Formation of 3,1-Perhydrobenzoxazines and their *N*-Methyl Derivatives. The Effects of Epimerization and Temperature

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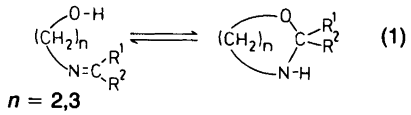
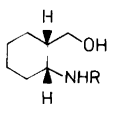
The cyclization reactions of *p*-nitrobenzaldehyde with *cis*- and *trans*-2-hydroxymethylcyclohexylamine and of their *N*-methyl derivatives have been studied by ^{1}H NMR spectroscopy in $CDCl_3$ solution. Time-dependent spectra confirmed that the reactions with both cyclohexylamines proceeded via open-chain intermediates whereas those with the *N*-methyl derivatives showed no signs of such intermediates. In all but one case the thermodynamically more stable 3,1-perhydrobenzoxazine epimer was also the kinetically favoured product. The effects of temperature and the presence of the minor epimer on the ring-chain tautomeric equilibria are also discussed.

In the ring-chain tautomeric equilibria of tetrahydro-1,3-oxazines and 1,3-oxazolidines[1–8] illustrated in eqn. (1) the relatively high basicity of the nitrogen atom favours the



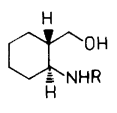
n = 2,3 (1)

formation of a very reactive C=N$^+$HR group, to which the nucleophilic part of the molecule is easily added.[1] To complement our studies on the hydrolytic decomposition of *N*-methyl-substituted tetrahydro-1,3-oxazines and 1,3-oxazolidines in strongly protonating conditions, the cyclization of *p*-nitrobenzaldehyde with *cis*- (**1**) and *trans*-2-hydroxymethylcyclohexylamine (**2**) and with their *N*-methyl derivatives (**1m** and **2m**) were investigated to understand better the factors controlling the formation of especially epimeric 3,1-oxazine derivatives. Since the roles of temperature and of the minor epimers in the ring-chain tautomeric equilibria of the 2-substituted perhydro-3,1-benzoxazines are also of interest they were studied in some detail.



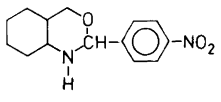
1 ; R = H

1m; R = CH_3



2 ; R = H

2m; R = CH_3



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Results and discussion

Formation of 2-*p*-nitrophenyl-3,1-perhydrobenzoxazines (**3**) from *p*-nitrobenzaldehyde and *cis*- (**1**) and *trans*-2-hydroxymethylcyclohexylamine (**2**) occurred via Schiff's base intermediates. This was demonstrated by a ^{1}H NMR spectrum taken on the reaction mixture of **1** and *p*-nitrobenzaldehyde in $CDCl_3$ solution at 303 K (Fig. 1). Fig. 2 shows the time-dependent ^{1}H NMR spectra of the aryl protons for the same reaction under the same conditions. The relative mole fraction of the Schiff's base intermediate was quite high at the beginning of the reaction (Fig. 3) but decreased rather quickly. The less stable ring-epimer, N_{out} ring form, was the predominant cyclization product in the early stages of the reaction owing to kinetic control. It was

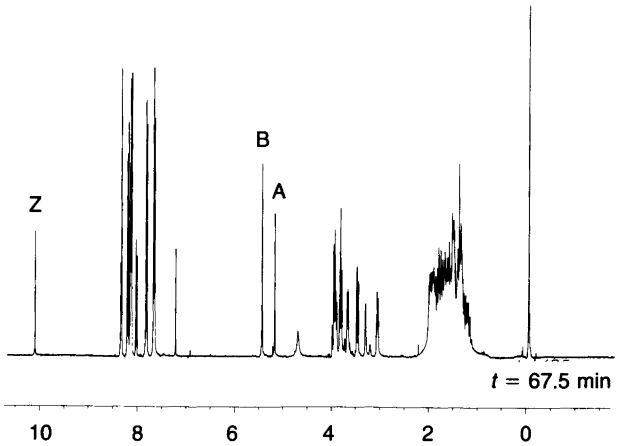


Fig. 1. ^{1}H NMR spectrum on the reaction mixture of *cis*-2-hydroxymethylcyclohexylamine with *p*-nitrobenzaldehyde in $CDCl_3$ solution at 303 K, relative to internal Me_4Si. A, ring form N_{in}, C(2)–H; B, ring form N_{out}, C(2)–H; Z, *p*-$NO_2C_6H_4CHO$.

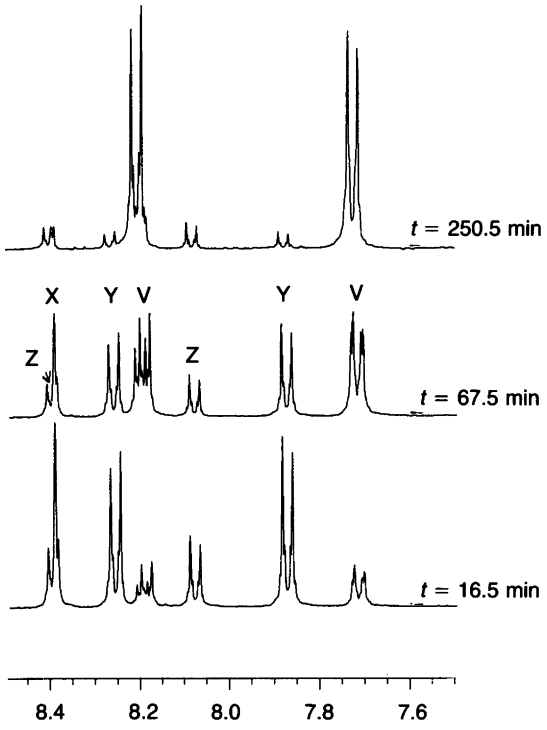


Fig. 2. The time-dependent ^{1}H NMR spectra of the aryl protons for the reaction between *cis*-2-hydroxymethylcyclohexylamine and *p*-nitrobenzaldehyde in $CDCl_3$ solution at 303 K, relative to internal Me_4Si. V, ring forms; X H–C=N–; Y, *p*-$NO_2C_6H_4C$=N–; Z, *p*-$NO_2C_6H_4CHO$.

converted, however, to the more stable epimer, N_{in} form[7] until the thermodynamic equilibrium was reached. At 303 K the equilibrium between the N_{in}- and N_{out}-ring forms (N_{in}/N_{out} ratio being ca. 13 ± 1) was reached within about 4 h. At 313 and 323 K the corresponding parameters were ca. 2 h and 25 min and 13 ± 1 and 12 ± 1, respectively.

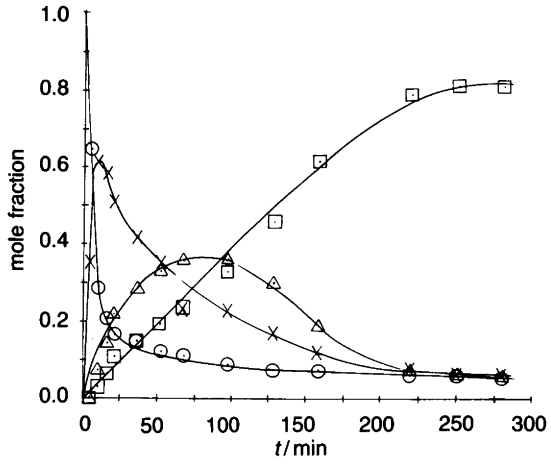


Fig. 3. The relative mole fractions of the epimeric ring forms, the Schiff's base intermediate and the aldehyde in the cyclization of *p*-nitrobenzaldehyde with *cis*-2-hydroxymethylcyclohexylamine in $CDCl_3$ at 303 K against time: □, N_{in} ring form; △, N_{out} ring form; ×, Schiff's base intermediate; ○, aldehyde.

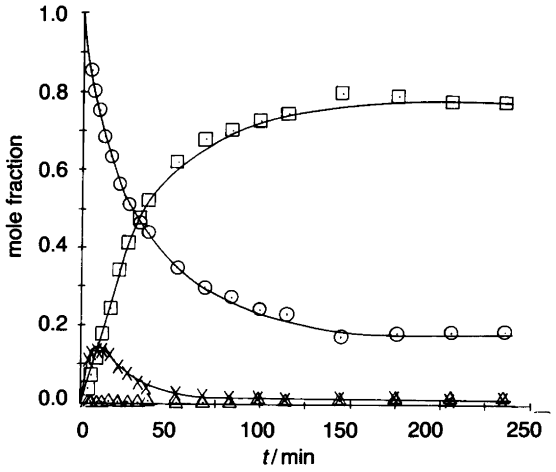
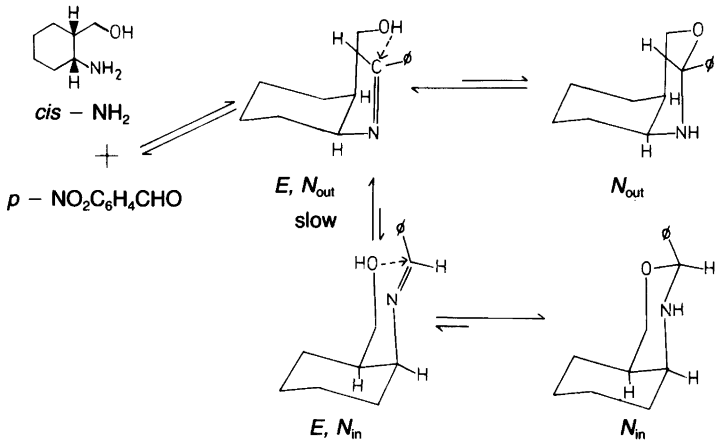


Fig. 4. The relative mole fractions of the epimeric ring forms, the Schiff's base intermediate and the aldehyde in the cyclization of *p*-nitrobenzaldehyde with *trans*-2-hydroxymethylcyclohexylamine in $CDCl_3$ at 303 K against time: □, Ph_{eq} ring form; △, Ph_{ax} ring form; ×, Schiff's base intermediate; ○, aldehyde.

Similar behaviour has been found in the reaction of (−)-ephedrine and acetaldehyde[9] with the simultaneous disappearance of ephedrine signals and appearance of signals due to two diastereomeric 2,3,4-trimethyl-5-phenyloxazolidines. The signals belonging to the other diastereoisomer were reduced in intensity as the signals due to the other diastereoisomer increased. It has also been shown[10] that stereoselectivity in oxazolidine formation is solvent dependent; non-stereoselective ring closure occurred in chloroform.

In the cyclization reaction of *p*-nitrobenzaldehyde with **2** in $CDCl_3$ solution, the relative mole fraction of the Schiff's base intermediate was lower than above (Fig. 3) and its formation could be followed at 303 K only. At 313 and 323 K we could only see its decomposition. In the case of *trans*-2-hydroxymethylcyclohexylamine (**2**) the more stable epimer, the 2-Ph_{eq} ring form[7] was also the kinetically controlled product, and the relative mole fraction of the 2-Ph_{ax} ring form was very low throughout the whole reaction (Fig. 4). The equilibrium state between the 2-Ph_{eq} and 2-Ph_{ax} ring forms was, in this case, reached within ca. 2.5 h at 303 K, less than 2 h at 313 K and in about an hour at 323 K, the ratio of the ring forms being in all cases 45 ± 10 in favour of the 2-Ph_{eq} form.

In contrast with the situation in the hydrolytic decomposition of *N*-alkyl-substituted 1,3-oxazolidines[11–14] and tetrahydro-1,3-oxazines[15] and also with that in the cyclization of *cis*- (**1**) and *trans*-2-hydroxymethylcyclohexylamines (**2**)[16] no sign of the open-chain intermediate could be detected in the cyclizations of the *N*-methyl derivatives of the latter (**1m** and **2m**, respectively) with *p*-nitrobenzaldehyde. For **2m** the relative mole fraction of the 2-Ph_{ax} ring form was very low throughout the whole reaction and the formation of the 2-Ph_{eq} ring form was also very slow (50 % conversion occurred within about 20 h).



Scheme 1.

The formation of the major N_{out}[17] epimer from *p*-nitrobenzaldehyde and compound **1m** was much slower, the relative mole fraction of this ring form being only about 0.2 and that of the N_{in} epimer about 0.025 after 68.5 h at 323 K. It can be postulated that in this case the cyclization process occurs only in the presence of traces of acidic impurities in the solvent; a theory which finds support in our observation that addition of CD_3COOD accelerated these reactions by a factor of ca. 20.

As can be seen from Figs. 1–4 there are two ring forms present in the reactions of *cis*- (**1**) or *trans*-2-hydroxymethylcyclohexylamine (**2**) and *p*-nitrobenzaldehyde. In the case of **1** the less stable ring form, the N_{out} epimer, predominates initially due to kinetic control and is then converted into the more stable N_{in} epimer (Scheme 1). In a previous paper[7] when discussing the ring-chain tautomeric equilibria of several perhydrobenzoxazines the formation of the ring forms was thought to be stereospecific. This is not true, however as can be seen from the preceding discussion.

In the case of 2-substituted 3,1-perhydrobenzoxazines derived from benzaldehyde or its monosubstituted derivatives and *cis*-2-hydroxymethylcyclohexylamine (**1**), the amount of the predominant ring form varied from 27 [*p*-N$(CH_3)_2$] to 97 % (*p*-NO_2).[7] For the derivatives of *trans*-2-hydroxymethylcyclohexylamine (**2**) the corresponding range was from 60 [*p*-N$(CH_3)_2$] to 99 % (*p*-NO_2).[7] In order to gain further insight into the role of epimeric equilibria and the effect of temperature on the ring-chain tautomerism the equilibrations of **1** and **2** with benzaldehyde and four *p*-substituted benzaldehydes were carried out (Table 1). According to these experiments at 323 K the total equilibrium percentage of the ring isomers ranged from 53 [*p*-OCH_3] to 91 % (*p*-NO_2) for (**1**) and from 78 (*p*-OCH_3) to 96 % (*p*-NO_2) for **2**. In all cases the total amount of the ring forms decreases with increasing temperature.

Table 1. The ring-chain tautomeric equilibria of *cis*-2-hydroxymethylcyclohexylamine (**1**) and *trans*-2-hydroxymethylcyclohexylamine (**2**) with various *p*-substituted benzaldehydes.

Compound	Substituent	*K* I/II[a]	*K* (I + II)/o.c.[b]	σ^+
1	NO_2	9.3	9.73	0.790
	Cl	10.4	4.69	0.114
	H	12.7	2.66	0
	Me	13.2	1.94	−0.311
	OMe	13.1	1.12	−0.778
	ϱ = 0.58 ± 0.04 (0.76 ± 0.04 at 293 K)			
	c = 0.51 ± 0.03; r = 0.992			
2	NO_2	38.6	24.88	0.790
	Cl	56.5	11.37	0.114
	H	58.1	8.94	0
	Me	80.2	6.82	−0.311
	OMe	75.3	3.45	−0.778
	ϱ = 0.54 ± 0.02 (0.76 ± 0.04 at 293 K)			
	c = 0.98 ± 0.01; r = 0.997			

[a] I is the predominant and II the minor ring form. [b] o.c. is the open chain form.

It is evident that the less stable ring epimer was always obtained in final amounts corresponding to its thermodynamic stability. The amount, however, was consistently so low that it has no influence on our previous conclusions.[7] Plots[7] of log $K_x = \varrho\sigma^+ + c$ at 323 K for the ring-chain tautomeric equilibria (K = [ring]/[chain]) of **1** and **2** were nicely linear (r = 0.992 and 0.998, ϱ = 0.58 ± 0.04 and 0.54 ± 0.02 and c = 0.51 ± 0.03 and 0.98 ± 0.01, respectively). Both the slope and intercept values are clearly temperature dependent (Table 1). The slope, however, has a constant value for the different derivatives at a given temperature and the intercept restores the stability difference despite the change in its absolute values.

Experimental

Materials. The amino alcohols were available from a previous study.[17,18]

Measurements. The time-dependent ^{1}H NMR spectra taken with 4 scans and 32 K data points at intervals on the cyclization reaction of *cis*- and *trans*-2-hydroxymethylcyclohexylamines and their *N*-methyl derivatives with *p*-nitrobenzaldehyde were recorded on a Jeol GX-400 FT-NMR spectrometer in $CDCl_3$ solutions (about 10 mg of both substances per 0.8 ml) using Me_4Si as an internal standard.

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