Tetrahedron Vol. 33, pp. 1979 to 1981 Pergamon Press 1977 Printed in Great Britain

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

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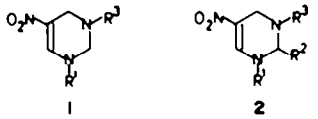
(*Received in UK 6 January 1977, accepted for publication 13 February 1977*)

Abstract—^{1}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.

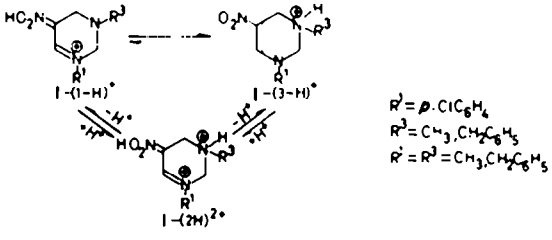
Continuing the work on 5-nitro-1,2,3,4-tetrahydropyrimidine[1,2] we examined the ^{1}H NMR spectra of its derivatives in trifluoroacetic acid (TFA).



1 2

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$^+$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.



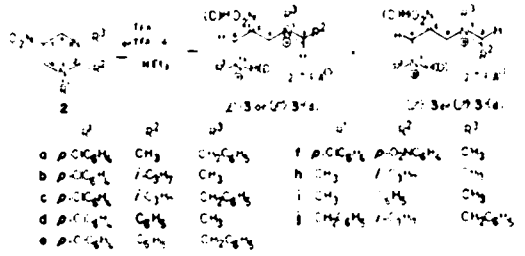
$R^2 = p\text{-}ClC_6H_4$
$R^3 = CH_3, CH_2C_6H_5$
$R^2 = R^3 = CH_3, CH_2C_6H_5$

Scheme 1.

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)$^+$ 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.

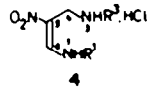
In the instance of 2-alkyl- and 2-arylsubstituted 5-nitro-1,2,3,4-tetrahydropyrimidines **2** the ^{1}H NMR spectra indicate that TFA brings about ring opening yielding two geometric isomers *E* and *Z* (Scheme 2). The reaction is reversible and ring closure occurs with triethylamine.



Scheme 2.

The following facts help establish the structure of the linear compounds **3**.

(a) The signal of the H-6 proton is a doublet with a vicinal coupling constant $J_{16} = 14.2$ 14.9 cps (Table 1). Almost the same signals are present in the spectra of compounds **4a** and **4b**.[4]



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4a, $R^1 = CH_3$, $\delta_6 = 8.24$ ppm, $J_{16} = 14.5$ cps
4b, $R_1 = CH_2C_6H_5$, $\delta_6 = 8.14$ ppm, $J_{16} = 14.6$ cps

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

(b) Chemical shifts of H-2 protons are in the region $\delta = 8.16$ 9.39 ppm (Table 1). Signals of protons in the system N = CH in TFA are in the same region: $\delta = 8.19 - 9.22$ ppm.[4,5]

(c) Signals of the methylene group protons in compounds **3** in TFA are singlets while in compounds **2** they are AB quartets. The latter shape is due to the presence of asymmetric carbon, whereas in TFA the asymmetric center disappeared through ring opening.

Formerly we established[2] 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 coupling with H-6 protons and those in substituents R^1 CH_3, $CH_2C_6H_5$ disappeared.

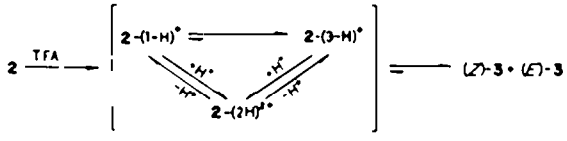
Table 1. ^{1}H NMR Spectra of compounds 3.

No Compound	H-2 δ(ppm)	J(c/s)	4-CH_3(s)	H-6 (d)[a] δ(ppm)	$J_{5,6}$(c/s)	R' δ(ppm); J(c/s)	p[b]
3a	8.95(q)	6.1	5.12 5.28[c]	7.69	14.2	—	0.67
	8.69(q)	6.0		7.83	14.2		0.33
3b	8.39(d)	9.4	5.06	8.22	14.3	—	0.83
	8.22(d)	9.4	5.13	7.70	14.2		0.17
3c	8.61(d)	9.7	5.09 – 5.26[c]	7.77	14.3		0.75
	8.37(d)	9.6					0.25
3d	9.13(s)	—	5.21	8.32	14.4	—	1.00
3e	9.39(s)	—	5.24 – 5.55[c]	—[d]	—[d]	—	0.87
	9.19(s)	—					0.13
3f	9.48(s)	—	5.35	8.36	14.3	—	1.00
3h	8.30(d)	9.4	4.91	7.76	14.9	3.41(d); J = 5.3[e]	0.88
	8.15(d)	9.5	4.98				0.12
3i	9.05(s)	—	5.09	—[d]	—[d]	3.44(d); J = 5.3[e]	1.00
3j	8.51(d)	9.5	4.90 5.12[c]	—[d]	—[d]	4.64(d); J = 5.4[e]	0.75
	8.32(d)	9.6				4.69(d); J = 5.4[e]	0.25

d–doublet; q–quartet; S–singlet.

[a]In TFA-d this signal is a singlet. [b]Molar fraction of the isomer established on the basis of NMR spectrum integration after 24 h in TFA-d at room temperature (*ca* 20°). [c]Together with R' – C_6H_5-CH_2 protons. [d]Together with aromatic protons. [e]CH_2 protons.

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)$^{2+}$.



Scheme 3.

To explain the part played by TFA the ^{1}H MNR of compound **2h** were measured in deuterochloroform in the presence of TFA in different molar ratios of **2h** to TFA (1:1 and 1:2.5). In the first instance (ratio 1:1) the H-6 signal was a singlet, i.e. the compound maintains the ring structure. When the amount of TFA was increased (ratio 1:2,5) the H-6 signal became a doublet indicating that ring opening occured. These facts suggest that the monoprotonated chain form containing the reactive nucleophilic center (nitroenamine) which is able to react readily with the C = N double bond is less probable than the monoprotonated cyclic form **2**-(3 – H)$^+$ and/or **2**-(1 – H)$^+$. In excess TFA the nitroenamine part of the molecule can also be protonated, thus stabilizing the chain structure in the diprotonated form.

The ring ⇌ chain tautomerism is known in several groups of compounds, e.g. oxazolidines,[6] 1,3-oxazines[6] and their derivatives,[4,7,8] 1,3,4,-oxadiazines[9] and hexahydropyrimidines.[10-13] An essential condition for the tautomerism is the presence of a hydrogen atom attached to the ring nitrogen.

As far as measurements in TFA are concerned, only 3,4-dihydro-2*H*-1,3,-benzoxazines[4] and 2,3-dihydro-1*H*-naphth-[1,2-e][1,3] oxazines[8] 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 CCl_3 preserve their ring structure. However in the instance of dihydronaphth-1,3-oxazines a ring ⇌ 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' and R^2. When R^2 = *i* C_3H_7- and R' = *p* – Cl C_6H_4 or $CH_2C_6H_5$, 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' 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 then 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

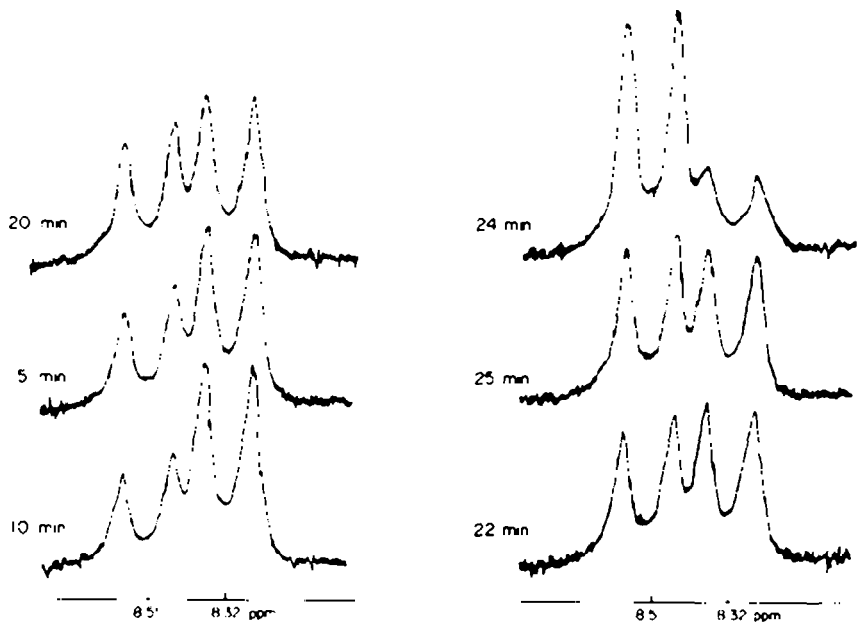


Fig. 1. Time dependence of H-2 signals of compound **3j** in TFA-d.

cyclic protonated forms. Comparison of coupling constants J_{16} in compounds **4a** and **4b** with J_{36} in the corresponding compounds **3**, $R^1 = p$ Cl C_6H_4 indicates that the concentration of cyclic forms does not exceed 5 mole %.

EXPERIMENTAL

All ^{1}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 δ 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**.[1,2]

Compound **2f** Compound **4a** (1.78 g, (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 *n*-propanol to give compound **2f** (3.0 g, 90%). It decomposed at 166°. (Found: C, 54.3; H, 4.0; N, 15.0. $C_{13}H_{13}ClN_4O_4$ requires: C, 54.5; H, 4.0; N, 14.9%).

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