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 1H NMR spectroscopy in CDCl3 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-oxazolidines1-8 illustrated in eqn. (1) the relatively high basicity of the nitrogen atom favours the 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.

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 1H NMR spectrum taken on the reaction mixture of 1 and p-nitrobenzaldehyde in CDCl3 solution at 303 K (Fig. 1). Fig. 2 shows the time-dependent 1H 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, Nmep, ring form, was the predominant cyclization product in the early stages of the reaction owing to kinetic control. It was

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![Fig. 1. 1H NMR spectrum on the reaction mixture of cis-2-hydroxymethylcyclohexylamine with p-nitrobenzaldehyde in CDCl3 solution at 303 K, relative to internal Me4Si. A, ring form Nmep, C(2)-H; B, ring form Nmep, C(2)-H; Z, p-NO2C6H4CHO.](image-url)
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$_2$Si. X, V, ring forms; X, H-C=N--; Y, p-NO$_2$C$_6$H$_4$C=N--; Z, p-NO$_2$C$_6$H$_5$CHO.

converted, however, to the more stable epimer, $N_a$ form until the thermodynamic equilibrium was reached. At 303 K the equilibrium between the $N_a$- and $N_{ac}$-ring forms ($N_a/N_{ac}$ 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: □, $N_a$ ring form; Δ, $N_{ac}$ ring form; x, Schiff's base intermediate; ○, aldehyde.

Similar behaviour has been found in the reaction of (-)-ephrine and acetaldehyde with the simultaneous disappearance of ephrine signals and appearance of signals due to two diastereomeric 2,3,4-trimethyl-5-phenyl-oxazolidines. 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 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-$Ph_{ac}$ ring form was also the kinetically controlled product, and the relative mole fraction of the 2-$Ph_{ac}$ ring form was very low throughout the whole reaction (Fig. 4). The equilibrium state between the 2-$Ph_{ac}$ and 2-$Ph_{ac}$ 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-$Ph_{ac}$ form.

In contrast with the situation in the hydrolytic decomposition of $N$-alkyl-substituted 1,3-oxazolidines and tetrahydro-1,3-oxazines and also with that in the cyclization of cis- (1) and trans-2-hydroxymethylcyclohexylamines (2) 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-$Ph_{ac}$ ring form was very low throughout the whole reaction and the formation of the 2-$Ph_{ac}$ ring form was also very slow (50% conversion occurred within about 20 h).
The formation of the major $N_{en}$ 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 $N_{en}$ 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$_3$COOD 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 $N_{en}$ epimer, predominates initially due to kinetic control and is then converted into the more stable $N_{en}$ epimer (Scheme 1). In a previous paper 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(OCH$_3$)$_2$] to 97% (p-NO$_2$). For the derivatives of trans-2-hydroxymethylcyclohexylamine (2) the corresponding range was from 60 [p-N(CH$_3$)$_2$] to 99% (p-NO$_2$). In order to gain further insight into the role of epimeric equilibria and the effect of temperature on the ring-chain tautomerism the equilibriations 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.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Substituent</th>
<th>$K$ (I/II)</th>
<th>$K$ (I + II)/o.c.</th>
<th>$\sigma^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NO$_2$</td>
<td>9.3</td>
<td>9.73</td>
<td>0.790</td>
</tr>
<tr>
<td></td>
<td>Cl</td>
<td>10.4</td>
<td>4.69</td>
<td>0.114</td>
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<tr>
<td></td>
<td>H</td>
<td>12.7</td>
<td>2.66</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>13.2</td>
<td>1.94</td>
<td>-0.311</td>
</tr>
<tr>
<td></td>
<td>OMe</td>
<td>13.1</td>
<td>1.12</td>
<td>-0.778</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$q = 0.58 \pm 0.04$ (0.76 $\pm 0.04$ at 293 K)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$c = 0.51 \pm 0.03$; $r = 0.992$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NO$_2$</td>
<td>38.6</td>
<td>24.88</td>
<td>0.790</td>
</tr>
<tr>
<td></td>
<td>Cl</td>
<td>56.5</td>
<td>11.37</td>
<td>0.114</td>
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<tr>
<td></td>
<td>H</td>
<td>58.1</td>
<td>8.94</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>80.2</td>
<td>6.82</td>
<td>-0.311</td>
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<td></td>
<td>OMe</td>
<td>75.3</td>
<td>3.45</td>
<td>-0.778</td>
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<tr>
<td></td>
<td></td>
<td>$q = 0.54 \pm 0.02$ (0.76 $\pm 0.04$ at 293 K)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$c = 0.98 \pm 0.01$; $r = 0.997$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*I* is the predominant and II the minor ring form. *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 \(K_x = \log^+ + c\) at 323 K for the ring-chain tautomeric equilibria (\(K = [\text{ring}]/[\text{chain}]\)) of 1 and 2 were nicely linear (\(r = 0.992\) and 0.998, \(\varphi = 0.58 \pm 0.04\) and 0.54 \(\pm 0.02\) and \(c = 0.51 \pm 0.03\) and 0.98 \(\pm 0.01\), 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.\(^1^7,^1^8\)

**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\(_4\)Si as an internal standard.

**References**


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