Kinetics and Mechanisms of Hydrolysis of Cyclic Sulphinamidates. Part 1. Ring Opening of 3-Phenylperhydro-1,2,3-oxathiazin-2-one

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The hydrolysis of 3-phenylperhydro-1,2,3-oxathiazin-2-one gives rise to two ionic intermediates depending on the pH: (i) in acidic and slightly alkaline solutions, 3-*N*-phenylaminopropyl hydrogensulphite ion is sufficiently stable to be characterised by u.v. spectrophotometry; (ii) in strongly alkaline solutions, 3-hydroxypropyl *N*-phenylsulphinamidate ion, which does not build up in the reaction medium, is formed. Only the first step of the hydrolysis reaction, *i.e.* the opening of the sulphinamidate ring, is reported here. The rate equation is $k_{obs} = k_H a_H + k_{OH}[OH^-] + k_{BH}[BH^+]$. Two reaction schemes are proposed: (i) in acidic and slightly alkaline media, base-assisted water attack on the *N*-protonated substrate explains the results obtained from general acid catalysis and isotopic effects; (ii) in strongly alkaline media, the values of the isotope effect and the entropy of activation suggest hydroxide ion attack on the neutral substrate. Both reaction schemes may involve either a concerted or a stepwise (*via* a tetraco-ordinate intermediate) mechanism. The experimental data do not allow them to be differentiated.

THE hydrolysis of carboxylate has been the subject of intensive study.[1-3] However hydrolysis of compounds resulting from the replacement of the ester carbonyl group by a sulphinyl group has received little attention. Related structures investigated have been sulphurous acid esters [4-6] and 3-t-butyl-1,2,3-oxathiazolidin-2-one which is derived [7] from sulphinamidic acid.

This paper, the first of two, is concerned with the hydrolysis of cyclic sulphinamidates over a wide pH range. The first step is the ring opening of the neutral (I) or *N*-protonated (III) species and leads to the formation of two different intermediates depending on the pH (Scheme 1). These are, respectively, sulphinamidate ion (II) in alkaline media or hydrogensulphite ion (IV) in acidic or slightly alkaline media. These intermediate ions are subsequently converted into amino-alcohol (V) in a second step

The first step only is dealt with here (Scheme 1). The substrate was 3-phenylperhydro-1,2,3-oxathiazine 2-one (Ia). Tillett and his co-workers [7] had suggested, for the hydrolysis of 3-t-butyl-1,2,3-oxathiazolidin-2-one in strongly acidic media, the occurrence of a $Bu^tNH(CH_2)_2OSO\overset{+}{O}H_2$ intermediate along the reaction pathway, but did not isolate it. Using Bunnett's approach, they showed the involvement of water both as a nucleophile and as a proton transfer agent. In acidic and slightly alkaline solutions, the formation of an analogous intermediate was observed during the hydrolysis of 3-phenylperhydro-1,2,3-oxathiazin-2-one, and the involvement of water both as a nucleophile and catalyst was corroborated. In strongly alkaline media, however, no build up of an intermediate was observed, and the amino-alcohol was obtained directly.

The decomposition of intermediates (IV), in acidic and slightly alkaline media, and (II), in strongly alkaline media, was studied using a different sulphinamidate, 3-phenyl-3,4-dihydro-1,2,3-benzoxathiazin-2-one (Ib), for which there is a build up of both intermediates. The mechanism of hydrolysis of (Ib) is described in the following paper.[8]

EXPERIMENTAL

Substrates.—Cyclic sulphinamidates were obtained using a three-step synthesis (Scheme 2). The carbamates were prepared by the method of Dox and his co-worker.[9] Hydrolysis in boiling ethanol [10,11] led to the amino-alcohols. Finally the amino-alcohols were cyclised to the sulphinamidates by reaction with thionyl chloride in the presence of an organic base,[12-14] (Ia), b.p. 160° at 0.04 mmHg; (Ia_1) m.p. 35°; (Ia_2) m.p. 30°. Purity was determined by g.l.c. and n.m.r.

Apparatus.—A Cary model 15 and a Unicam model SP 1800 spectrophotometer fitted with a SP 1805 program controller and a thermostatted multiple cell compartment were used for the spectroscopic measurements. pH Measurements were carried out using a Beckman Research pH meter.

Kinetic Measurements.—The kinetics of hydrolysis of sulphinamidates were followed spectrometrically by recording the increase in absorbance at 258 nm resulting either from the appearance of amino-alcohol (Va) in alkaline media or from that of intermediate (IVa) in acidic or slightly alkaline solutions. The pseudo-first-order constants were calculated either graphically or using a weighed least-squares program written for the Olivetti–Underwood Programma 102.

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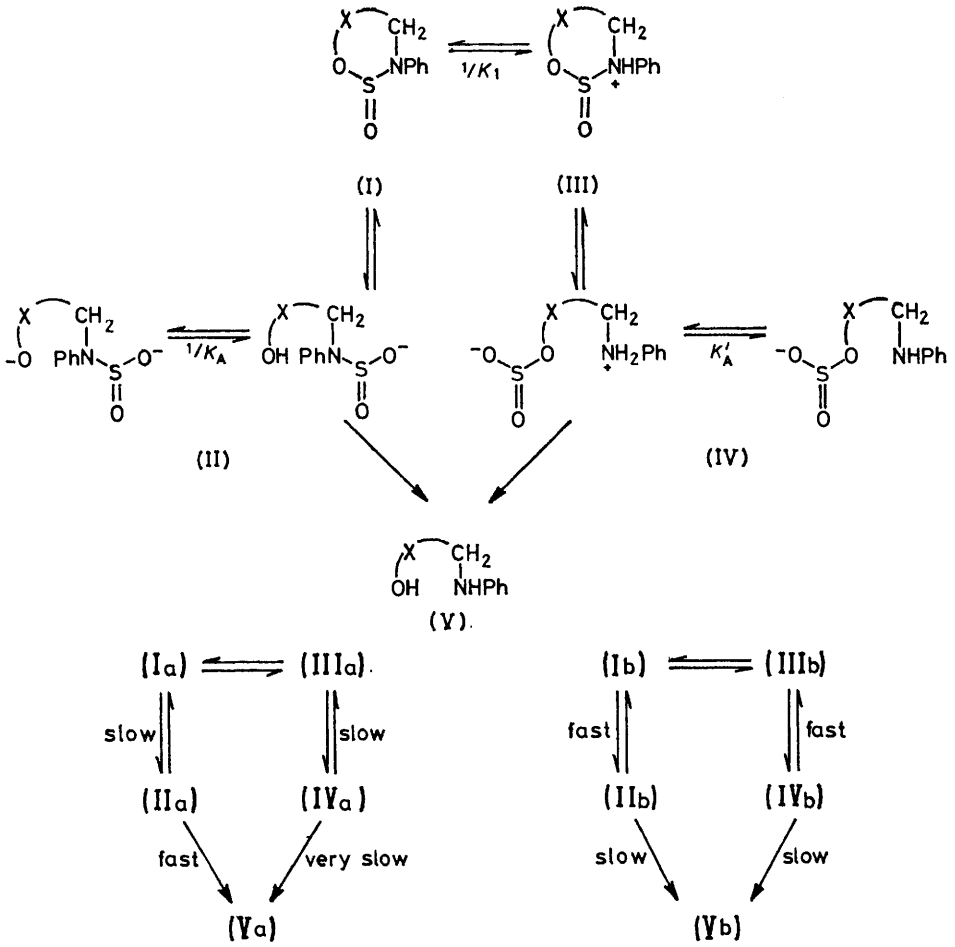
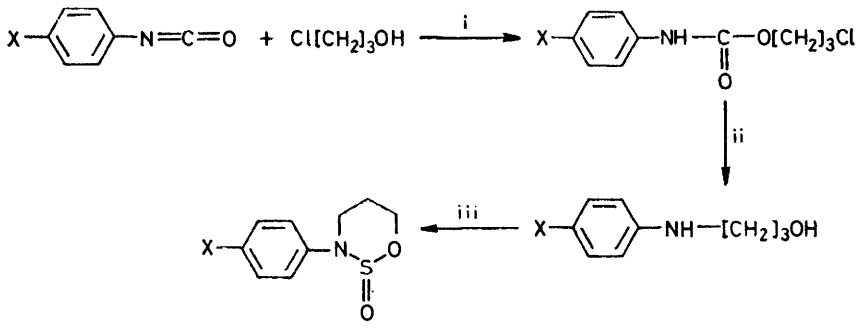


a; X = $[CH_2]_2$

b; X =  (see Part 2)

SCHEME 1



(I)

a; X = H

a_1; X = 4-MeO

a_2; X = 4-Cl

SCHEME 2 Reagents: i, Et_3N–CH_3CN; ii, NaOH–EtOH; iii, $SOCl_2$–Et_3N

RESULTS

Product Analysis.—In concentrated sodium hydroxide solutions, the final product was the amino-alcohol identified by u.v., $\lambda_{max.}$ 240 (ε 9 750) and 283 nm (1 650), and n.m.r. spectroscopy. In acidic and slightly alkaline solution, intermediate (IVa), $\lambda_{max.}$ 250 nm, was characterised by its pK_a' value. The absorbance of the amino-alcohol and that of compound (IVa) both increase with pH in the range 3—7

as does that of aniline. A pK_a value of 5.0 was obtained for the amino-alcohol at 25°; the pK_a' value found for (IVa)

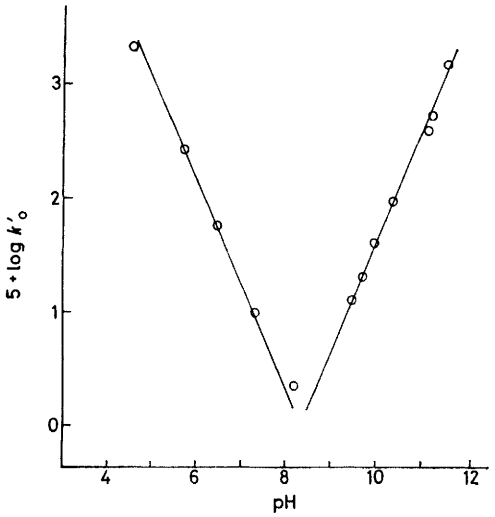


FIGURE 1 pH–Rate profile for the hydrolysis of 3-phenylperhydro-1,2,3-oxathiazin-2-one in the absence of buffers (70°; μ 1.0, KCl)

was 4.8 ± 0.2. This pK_a' value cannot be assigned to the protonation of the nitrogen atom of (Ia) which should be much lower.[7] Only open chain structures such as (IVa) or (IIa) can give rise to this pK_a' value. Only 3-*N*-phenylaminopropyl hydrogensulphite ion (IVa) contains a group the pK_a of which is consistent with the experimental value; the observed equilibrium constant corresponds to proton abstraction from an anilinium ion. It seems likely that the OSO_2^- group is too far from the nitrogen atom to cause any change in the proton affinity of the CH_2NHPh group. Therefore the open-chain structure (IVa) only is considered. Moreover, this is consistent with the reaction intermediate postulated by Tillett and his co-workers in acidic media.

Effect of Buffer Concentration.—Plots of k_{obs} against total buffer concentration $[B_t]$ are linear and obey the equation $k_{obs} = k_1'[B_t] + k_0'$. The pH–rate profile (Figure 1) was

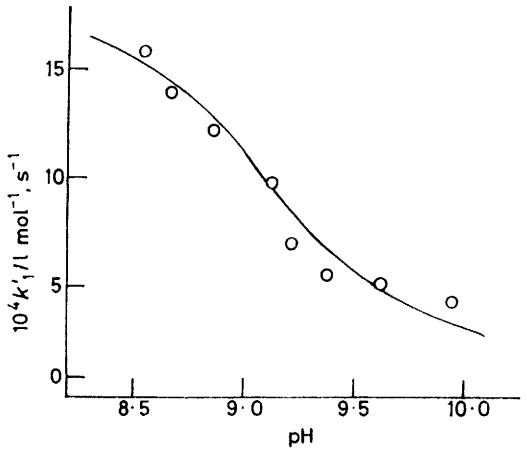


FIGURE 2 Plot of k_1' *versus* pH for the hydrolysis of 3-phenylperhydro-1,2,3-oxathiazin-2-one in carbonate buffer at 70° (μ 1.0, KCl) ($k_{obs} = k_1'[B_t] + k_0'$)

established from the rate constants k_{OH} measured in sodium hydroxide solutions, and from those (k_0') extrapolated to zero buffer concentration in acidic or slightly alkaline media.

The plot of k_1' *versus* pH exhibits the sigmoidal shape characteristic of general acid catalysis (Figure 2). No base catalysis could be detected; the k_{BH} values are listed in Table 1. Over the pH range investigated, the rate law is

TABLE 1

Catalytic constant values for the hydrolysis of 3-phenylperhydro-1,2,3 oxathiazin-2-one (70°; μ 1.0, KCl)

k_{BH}/l mol^{-1} s^{-1}	log k_{BH}	pK_{BH}	Buffer
1.6×10^3	3.20	−1.74	H_3O^+
2.5×10^{-2}	−1.60	4.80	Acetate
7.5×10^{-4}	−3.12	8.15	Tris
1.9×10^{-3}	−2.72	9.28	Carbonate
2.0×10^{-1}	−0.70	14.5	OH^-

$k_{obs} = k_H a_H + k_{OH}[OH^-] + k_{BH}[BH^+] = k_0' + k_{BH}[BH^+]$, with k_H 1.6×10^3 l mol^{-1} s^{-1} and k_{OH} 2.0×10^{-1} l mol^{-1} s^{-1}. A Brönsted plot of log k_{BH} *versus* pK_{BH} gives a straight line (α 0.6) although the point for hydroxide ion deviates from the line by *ca.* 5 log units (Figure 3).

Deuterium Oxide Solvent Isotope Effect.—The kinetic study carried out in heavy water at 10° at pH 3.0 led to an isotope

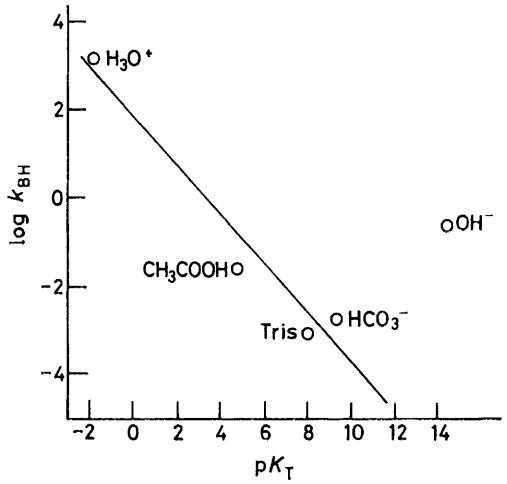


FIGURE 3 Brönsted plot for the hydrolysis of 3-phenylperhydro-1,2,3-oxathiazin-2-one (70°; μ 1.0, KCl)

effect k_H/k_D of 0.71. In 0.69M-sodium hydroxide at 25°, the isotope effect k_{OH}/k_{OD} was 0.73.

Thermodynamic Functions of Activation.—The rate constants measured in sodium hydroxide solution (pH > 11) between 25 and 70° were used to compute the energy of activation (E_a 12.7 kcal mol^{-1}) and the entropy of activation ($\Delta S^{\ddagger}$ −28 cal mol^{-1} K^{-1}).

Substituent Effects.—Investigation of the effects of

TABLE 2

Bimolecular rate constants k_{OH} for the hydrolysis of 3-arylperhydro-1,2,3 oxathiazin-2-one at 25° (μ 1.0, KCl)

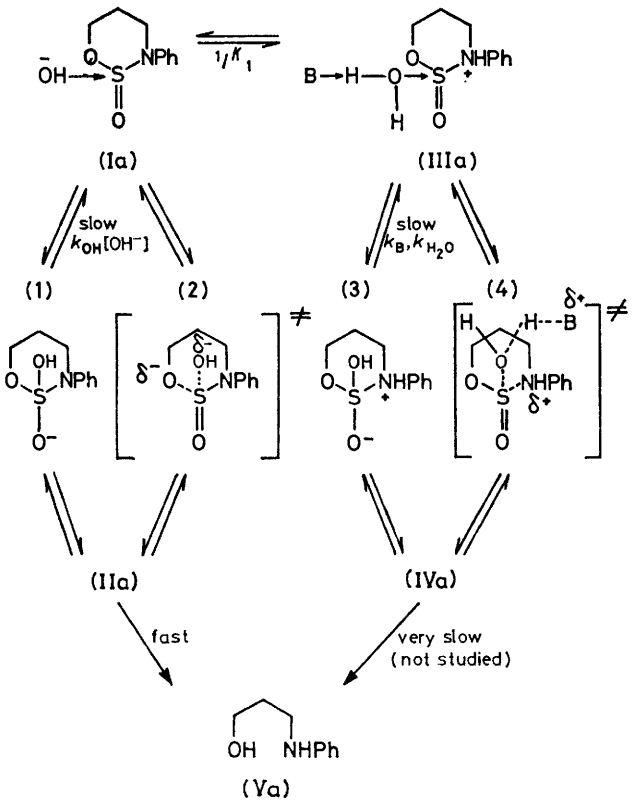
Aryl substituent	k_{OH}/l mol^{-1} s^{-1}	σ
p-MeO	5.13×10^{-3}	−0.268
H	8.43×10^{-3}	0
p-Cl	17.5×10^{-3}	+0.227

substituents in the aromatic ring in 1.0M-NaOH at 25° led to a Hammett ρ value of 1.1 (Table 2).

DISCUSSION

The results for the hydrolysis of compound (Ia) can be rationalized in terms of Scheme 3. In alkaline media,

slow hydroxide ion attack on (Ia) results in the formation of intermediate (IIa) which rapidly decomposes to the

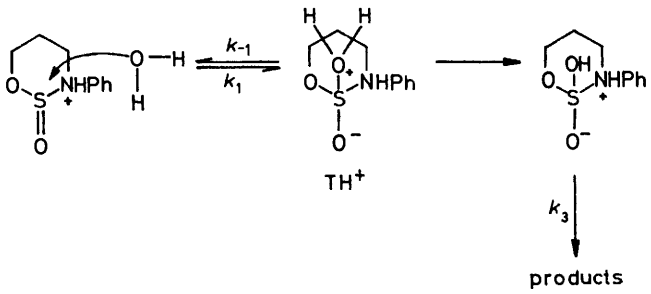


SCHEME 3

amino-alcohol (Va). The existence of two tight isosbestic points shows that no intermediate builds up during the reaction. Compound (IIa) was not detected. The structure is assumed * to correspond to cleavage of the O–S bond, as in alkaline media the CH_2O^- group is likely to be a better leaving group than $CH_2(Ph)N^-$. The conversion of (Ia) into (IIa) might involve either a tetraco-ordinate intermediate [15] (mechanism 1), *i.e.* a $B_{AC}2$ pathway analogous to that suggested by Bender [3] for the hydrolysis of carboxylates, or a concerted process (mechanism 2). The above mechanisms are consistent with an entropy of activation of −28 cal mol^{-1} K^{-1}, which reflects the decrease in the degrees of freedom of the hydroxide ion in the adduct. The isotope effect (k_{OH}/k_{OD} 0.73) results from a slight increase in nucleophilic strength [16,17] when OH^- is replaced by OD^-. The ρ value of 1.1 indicates that the electron-withdrawing groups make hydroxide ion addition onto the sulphinyl group easier. As few model compounds have been studied, a possible approach might be a comparison with the hydrolysis of acetanilides [18] (ρ 1.0) which is known to proceed *via* a $B_{AC}2$ mechanism. In both mechanisms, as hydroxide ion acts as a nucleophilic agent (and not as a base catalyst), log k_{OH} markedly deviates from the Brönsted plot obtained for the other catalysts.

In acidic or slightly alkaline media, mechanisms 3 and 4 come into consideration. In mechanism 3, base-assisted water attack on the conjugate acid (IIIa) of the substrate is followed by fast ring opening leading to (IVa); in mechanism 4 these two reactions are concerted. The protonation on the nitrogen atom produces the $CH_2(Ph)NH$ function which is a better leaving group than CH_2O^-. Intermediate (IVa) is subsequently hydrolysed to amino-alcohol (Va) in a slow step which was not studied. General acid catalysis can be the combination of specific acid catalysis and general base catalysis; in this case $k_{BH} = k_B K_{BH}/K_1$. In the absence of buffer, a plot of log k_0' *versus* pH, which gives a straight line of slope − 1 can be interpreted in terms of the attack of a water molecule assisted by another water molecule on the protonated substrate (IIIa); then $k_H = k_{H_2O}[H_2O]/K_1$. According to Tillett and his co-workers, the pK_1 value for (IIIa) should lie within the range of acidity functions: this explains why this ionisation could not be observed in the pH–rate profile (Figure 1). The Brönsted α value of *ca.* 0.6 identical with that derived from the results of Pollack and his co-workers [19] for general base-catalysed water attack on 2,2,2-trifluoro-*N*-(3-methylcyclohex-2-enylidene)ethylamine (β 0.4). The same authors also found an isotope effect k_{H_2O}/k_{D_2O} of 2.44. In acidic media, the ratio k_H/k_D was found to be 0.71. From $k_H = k_{H_2O}[H_2O]/K_1$ and $K_1^{H_2O}/K_1^{D_2O} = 3.4$ (as reported for nitrogen acids [20]) a value of 2.4 for k_{H_2O}/k_{D_2O} can be calculated. Mechanisms 3 and 4 are both in good agreement with this isotope effect and lead to the same conclusions as those of Tillett and his co-workers. Unfortunately, the above data do not provide any decisive argument supporting either mechanism.

Another possible mechanism is water attack on the protonated substrate, followed by the rate-determining proton transfer from TH^+ to a base (Scheme 4). As the



SCHEME 4

number of points used in the Brönsted plot is small, the possibility of an Eigen-type plot and hence the possibility of such a mechanism cannot be ignored.

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* This structure was corroborated for intermediate (IIb) which was found to build up in the reaction medium.[8]

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