Investigation of N–NO_2 ⟶ C–NO_2 Rearrangement of 2-Nitroaminothiazoles by Carbon-13 and Nitrogen-15 Nuclear Magnetic Resonance [1]

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The amino ⇌ imino tautomerism of 2-aminothiazoles and their salts has been studied. It has been established that in the acid-catalysed nitramin rearrangement of 2-nitroaminothiazoles the second protonation of the compounds protonated at the *exo*-nitrogen atom in concentrated sulphuric acid initiates the cleavage of the nitro group. The intermediate exists also in salt form, in which the nitro group is attached to the N(3) atom. The slow protonation results in the heterolytic fission of the N(3)–NO_2 bond, which is followed by the formation of the 5-nitro final product *via* a σ-complex.

In the 1950s great achievements were attained by Ingold and his co-workers in the elucidation of the mechanism of the nitration of aromatic compounds. The well known concept of electrophilic attack of the nitronium cation *via* a σ-complex proved to be very useful. This concept, apart from some minor modifications about the role of the π-complexes, seemed to be generally accepted up to the end of the 1970s.[2] In 1977 Perrin suggested a novel mechanism for the nitration of highly reactive aromatic compounds.[3] The key step in this mechanism is an electron transfer from the aromatic compound to the nitronium cation followed by the addition of the aromatic radical cation to the nitrogen dioxide radical yielding the σ-complex. More recently Ross [4] suggested a general mechanism for the nitration of aromatic compounds, shown in Scheme 1.

Recent investigations showed that the NO_2^+ was not regarded as the nitrating agent, and the radical character of the reaction was supported. Consequently, it is not surprising that the mechanism of the rearrangement of nitramines described by Bamberger as early as in 1893,[5] is still disputed. At the beginning of the 1970s White and his co-workers [6] studied this reaction in detail and suggested a mechanism involving an aromatic radical cation and a nitrogen dioxide radical as the reactive intermediates, held together by a common solvate cage. The basic problem of this spectacular study is that the existence of the assumed radicals could not have been verified by physicochemical or any other methods. Of the heterocyclic analogue, the mechanism of the rearrangement of 2-nitroaminopyridines has been studied by Deady *et al.*[7] On the basis of the substituent effect on the reaction rate, it has been concluded that *in situ* formation of a nitronium cation resulted in 3-nitro-2-aminopyridine. Further rearrangement of the latter led to the corresponding 5-nitro product. The acid-catalysed rearrangement of 2-nitroaminothiazole has been observed by Dickey *et al.*[8] Kasman and Taurins, after a qualitative examination of the reaction mechanism, concluded that this reaction proceeds in an analogous way to the rearrangement of the aromatic nitramines.[9]

We previously carried out a detailed study of the N–NO_2 ⟶ C–NO_2 rearrangement of 2-nitroaminothiazole and its *N*-alkyl derivatives.[10] We established, with reaction kinetics investigations, that the reaction consists of two steps with general acid catalysis and follows pseudo-first-order kinetics. The first step is the faster, resulting in an enrichment of the intermediate in the mixture. The isolation of this, however, has so far been unsuccessful. On the basis of the ^1H n.m.r. spectrum of the reaction mixture we established that the intermediate shows no aromatic character. By examining the derivative deuteriated in the 5-position, a first-order isotopic effect was found, indicating that the decomposition of the σ-complex is also a relatively slow process. The mass spectrometric investigation of the products, afforded by cross-rearrangement of compounds labelled in various positions, showed that the reaction proceeds with both intramolecular and intermolecular rearrangement. In this paper we report on the ^{13}C and ^{15}N n.m.r. investigation of the N–NO_2 ⟶ C–NO_2 rearrangement in 2-nitroamino- and 2-*N*-methylnitroaminothiazoles, namely a discussion of the spectra of the starting material, the intermediate, and the final product in the reaction medium.

$$H^+ + ArH + NO_2 \longrightarrow HONO + ArH^{+\cdot}$$
$$ArH^{+\cdot} + NO_2 \longrightarrow ArHNO_2^+ \longrightarrow \text{product}$$
$$HONO + HNO_3 \longrightarrow 2NO_2 + H_2O$$

Scheme 1.

Results and Discussion

Investigation of the Protonation of the Model Compounds.— In order to study the nitramine rearrangement we investigated the amino ⇌ imino tautomerism and the acid-induced effects on the tautomerism.

In the tautomerism of 2-phenylamino-2-thiazoline, we showed earlier that in a chloroform solution the proportion of the amino tautomer with respect to the imino form was considerable.[11] In the case of 2-aminopyridine, however, despite the non-aromatic character of the imino species, the co-existence of this compound in the equilibrium has been established.[12] In an earlier investigation of 2-aminothiazoles the chemical shifts of 5-H and 4-H gave sufficient evidence for the aromatic amino structure.[13] Further support of this fact has been given by our measurements on the ^{15}N chemical shifts (−300.0 and −125.5 p.p.m.), which are in good agreement with those measured in 2-aminobenzothiazole,[14] and which give evidence for the amino character of C(2)–N and for the imino character of N(3) (Table 1).

Taking into consideration the canonical formulae represented in Scheme 2, the protonation of 2-aminothiazole is expected at the N(3) atom. This fact is supported by the appearance of the NH^+ and NH_2 signals in trifluoroacetic acid (*cf.* Table 1), and a decrease in the chemical shift of C(4), analogous with the literature data.[15] The signals of C(2), C(4), and C(5) in sulphuric acid appear at similar

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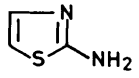
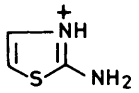
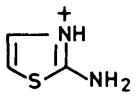
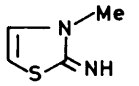
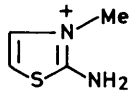
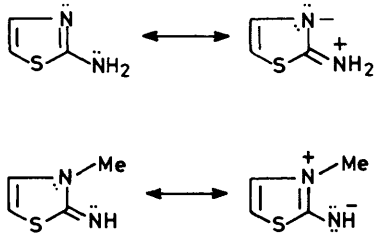
Table 1. Characteristic n.m.r. data of 2-aminothiazole and 3-methyl-2-imino-4-thiazoline

$\delta(Me_4Si) = 0.0$ p.p.m., $\delta(MeNO_2) = 0.0$ p.p.m.; J (Hz); negative values denote upfield shift

Species	$\delta_{C(2)}$	$\delta_{C(4)}$	$\delta_{C(5)}$	$^1J_{C(4),H}$	$^1J_{C(5),H}$	δ_{NH}	$\delta_{N(3)}$	Others	Solvent
	169.1	138.1	106.7	182.7	191.0	−300.0	−125.5	$^2J_{C(5),4-H} = 14.6$ Hz $^2J_{C(4),5-H} = 5.8$ Hz	[$^2H_6$]DMSO
	172.3	126.8	109.1					$\delta_{NH_2} = 8.08$ p.p.m. $\delta_{NH} = 11.97$ p.p.m.	[^2H]TFA
	171.4	126.9	109.9	200.2	201.4	−296.2	−225.9	$^2J_{C(5),4-H} = 6.6$ Hz $^2J_{C(4),5-H} = 5.8$ Hz	90% H_2SO_4
	164.5	128.1	96.9	186.7	195.6			$\delta_{Me} = 32.8$ p.p.m. $^1J_{Me,H} = 139.7$ Hz	[^2H]$CHCl_3$
	169.1	132.4	108.9	195.3	202.6			$\delta_{Me} = 36.4$ p.p.m. $^1J_{Me,H} = 144.0$ Hz	90% H_2SO_4



Scheme 2.

chemical shifts to those in trifluoroacetic acid, indicating similar protonated structures in both acids. The increase in the $^1J_{C(4),4-H}$ and $^1J_{C(5),5-H}$ coupling constants and the decrease in $^2J_{C(5),4-H}$ are characteristic of salt formation. This latter observation gives further proof for protonation at the ring [16] and all of these results show that the structure containing an NH_3^+ group, as suggested by Sohár,[17] might be incorrect.

The ^{15}N chemical shifts are also in good agreement with the 2-amino structure of the salt, *i.e.*, the NH_2 signal is hardly changed, as was expected,[18] whereas the N(3) signal underwent a *ca.* 100 p.p.m. upfield shift compared with that measured in the free base.

Another model with a fixed imino structure, 3-methyl-2-imino-4-thiazoline, has also been investigated. It is characteristic that the absence of aromatic character leads to an upfield shift of 10 p.p.m. of C(4) and C(5) compared with those of 2-aminothiazole. On considering Scheme 2, the protonation is now expected at the *exo*-nitrogen atom. The chemical shifts measured in 90% sulphuric acid are, after deduction of the substituent effect of the methyl group, in good agreement with those measured in protonated 2-aminothiazole. Thus, in this case the *exo*-nitrogen atom seems to be protonated, resulting in the formation of an aromatic structure, whereas the positive charge is centred on the ring nitrogen atom. This is also corroborated by the pronounced increase in the chemical shift of the methyl group and of the value of $^1J_{Me,H}$ (3.6 p.p.m. and 4.3 Hz, respectively). From an i.r. study of 2-nitroaminothiazole, Taurins obtained evidence supporting the imino tautomer.[19] Our earlier ^1H [10a] and the present ^{13}C and ^{15}N n.m.r. data clearly show the predominance of the amino tautomer. After nitration of the amino group, a paramagnetic shift of 87 p.p.m. was observed, as was expected [20] (Table 2). The introduction of the electron-attracting nitro group decreased the basicity of the compounds, therefore in trifluoroacetic acid no protonation occurs, as supported by the good agreement between the chemical shifts measured in dimethyl sulphoxide and in trifluoroacetic acid. In concentrated [$^2H_2$]sulphuric acid, however, protonation takes place and, at the same time, the N–$NO_2 \longrightarrow C$–NO_2 rearrangement is also initiated.

Monitoring of the Reactions by N.m.r.—In order to obtain spectra of an acceptable signal to noise ratio, despite the significantly low sensitivity of ^{13}C and ^{15}N n.m.r., the rearrangement was carried out in 92% [$^2H_2$]sulphuric acid at 10 °C. Under such conditions the reaction rate was low enabling us to determine chemical shifts and coupling constants not only for the starting material but also for the intermediate and for the final product (Tables 2 and 3). For the ^{15}N n.m.r. measurements samples of 50% enriched $^{15}NO_2$ were prepared. The protonation of the nitroamino-derivatives took place at the *exo*-nitrogen atom, which was supported by the markedly decreased (*ca.* 10 p.p.m.) chemical shift of C(2); similar shifting was found for the signal of the *ipso*-carbon atom of protonated anilines.[21] The higher values of $^1J_{C(4),4-H}$ and $^1J_{C(5),5-H}$ are due to the increased electron-withdrawing character of the nitroamino group. Protonation causes a 3.6 p.p.m. downfield shift of the NCH_3 signal and also the value of $^1J_{Me,H}$ increases. The upfield shift of almost 34 p.p.m. of the signal of the nitro group is very characteristic. It is known that in the case of *N*-nitro compounds the introduction of an electron-withdrawing substituent to the *N*-atom induces a similar shift for the signal of the NO_2 group.[22]

Our earlier ^1H n.m.r. investigations permitted us to conclude that the intermediate is not aromatic.[10a] This is confirmed by the present ^{13}C n.m.r. investigations, since a large upfield shift has been observed at the C(4) and C(5) signals. This change was expected on the basis of a comparison of thiazole–thiazoline model compounds. The earlier hypothesis, however, in which a sulphuric acid molecule is added to the C(2)=N(3) double bond as a loose complex, must be modified, because

Table 2. Characteristic n.m.r. data of 2-nitroaminothiazole and rearrangement products

$\delta(Me_4Si) = 0.0$ p.p.m., $\delta(MeNO_2) = 0.0$ p.p.m.; J (Hz); negative values denote upfield shift

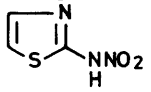
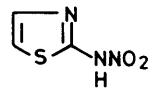
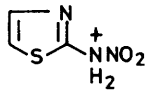
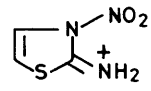
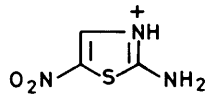
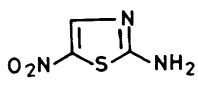
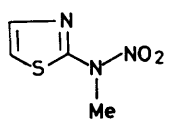
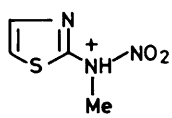
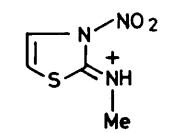
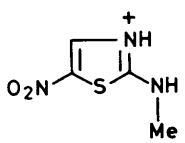
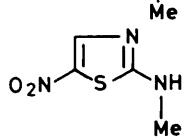
	Species	$\delta_{C(2)}$	$\delta_{C(4)}$	$\delta_{C(5)}$	δ_{NO_2}	Others	Solvent
Starting material		170.2	126.2	112.8	−15.6	$\delta_{NH} = -212.9$	[$^2H_6$]DMSO
		170.2	128.6	116.3			[^2H]TFA
Intermediate		160.8	129.9	119.3	−49.8		92% [$^2H_2$]H_2SO_4
		173.7	93.6	87.9	−3.7		92% [$^2H_2$]H_2SO_4
		171.4	137.4	132.4	−24.2	$^1J_{C(5),^{15}N} = 25.0$ $^1J_{C(4),4\text{-}H} = 205.9$	92% [$^2H_2$]H_2SO_4
Final product		173.5	147.3	135.4	−17.6	$\delta_{NH_2} = -281.3$	[$^2H_6$]DMSO

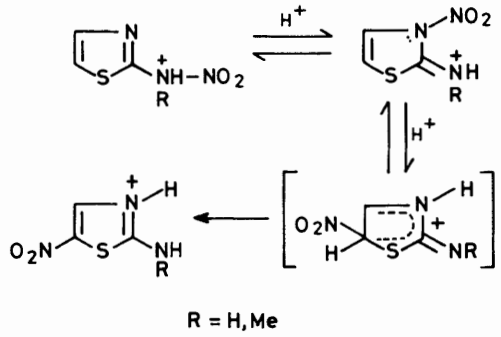
Table 3. Characteristic n.m.r. data of *N*-methyl-2-nitroaminothiazole and rearrangement products

$\delta(Me_4Si) = 0.0$ p.p.m., $\delta(MeNO_2) = 0.0$ p.p.m.; J (Hz); negative values denote upfield shift

	Species	$\delta_{C(2)}$	$\delta_{C(4)}$	$\delta_{C(5)}$	δ_{Me}	$^1J_{C(4),H}$	$^1J_{C(5),H}$	$^1J_{Me,H}$	δ_{NO_2}	Others	Solvent
Starting material		167.3	130.9	111.5	36.6	196.5	197.8	142.8	−17.2		[$^2H_6$]DMSO
Intermediate		159.3	135.1	119.4	40.2	203.9	203.9	146.5	−51.6	$^2J_{C(5),4\text{-}H} = 7.3$	[$^2H_2$]H_2SO_4
		169.6	93.5	90.5	33.7	175.8	173.3	142.8	−4.5		[$^2H_2$]H_2SO_4
		169.9	136.7 [a]	135.9 [a]	38.0				−25.9	$^1J_{N,C(5)} = 23$	[$^2H_2$]H_2SO_4
Final product		173.1	147.3	135.1	30.9						[$^2H_6$]DMSO

[a] Tentative assignment only is possible.

the chemical shift of C(2) is not decreased, but increased in the intermediate (by *ca.* 10—13 p.p.m.). The chemical shifts of C(4) and C(5) and the corresponding $^1J_{C,H}$ couplings render it possible to rule out intermediates in which an aziridine ring would be formed by addition of the nitro group on to the C(4)=C(5) double bond. This is also excluded by the fact that no $^1J_{C,^{15}N}$ couplings have been found in experiments with $^{15}NO_2$-labelled samples, while $^1J_{C(5),^{15}N}$ values of 23 and 25 Hz have been found in the 5-nitro derivative. The assumption that in the course of the rearrangement the nitro group had been cleaved and existed in the form NO_2^+ can be ruled out unambiguously on the basis of chemical shifts of the $^{15}NO_2$ signals, −3.7 and −4.5 p.p.m.[23] Monitoring the rearrangement by ^1H, ^{13}C, or ^{15}N signals the same kinetics have always been found, therefore we may conclude that in the course of rearrangement no radical bond fission took place, otherwise



R = H, Me

Scheme 3.

anomalous signal intensities would have been observed owing to the CIDNP effect.

In the broadband proton decoupled ^{15}N n.m.r. spectrum of the intermediate, the NOE for $^{15}NO_2$ was about -1, resulting in zero extinction of the signal. This allows the conclusion that the nitro group migrated to the *endo*-nitrogen in the intermediate, and the 2-imino-4-thiazoline structure was formed. The relatively low field signal of $^{15}NO_2$ indicates that the positive charge in the intermediate is on the *exo*-nitrogen and not on the *endo*. The final product is protonated at the N(3) atom in the reaction mixture. This can be supported by comparing the C(4) chemical shifts of the final product in the reaction mixture with that taken in [$^2H_6$]DMSO after neutralisation, because as in the case of 2-aminothiazole a downfield shift of 10 p.p.m. has been found. In the ^{15}N n.m.r. spectrum of the final product the NO_2 signal was found at -17.6 p.p.m.; this chemical shift does not differ significantly from the value measured in the starting compound. Owing to the electron-withdrawing substituent at C(5), a pronounced downfield shift of the NH_2 signal was observed, similar to that in substituted anilines.[20] On the basis of the aforementioned results we may state that the reaction path of the rearrangement is not analogous to the radical mechanism suggested by White and his co-workers [6] but the cleavage of the nitronium cation takes place and this ion migrates first to N(3) then to the C(5) the position (Scheme 3). In sulphuric acid the 2-nitroamino compounds are protonated at the *exo*-nitrogen atom. A second, relatively slow protonation, showing a first-order kinetic isotopic effect, initiates the cleavage of the NO_2^+ cation. The slow protonation, also showing a first-order isotopic effect, of the N(3)–NO_2 intermediate,[10a] causes the heterolytic fission of the N(3)–NO_2 bond, which is followed by a somewhat faster process, the formation of the 5-nitro final product *via* a σ-complex.

Experimental

The preparation of nitroamino compounds has been described earlier.[10] 3-Methyl-2-imino-4-thiazoline was prepared from 2-aminothiazole by a method given in the literature.[24]

^1H, ^{13}C, and ^{15}N n.m.r. spectra were recorded at 99.6, 25.0, and 10.04 MHz, respectively, using a JEOL FX-100 spectrometer. Measurements in concentrated [$^2H_2$]sulphuric acid solutions were performed using a 5 mm o.d. coaxial tube in a 10 mm o.d. tube. In ^{13}C studies the coaxial tube contained [$^2H_6$]acetone with Me_4Si, and in the ^{15}N studies it contained saturated $K^{15}NO_3$ in heavy water for lock and reference. No bulk susceptibility correction was made. ^{15}N Chemical shifts were converted into external nitromethane ($\delta_{KNO_3} = -3.55$ p.p.m.), upfield shifts are negative.

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1 This paper is to be considered as Part IV of the Series 'The Acid-catalysed Rearrangement of *N*-Nitro Derivatives of 2-Aminothiazole.' For Part III see A. Nemes, G. Tóth, and O. Fuchs, *Acta Chim. Acad. Sci. Hung.*, 1977, **95**, 295.
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