THE RING-CHAIN EQUILIBRIUM IN DERIVATIVES OF 5-NITRO-1, 2, 3, 4-TETRAHYDROPYRIMIDINE IN TRIFLUOROACETIC ACID

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Abstract—'H NMR spectra of derivatives of 5-nitro-1,2,3,4-tetrahydropyrimidine were examined in trifluoroacetic acid solution. It was found that the compounds, unsubstituted in position 2, preserve their ring structure, whereas 2-alkyl- and 2-aryl derivatives are subjected to ring opening.

Continuing the work on 5-nitro-1,2,3,4-tetrahydropyrimidines\(^1,2\) we examined the \(^1\)H NMR spectra of its derivatives in trifluoroacetic acid (TFA).

![Scheme 1](image1)

The spectra of derivatives of 1, unsubstituted in position 2, indicate that the compounds preserve their ring structure, and the spectra differ from those in deuterochloroform\(^1\) only by broadening of the signals.

Protonation of pyrimidines 1 produced only a partial inhibition of the inversion of the nitrogen atom N-3. The absence of completely inhibited inversion and of vicinal coupling with the 3-N'\(^1\)H proton seems to indicate the presence of an equilibrium between two monoprotonated forms of 1, viz 1-(1-H) and 1-(3-H), and the diprotonated form 1-(2H)\(^2\) according to Scheme 1.

![Scheme 2](image2)

We assume that the protonation of the nitroenamine at the oxygen atom of the nitro group preserves the length of the conjugated system. It is also known that the amides are protonated mainly at the oxygen atom.\(^3\)

The existence of form 1-(1-H)\(^1\) explains the absence of completely inhibited inversion at N-3. The equilibrium of mono- and diprotonated forms makes possible fast (in NMR time scale) exchange of the ammonium proton with that of TFA. This is manifested by the absence of the vicinal coupling as pointed out before.

In the instance of 2-alkyl- and 2-arylsubstituted 5-nitro-1,2,3,4-tetrahydropyrimidines 2 the \(^1\)H NMR spectra indicate that TFA brings about ring opening yielding two geometric isomers E and Z (Scheme 2). The reaction is reversible and ring closure occurs with triethylamine.

Signals of protons of R' substituents in compounds 4 are also doublets. Compounds 1 which preserve their ring structure in TFA show H-6 protons as singlets.

We established that compounds 2 in deuterochloroform or as crystals exist solely in the ring form. To investigate the trend of ring opening we examined the NMR spectra of tetrahydropyrimidines 2 in deuterated trifluoroacetic acid (TFA-d). We established the deuterium only at N-1, as doublets with H-6 protons and those in substituents R' \(\text{CH}_3\), \(\text{CH}_3\text{C}_2\text{H}_5\) disappeared.
The ring nitrogen.

Tautomerism is the presence of a hydrogen atom attached to M-hydropyrimidines. An essential condition for the tautomerism is the presence of a hydrogen atom attached to 1,3,4-oxadiazines and hexa-1,3-oxazines groups of compounds, e.g. oxazolidines, 1,3-oxazines suggest three protonated forms: 2-(l-H)\(^{+}\), 2-(3-H)\(^{+}\), and 2-(2H)\(^{+}\). 

Scheme 3.

\[
\begin{array}{c}
\text{2 TFA} \\
\text{2-(0-H)} \\
\text{2-(3-H)} \\
\text{2-(2H)} \\
\end{array} \quad \Rightarrow \quad \begin{array}{c}
(\text{E})-3 \\
(\text{Z})-3 \\
\end{array}
\]

These results suggest that ring opening occurs via the protonated forms of 1,2,3,4-tetrahydropyrimidines 2 (Scheme 3) and by analogy to compounds 1 we may suggest three protonated forms: 2-(1-H)\(^{+}\), 2-(3-H)\(^{+}\) and 2-(2H)\(^{+}\).

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>(\delta) (ppm) H-2</th>
<th>(J) (c/s)</th>
<th>4-CH(_3) (s)</th>
<th>(\delta) (ppm) H-6</th>
<th>(\delta) (ppm) H-6 (d)</th>
<th>(J) (c/s)</th>
<th>(\delta) (ppm) R(^1)</th>
<th>(\delta) (ppm) R(^1)</th>
<th>(\delta) (ppm) R(^1)</th>
<th>p(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>8.95(q)</td>
<td>6.1</td>
<td>5.12 - 5.28'</td>
<td>7.69</td>
<td>14.2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3b</td>
<td>8.39(d)</td>
<td>9.4</td>
<td>5.06</td>
<td>8.22</td>
<td>14.3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3c</td>
<td>8.1(d)</td>
<td>9.7</td>
<td>5.09 - 5.26'</td>
<td>7.77</td>
<td>14.3</td>
<td>—</td>
<td>—</td>
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<tr>
<td>3d</td>
<td>9.13(s)</td>
<td>—</td>
<td>5.21</td>
<td>8.32</td>
<td>14.4</td>
<td>—</td>
<td>—</td>
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<tr>
<td>3e</td>
<td>9.39(s)</td>
<td>—</td>
<td>5.24 - 5.55'</td>
<td>—</td>
<td>—</td>
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</tr>
<tr>
<td>3f</td>
<td>9.19(s)</td>
<td>—</td>
<td>5.35</td>
<td>8.36</td>
<td>14.3</td>
<td>—</td>
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<td>3g</td>
<td>9.48(s)</td>
<td>—</td>
<td>5.35</td>
<td>8.36</td>
<td>14.3</td>
<td>—</td>
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<tr>
<td>3h</td>
<td>8.30(d)</td>
<td>9.4</td>
<td>4.91</td>
<td>7.76</td>
<td>14.9</td>
<td>3.41(d); (J = 5.3^*)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>3i</td>
<td>9.05(s)</td>
<td>—</td>
<td>5.09</td>
<td>—</td>
<td>—</td>
<td>3.44(d); (J = 5.3^*)</td>
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<tr>
<td>3j</td>
<td>8.51(d)</td>
<td>9.5</td>
<td>4.90 - 5.12'</td>
<td>—</td>
<td>—</td>
<td>4.64(d); (J = 5.4^*)</td>
<td>—</td>
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\(d\)-doublet; \(q\)-quartet; \(S\)-singlet.

In TFA this signal is a singlet. Molar fraction of the isomer established based on the spectra integration after 24 h in TFA at room temperature (ca 20\(^\circ\)). Together with aromatic protons. °CH protons.

The concentrations in question depend mainly on the protonated forms of 3, 4-di(hydroxy)-2H-1,3-benzoxazines\(^6\) and 2,3-di(hydroxy)-1H-naphth[1,2-e][1,3] oxazines\(^4\) were investigated. Smith and coworkers have found that most of the dihydrobenz-1,3-oxazines in TFA exist solely in the chain form, and only unsubstituted in position 2, or substituted by CI, preserve their ring structure. However in the instance of dihydrobenz-1,3-oxazines a ring \(\Rightarrow\) chain equilibrium is found in TFA.

Considering the former investigations\(^4\) and our findings it seems that the formation of the chain form in TFA can occur in compounds in which the N = C bond is stabilized by hyperconjugation or conjugation.

The formation of \(E\)- and \(Z\)-3 isomers was found to be controlled by kinetic factors. The initial concentration of both isomers was determined after not more than 8 minutes after compound 2 was dissolved in TFA. The concentrations in question depend mainly on the substituents R\(^1\) and R\(^2\). When R\(^1\) = CI CH\(_2\)H\(_2\) and R\(^2\) = \(p\) = CI CH\(_3\) or CH\(_3\)CH\(_2\)H\(_2\), the mixture contained more of the less stable isomer (Fig. 1). Its quantity diminished with time to give finally the equilibrium concentration. With other substituents, R\(^1\) and R\(^2\), the concentration of the two isomers found after ca. 8 min did not change considerably with time. The difference in the isomer ratio under kinetic (not more than 8 min after dissolving in TFA) and thermodynamic (24 h) control could only be observed when the isomers equilibrated slowly. In other instances the ratio of isomers measured after a few minutes represented the equilibrium composition.

The equilibrium was also examined in TFA-d during 24 h. After this time no hydrogens (except H-1) in compounds 3 were exchanged with deuterium. This observation indicates that one geometrical isomer passes into another through the protonated cyclic form. It also seems that compounds 3 are in dynamic equilibrium with...
cyclic protonated forms. Comparison of coupling constants \( J_{16} \) in compounds 4a and 4b with \( J_{16} \) in the corresponding compounds 3, \( R' = p-\text{Cl} \), indicates that the concentration of cyclic forms does not exceed 5 mole%.

**EXPERIMENTAL**

All 'H NMR spectra were recorded at 100 MHz on Jeol JNM-MH-100 spectrometer at 31 ± 1°C as solutions of ca. 0.2 mmol of compound 2 in 1 ml of TFA or TFA-d. Chemical shifts are given on \( \delta \) scale in ppm relative to TMS as internal standard.

The preparation of compounds 2a-e and 2h-j was described previously\(^2\) as well as of compounds 4a, b,\(^2\)

**Compound 2f.** Compound 4a (1.78 g, 0.01 mol) was added under vigorous stirring to a mixture of p-nitrobenzaldehyde (3.8 g, 0.025 mol) and pyridine (5 ml) in methanol (50 ml). Compound 2f precipitated out almost immediately. The stirring was continued for 5 h, and was left overnight. The precipitate was collected washed with methanol, and crystallized from \( \alpha \)-propanol to give compound 2f (3.0 g, 90%). It decomposed at 166°C.

(Found: C, 54.3; H, 4.0; N, 15.0. \( \text{C}_{12}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_2 \) requires: C, 54.5; H, 4.0, N, 14.9%).

**REFERENCES**