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ACID HYDROLYSIS OF 2-SUBSTITUTED 3-METHYL-TETRAHYDRO-1,3-OXAZINES: SIMPLE MODELS FOR TERTIARY GLYCOSYLAMINES

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The hydrolytic decomposition of 2-phenyl- and 2-isopropyl-3-methyltetrahydro-1,3-oxazines to 3-methylaminopropan-1-ol and appropriate aldehydes was studied by ^{1}H NMR and UV spectroscopy in acidic solutions. The time-dependent spectra confirmed that the formation of the final products was preceded by an equilibration of three components, the two Schiff base intermediates and the starting material, of which the former produced a carbinolamine which in turn underwent heterolysis to the final products.

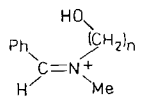
INTRODUCTION

Glycosylamines (GA), the condensation products of reducing sugars with ammonia or amines, are a group of substrates structurally related to the glycosides. The only difference is that an amine rather than an alcohol is the leaving group in the hydrolysis reaction.[1a] The mechanism of the acid hydrolysis of glycosylamines from primary amines has been more widely studied than that of those derived from secondary amines, whereas almost no data are available for tertiary amines.[1] These investigations have been complicated by uncertainties in the structure of the glycosylamines and difficulties in estimating free aldose or amine in the presence of unhydrolysed glycosylamines.[1b,c] These difficulties can be minimized with simplified models, e.g. 1,3-oxazolidine and tetrahydro-1,3-oxazine derivatives (cf. **1** and **2**) where the possible interference of the polar substituents and the excess heteroatoms can be avoided. 2-Substituted 3-alkyl/aryl-1,3-oxazolidines, the simplest models for tertiary glycosylamines, have been reported to hydrolyse via stable intermediates, very similarly to the corresponding acyclic Schiff bases [Scheme 1(A), $n = 2$].[2–4] On the other hand, the cyclic glycosylamine structures can be considered as potentially useful prodrugs for β- and γ-amino alcohol moieties or carbonyl groups.[5]

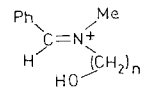
During the course of our studies we found that ^{1}H NMR together with UV spectroscopy offers a valuable means of obtaining a better insight into the reaction. As a continuation of our work,[6,7] we now describe the course of the acid hydrolysis of 3-methyltetrahydro-1,3-oxazines, the six-membered counterparts of 1,3-oxazolidines.

1a : R=Ph
1b : R=Pr^i

GA



n=2 : 1aZ
n=3 : 2aZ



n=2 : 1aE
n=3 : 2aE

2a : R=Ph
2b : R=Pr^i

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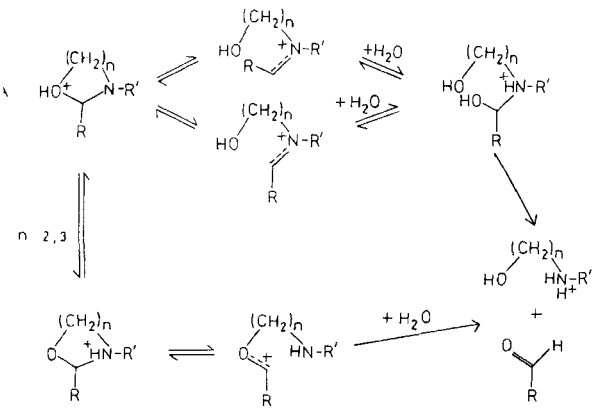


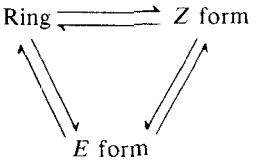
Scheme 1

RESULTS AND DISCUSSION

NMR spectra revealed the Schiff base intermediates in the hydrolysis of 2-substituted 3-methyltetrahydro-1,3-oxazines as demonstrated for 2-phenyl-3-methyltetrahydro-1,3-oxazine (**2a**) in 5 mol dm^{-3} $DClO_4$ at 343 K in Figure 1. By comparison with the respective chemical shifts of the *E* and *Z* forms of 2-phenyl-3-methyl-1,3-oxazolidines (**1a**),[7] it could be concluded that the methine hydrogen of **2a***Z* resonates at a lower field than that of **2a***E*. The signals of the ring and the amino alcohol *N*-methyl groups were easy to locate by spiking, whereas that of the carbinolamine was assigned by reference to literature data.[7,8] The time-dependent mole fractions of the molecular species involved in the hydrolytic decomposition of 2-phenyl-3-methyl-1,3-oxaxolidine (**1a**) [Figure 2(A)] and that of 2-phenyl-3-methyltetrahydro-1,3-oxazine (**2a**) [Figure 2(B)] showed that the concentrations of the Schiff base intermediates were much lower for the latter than for the former ring system. Also, the formation of the final products is much slower for the six-membered than for the five-membered ring system.

The hydrolysis of **2a** was followed also at 323 K and 343 K in 5 mol dm^{-3} $DClO_4$. Despite the fact that the initial rates of formation of both Schiff bases were very similar, the mole fraction of the *Z* form was higher than that of the *E* form after a few minutes (Figure 3). The experiment at 343 K indicated that carbinolamine also increased at first and then gradually disappeared.

Table 1 shows the first-order rate constants measured by the UV method at different temperatures in 5 mol dm^{-3} perchloric acid for the formation of acyclic Schiff base intermediates in the hydrolytic decomposition of **2a**. The solvent deuterium isotope effect for the formation of the Schiff base, $k_{HClO_4}/k_{DClO_4} \approx 3$, is close to those observed for the comparable step in the hydrolytic decomposition of some 2-alkyl-3-methyl-1,3-oxazolidines.[6] Nevertheless, the reaction is nearly completed even in 5 mol dm^{-3} $DClO_4$ before the first NMR spectrum (8·5 min from the beginning) could be obtained. Therefore, the only process to be observed by the NMR method was equilibration of the three components, two Schiff bases and the starting material:



Almost constant ratios of the three components prevailed for **2a** at 303 K from *ca* 10 to 100 min from

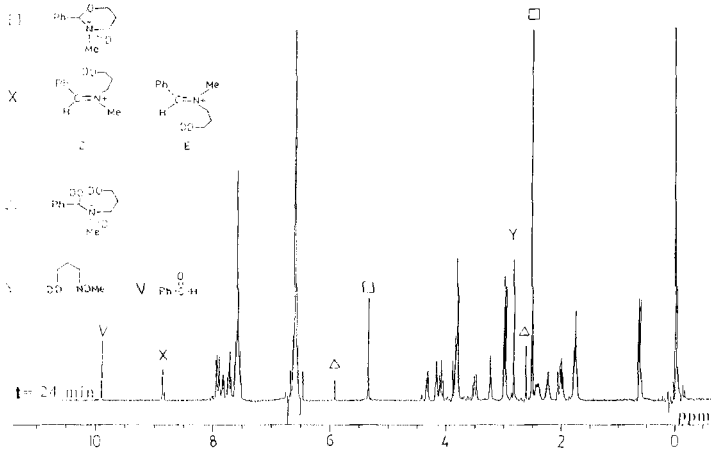


Figure 1. ^{1}H NMR spectrum of 2-phenyl-3-methyltetrahydro-1,3-oxazine in 5 mol dm^{-3} $DClO_4$ at 343 K. Internal reference: sodium 3-(trimethylsilyl)propanesulphonate

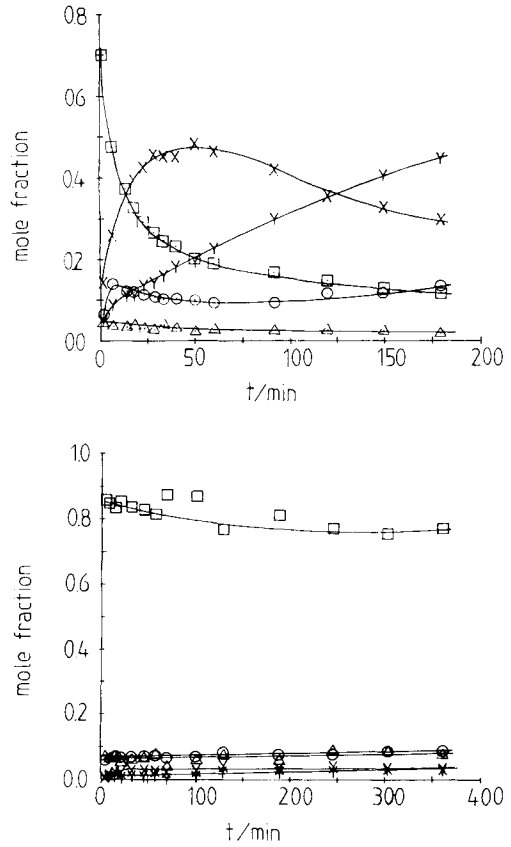


Figure 2. (A) Mole fractions of 2-phenyl-3-methyl-1,3-oxazolidine, the Schiff base intermediates, carbinolamine and amino alcohol as a function of time in 5 mol dm^{-3} $DClO_4$ at 303 K. (□) Ring form; (×) *E* isomer of the intermediate; (○) *Z* isomer of the intermediate; (△) carbinolamine; (Y) amino alcohol. (B) Mole fractions of 2-phenyl-3-methyltetrahydro-1,3-oxazine, the Schiff base intermediates, carbinolamine, and amino alcohol as a function of time in 5 mol dm^{-3} $DClO_4$ at 303 K. Symbols as in (A).

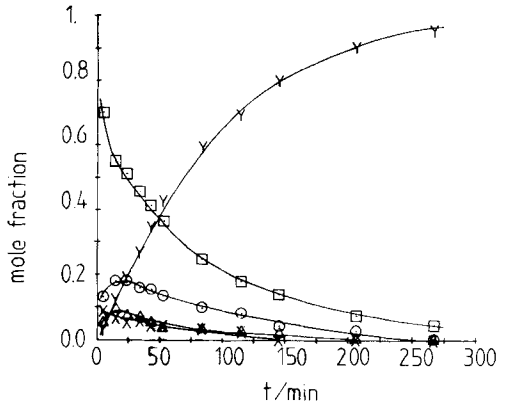


Figure 3. Mole fractions of 2-phenyl-3-methyltetrahydro-1,3-oxazine, the Schiff base intermediates, carbinolamine and amino alcohol as a function of time in 5 mol dm^{-3} $DClO_4$ at 343 K. Symbols as in Figure 2

Table 1. First-order rate constants at different temperatures, enthalpies and entropies of activation for the formation of acyclic Schiff base intermediates in the hydrolysis of 2-phenyl-3-methyltetrahydro-1,3-oxazines in 5 mol dm^{-3} $HClO_4$ (k_1) and those for the formation of benzaldehyde in 0·1 mol dm^{-3} $HClO_4$ (k_2)

T (K)	10^3k_1 (s^{-1})	10^3k_2 (s^{-1})
313·2		7·34 ± 0·24
308·2	31·2 ± 0·4	4·48 ± 0·08
303·2	20·7 ± 0·9	2·69 ± 0·08
298·2	13·1 ± 1·5	1·52 ± 0·06
293·2	8·04 ± 0·30	0·867 ± 0·009
288·2	4·93 ± 0·21	0·453 ± 0·015
283·2	2·67 ± 0·15	
ΔH (kJ mol^{-1})	68·4 ± 1·4	80·9 ± 1·0
ΔS (J K^{-1} mol^{-1})[a]	−51·6 ± 4·8	−27·7 ± 3·3

[a]At 298·2 K.

the beginning of the reaction: 38·7 ± 3·1 for the ratio of the mole fractions of the ring form and the *E* form, 12·5 ± 0·3 for that of the ring form and the *Z* form and 5·7 ± 0·25 for that of the ring form and the sum of the *E* and *Z* forms and the carbinolamine. In fact, the final products also begin to form but very slowly [Figure 2(B)]. The results of the UV spectroscopic experiments in 0·1 mol dm^{-3} perchloric acid at various temperatures are given in Table 1. The solvent deuterium isotope effect, k_{HClO_4}/k_{DClO_4}, at 303 K for the formation of the final products is about 4·7, again slightly higher than the comparable values for the 2-alkyl-3-methyl-1,3-oxazolidines.[6]

Some experiments were also made by NMR at 303 K. The peak belonging to the carbinolamine appeared at the beginning of the reaction and then disappeared when the reaction proceeded further. The mechanism established earlier[6,9] for the hydrolysis of Schiff bases in acidic solutions was obeyed by 2-phenyl-3-methyltetrahydro-1,3-oxazine (**2a**), similarly to 2-alkyl-3-methyl-1,3-oxazolidines [Scheme 1(A)]. The addition of water to the azomethine carbon of the cationic Schiff base produces a carbinolamine, which then undergoes heterolysis to an aminoalcohol and a carbonyl compound. In the case of 2-isopropyl-3-methyltetrahydro-1,3-oxazines (**2b**) the Schiff base intermediates are also present in the spectra taken in 5 mol dm^{-3} $DClO_4$ solution, but now the resonance position of the methine protons of the *E* and *Z* isomers of the Schiff bases are reversed with respect to those of the 2-phenyl derivative.[7] For **2b** and also for **2a** the time-dependent

concentrations of the Schiff base intermediates and also those of the final products were lower than for the corresponding five-membered ring systems. Also **2b** first gives the other Schiff base form (*Z*) which converts to the *E* form. The time-dependent mole fractions of the molecular species involved in the hydrolytic decomposition of 2-isopropyl-3-methyltetrahydro-1,3-oxazine (**2b**) in 5 mol dm^{-3} $DClO_4$ solution at 343 K are shown in Figure 4.

In 0·1 mol dm^{-3} $DClO_4$ solution at 308 K the signals corresponding to the *N*-methyl groups of the Schiff base intermediates for **2b** were too small to be integrated. The mole ratio of the carbinolamine to the ring form remained almost constant (*ca* 0.3) for about 75 min after the initiation of the reaction. The time dependence of the hydrolytic decomposition of 2-isopropyl-3-methyltetrahydro-1,3-oxazine (**2b**) at 308 K in 0·1 mol dm^{-3} $DClO_4$ is shown in Figure 5.

In conclusion, ^{1}H NMR spectroscopy allows us to follow closely the hydrolytic decomposition of 2-substituted 3-methyltetrahydro-1,3-oxazines. The results confirm the mechanistic deductions made earlier,[2,6,7] including the postulated formation of a carbinolamine which then produces 3-methylaminopropan-1-ol and an appropriate aldehyde from the Schiff base intermediates [Scheme 1(A), $n = 3$]. When comparing tetrahydro-1,3-oxazines with their five-membered counterparts, 1,3-oxazolidines, it can be seen that for the former the mole fractions of the Schiff bases are much lower than for the latter. Also, the formation of the final products is much slower for the six-membered than for the five-membered ring system. On the other hand, the mole fractions of the carbinolamine are higher with 2-alkyl-substituted tetrahydro-1,3-oxazines than with 2-alkyl-substituted 1,3-oxazolidines. However, the entropies and enthalpies of activation for

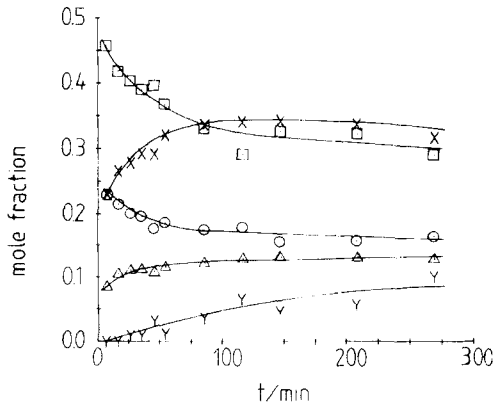


Figure 4. Mole fractions of 2-isopropyl-3-methyltetrahydro-1,3-oxazine, the Schiff base intermediates, carbinolamine and amino alcohol as a function of time in 5 mol·dm^{-3} $DClO_4$ at 343 K. Symbols as in Figure 2

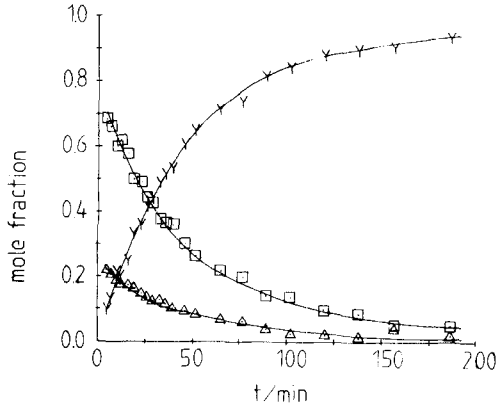


Figure 5. Mole fractions of 2-isopropyl-3-methyltetrahydro-1,3-oxazine, carbinolamine and amino alcohol as a function of time in 0·1 mol dm^{-3} $DClO_4$ at 308 K. (□) Ring form; (△) carbinolamine; (Y) amino alcohol

2a shown in Table 1 are almost identical with those reported earlier for 2-phenyl-3-ethyl-1,3-oxazolidine.[2]

These observations parallel those made in connection with the ring–chain tautomeric equilibria of 1,3-oxazolidines[10] and 1,3-oxazines.[11] The slopes for the σ^+ dependence of these equilibria for 2-aryl-substituted derivatives (0·57 for the former and 0·76 for the latter at ambient temperature) are shown to be ideal for estimation of electrophilic aromatic reactivities.[12]

EXPERIMENTAL

Materials 3-Methylaminopropan-1-ol was prepared from 3-chloropropan-1-ol and methylamine in ethanol solution.[13,14] 2-Isopropyl- and 2-phenyl-3-methyltetrahydro-1,3-oxazines were prepared from appropriate aldehyde and 3-methylaminopropan-1-ol in dichloromethane using a literature method.[15,16]

Kinetic measurements. ^{1}H NMR spectra were taken for $DClO_4$–D_2O solutions using a JEOL GX-400 instrument. The substrate concentration was *ca* 0·6% by volume. The progress of the hydrolysis of 2-phenyl-3-methyltetrahydro-1,3-oxazine was followed spectrophotometrically at 282 and 250 nm, the former wavelength referring to the cationic Schiff bases formed from 2-phenyl-3-methyltetrahydro-1,3-oxazine and the latter to the benzaldehyde formed as the final product. The measurements were performed in stoppered cells on a Cary 17D spectrophotometer. The temperature of the cell housing compartment was kept constant by water circulating from a thermostated bath and controlled from the cell with a thermistor. First-order rate constants were calculated by the method of Guggenheim.

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