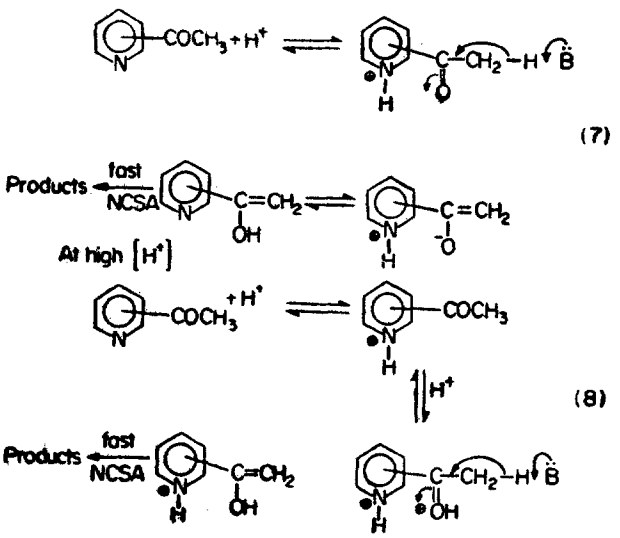
$$HOAc \rightleftharpoons H^+ + OAc^-. \tag{5}$$



(6)

When the reactions are conducted in aqueous acetic acid medium containing mineral acid, the order on all the acetylpyridines turns out to be unity. This suggests the absence of any general base catalysis by the acetylpyridine since they function mainly in the form of their conjugate acids. Therefore, the progressive protonation of the pyridines results in a rate retardation with increasing $[H^+]$, since a general base (acetylpyridine) is effectively removed in this process. The rate profile for the $[H^+]$ variation shows a minimum and thereafter the rate registers a gradual increase with increasing $[H^+]$. At the rate minimum, the reaction is one of chlorination of the protonated version of the acetylpyridine aided by a general base such as acetate. At higher concentrations of H^+, it is likely that a second protonation on the pyridine occurs at the carbonyl oxygen thereby facilitating the enol formation. Thus,

At low $[H^+]$,



Acetylpyridines being bases with pK_a values in the vicinity of the pH of the media employed, acid-base equilibrium involving the protonation of these systems cannot be overlooked. Increase in acetic acid in the composition of the solvent mixture would lead to a progressive removal by protonation of the acetyl-pyridine which also acts as a general base catalyst. The observed rate retardation for 3 and 4 acetylpyridines in a solvent system containing higher percentage of acetic acid may therefore be traced to this effect. However, under the same conditions, for 2 acetylpyridine there is a small rate acceleration. This is only to be expected in view of the operation of acetate-aided intramolecular catalysis [equation (6)] which would be enhanced by the increasing availability of acetate ions at compositions containing higher percentage of acetic acid.

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