NMR SPECTRAL STUDY OF THE STRUCTURE OF 2-AMINO-4-THIAZOLINONES

S. M. Ramsh, N. A. Smorygo,
E. S. Khrabrova, and A. I. Ginak

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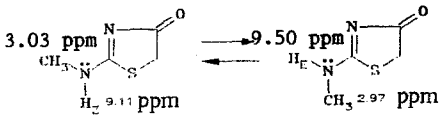
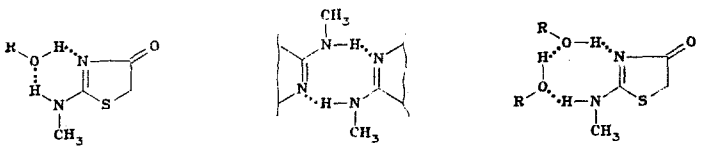
As a consequence of partial double bond nature of the exocyclic C–N bond, 2-methylamino-4-thiazolinone exists in DMSO-D_6 as a mixture of E and Z conformers of the amino form with predominance of the sterically favored E conformer. 2-Phenylimino-4-thiazolidinone in the same solvent exists as a mixture of the E and Z isomers of the imino form.

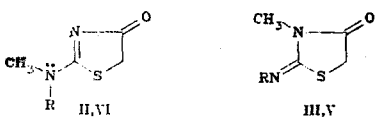
The tautomerism of 2-methylamino-4-thiazolinone (I) was studied previously employing UV spectroscopy [1]. The predominance of the amino form was concluded but experience in the study of the structure of cyclic amidines by various spectral methods [2, 3] has indicated the necessity of supporting this conclusion with NMR spectral data using model compounds II and III. The conclusion of Sheinker et al. [4] that 2-phenylimino-4-thiazolidinone (IV) exists as a mixture of the amino and imino tautomers raises doubt since the NMR spectra of IV were not compared to the spectra of models V and VI. These circumstances led us to carry out a detailed analysis of the ^1H and ^{13}C NMR spectra of potentially tautomeric I and IV using the NMR data for their metyylated derivatives II, III, V and VI.



I-E I-Z

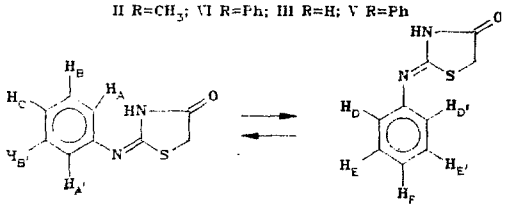


$I\text{-}Z_{solv}$ $I\text{-}Z_2$ $I\text{-}Z_{solv_2}$



II,VI III,V

II R=CH_3; VI R=Ph; III R=H; V R=Ph



$\delta_{H\,A,A'} \sim 7.0$ ppm $\delta_{H\,D,D'} \sim 7.6$ ppm

IV-E IV-Z

The ^{13}C NMR spectrum of I in DMSO-D_6 contains two sets of signals for the N–CH_3 group and the $C_{(2)}$ and $C_{(4)}$ atoms (Table 4) (Table 1). The signal for the $C_{(5)}$ atom is superimposed

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on the solvent signals and its minor component was not found. The downfield methyl group carbon at 36.4 ppm* is approximately three stronger than the upfield signal at 35.3 ppm. The addition of D_2O does not affect the spectral pattern. Comparison of the chemical shifts of I and model compounds, 2-dimethylamino-4-thiazolinone (II) and 2-imino-3-methyl-4-thiazolidinone (III) gives convincing evidence in favor of the amino structure for 2-methylamino-4-thiazolinone (I). The doubling of the resonance signals arises due to hindered rotation about the $C_{(2)}$—$N_{(2')}$ double bond [5] resulting in two conformations. Topomerization is found for II due to an analogous reason (Table 1).

The E conformer is sterically favored and predominates the equilibrium but the Z conformer is stabilized to some extent by specific solvation; the steric hindrance to such solvation is greater for the E conformer.† The stabilization of the Z conformer by hydrogen bonding with the solvent is indicated by the significant paramagnetic shift of the minor NH proton signal in the PMR spectrum of I by 0.4 ppm more than expected due to the different shielding by the $N_{(3)}$ and S atoms (Fig. 1a). The ratio of the intensities of the signals at 9.50 and 9.11 ppm was equal to ~1:3.

The signal of the methyl protons in thoroughly dried DMSO-D_6 is complex in nature (Fig. 1a) and analogous to that observed for 2-methylamino-5-benzylidene-4-thiazoline [6]. We assume that the signal of the methyl protons of the E conformer are split by the slowly exchanging NH protons with $J_{HNCH_3} \approx 4.6$ Hz and coupling is observed only for those molecules whose NH protons do not participate in exchange processes caused by solvent impurities. The unsplit signal of the CH_3 protons of the E conformer is found at 3.03 ppm. The NH protons of the Z conformer exchange much more rapidly and do not split the signal of the methyl protons at 2.97 ppm. The greater rate of exchange of the H_E protons is attributed to the capacity of the Z form to undergo self-association with the formation of $I\text{-}Z_2$ dimers and association with the formation of solvated complexes $I\text{-}Z_{solv}$ or $I\text{-}Z_{solv_2}$. The steric hindrance for solvation of the NH group in the E form may play a role in the reduced rate of exchange of the H_Z proton in this form as in the case of secondary amides [7]. The multiplet coalesces at about 65°C.

The methyl proton multiplet simplifies in most DMSO-D_6 by the action of impurities present in the solvent which catalyze exchange and after isotope exchange with heavy water: the doublet disappears and only the signals at 3.03 and 2.97 ppm remain (Fig. 1b). The signal at 3.03 ppm related to the E conformer is approximately three times stronger than the signal at 2.97 ppm for the Z conformer. The position and relative intensity of the signals for the NH protons in moist DMSO-D_6 are not altered but the signal at 9.50 ppm is broadened.

The PMR spectrum of I taken with suppression of the HN—CH_3 doupling does not show a concentration dependence of the relative intensity of the doubled signals. Hence, in contrast to the chloroform solution of an analogous oxazoline [8], the dimerization constant for the Z conformer in I-Z.

The participation of the Z conformer in an exchange process, in which the E conformer does not participate or participates to a much reduced extent, is indicated by the broadening of the signal at 9.50 ppm until it almost completely disappears upon the addition of a drop of acetic acid into a solution of I in dry DMSO-D_6, while the signal at 9.11 ppm does not broaden in this case and the splitting of the methyl proton signal of the E conformer does not disappear. This exchange apparently occurs in solvated complexes $I\text{-}Z_{solv}$ or $I\text{-}Z_{solv_2}$. Broadening of the signal at 9.50 ppm is sometimes observed in dry DMSO-D_6 along with HN—CH_3 coupling and always in the case of suppression of this coupling by rapid exchange of the NH protons of the E conformer. The ratio of the intensities of the H_E and H_Z protons is independent of their form.

Evidence for the existence of solvated complexes of the Z conformer with water is found in the splitting of the water proton signal in the PMR spectrum of I taken in moist DMSO-D_6 at 270 MHz. The weaker downfield signal at 3.38 ppm is related to protons of "excess" water molecules outside the solvation shell of the Z conformer. Indeed, if H_2O is now added (or the solution is diluted) or D_2O is added to the ampule, the downfield signal at 3.38 ppm (H_2O) or 3.48 ppm (DHO) becomes stronger, demonstrating the saturation of the solvate by H_2O or DHO molecules. In light of the integral intensity, the solvate has dihydrate structure $I\text{-}Z_{solv_2}$.

*The signals for $C_{(2)}$ and $C_{(4)}$ have low intensity.
†The significant positive charge on $N_{(3)}$ also facilitates the participation of the Z form in associative processes, while the positive charge on the sulfur atom is much less [5].

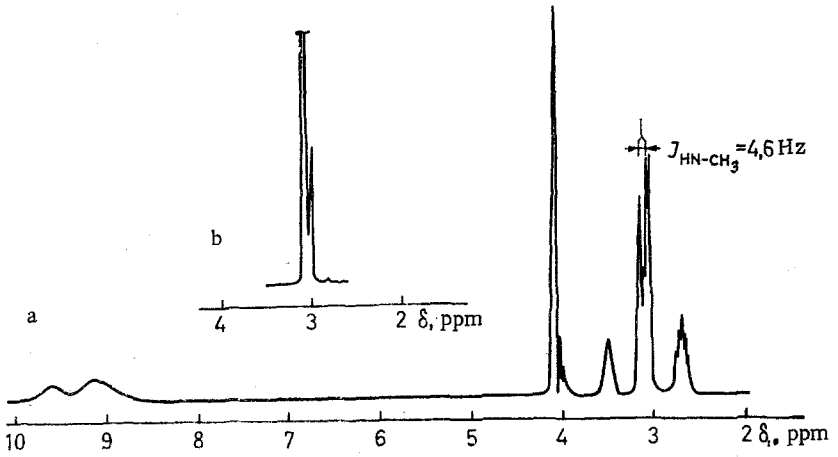

Fig. 1. PMR spectra of 2-methylamino-4-thiazoline (I), 80 MHz: *a*) in dry DMSO-D_6 and b) after isotope exchange with D_2O.

TABLE 1. Chemical Shifts in the ^{13}C NMR Spectra, ppm

Compound	Heterocycle			Substituent				
	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	methyl	phenyl			
					C_i	C_o	C_m	C_p
I	189,0; 185,0	191,7; 191,3	44,5	36,4; 35,3	—	—	—	—
II	188,4	193,0	47,6	47,0; 45,7	—	—	—	—
III	164,5	179,0	39,3	33,8	—	—	—	—
IV	178,2; 176,1	188,3	35,0	—	129,2	120,4	124,8	121,6

At this radio frequency, not only the methyl protons but also the methylene protons absorb as doublets.

The dynamic NMR spectra taken at 80 MHz in the absence of spin-spin coupling permitted us to determine the coalescence temperature for the signals of both the NH and CH_3 protons, which are 348 and 337 K, respectively. The temperature dependence of the line form is typical for bipositional exchange between states with different occupancies. The activation parameters $\Delta G^{\neq}_{E\to Z}$ = 79.9 and $\Delta G^{\neq}_{E\to Z}$ = 76.9 kJ/mole were determined at the coalescence temperature relative to the methyl proton signals* using the equations of Shanan-Atidi [9] and Gunther [10] and are approximate values since, in addition to the approximate nature of the solution of the line form equation [9], the temperature dependence of the occupancies of the exchanging states was not taken into account,† while the procedure for finding the coalescence temperature is complicated by the similarity of the chemical shifts and the unequal intensities of the CH_3 proton signals ($\Delta\nu$ = 4.8 Hz) [10].

Khovratovich and Chizhevskaya [11] proposed that 2-phenylimino-4-thiazolidinone (IV) in the crystal state exists in the imino form but our studies [12] showed that this proposal is incorrect. Since the amino form is stabilized by $\overset{\frown}{N_{(2)}-C_{(2)}=N_{(3)}-C_{(4)}=O_{(4)}}$, conjugation, the competing p—π conjugation should destabilize this form. On the other hand, p—π and π—π conjugation stabilizes the imino form. In other words, a phenyl ring at the exocyclic nitrogen atom increases the energy of the amino form and decreases the energy of the imino form of IV in the case of a conformation relative to the $N_{(2)}$—Ph bond favorable for the participation of the phenyl ring in conjugation. An effect of the structural factor on the position of the tautomeric equilibrium should be expected in solutions, especially, in apolar, aprotic solvents, in which stabilization is actually observed [4, 13]. The NMR data indicate that IV exists in the imino form also in a dipolar, aprotic solvent, namely, DMSO-D_6.

*The chemical shifts and the line form of the NH protons depend not only on the rate of the E ⇄ Z exchange.

†Neglecting the enthalpy component (ΔS° = 0), we have $k_{Z\to E} = k_{E\to Z}/K$, where K is the E ⇄ Z equilibrium constant at 29°C (0.3), $\Delta G^\circ = \Delta G_{E\to Z} - \Delta G_{Z\to E}$ = 3 kJ/mole.

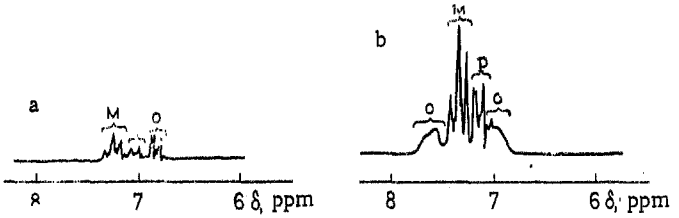

Fig. 2. PMR spectra of 2-phenylimino-3-methyl-4-thiazolidinone (V) (a) and 2-phenylimino-4-thiazolidinone (IV) (b) in DMSO-D_6 at 100 MHz.

The phenyl proton signals for 2-phenylimino-3-methyl-4-thiazolidinone (V) which is a model for the imino form correspond to an AA'BB'C system (Fig. 2a). This compound exists exclusively as the Z isomer due to steric hindrance between the methyl and phenyl groups [14]. Thus the signals of the CH_2 and CH_3 protons are unsplit. The PMR spectrum of this compound in deuterochloroform is analogous.

The aromatic protons of 2-methylphenylamino-4-thiazolinone (VI) which is a model for the amino form, in $CDCl_3$ also give rise to a multiplet but the chemical shifts of the ortho, meta and para protons differ not as significantly as in the imino form model V. Splitting of the methyl proton signal is noted due to hindered rotation about the $C_{(2)}$—$N_{(2)}$ bond.* In DMSO-D_6, the aromatic signal coalesces into a broad peak but the methyl proton signal as previously remains an asymmetric doublet. The relative intensities of the doublet components indicates that the Z isomer predominates in DMSO-D_6, while the E isomer predominates in $CDCl_3$. The difference in the isomer content is apparently a consequence of specific solvation in chloroform due to formation of an intermolecular hydrogen bond. A specific solvation polarizing VI enhances the partial positive charge on the exocyclic nitrogen atom, which leads to the observed inequivalence of the ortho, meta and para protons of the phenyl ring.

The PMR spectrum of IV could not be taken in $CDCl_3$ due to poor solubility. In DMSO-D_6, the multiplet for the aromatic meta and para protons has the same form as in V, but the ortho protons give rise to two unresolved multiplets. The multiplet centered at 8.0 ppm occupies the same position relative to the meta and para protons as the ortho protons in the spectrum of V (see Fig. 2a and 2b). This form of the spectrum is attributed to E-Z isomerization occurring by inversion [4]. The aromatic proton signal is the superposition of AA'BB'C and DD'EE'F systems with BB'C similar to EE'F. The isomers differ only in the signals of the AA' and DD' ortho protons. The Z isomer is somewhat favored over the E isomer. The signal of the heterocycle methylene protons is not split. The similar nature of the singals in the PMR spectra of IV and the model imino form V indicates the imino structure of IV in DMSO-D_6. The chemical shifts of the two isomers differ sufficiently so that this difference may be detected in the ^{13}C NMR spectrum (Table 1) only for $C_{(2)}$.

EXPERIMENTAL

The PMR spectra were taken on a Tesla BS-467 spectrometer at 60 MHz, RYa 2305 spectrometer at 80 MHz and Bruker HX-270 and 270 MHz in DMSO-D_6 and $CDCl_3$ with HMDS as the internal standard. The sample of DMSO-D_6 was maintained for 24 h over 4-Å molecular sieves and distilled at 2-3 mm in a dry nitrogen stream.

2-Methylamino-4-thiazolinone (I). A sample of 2 ml 25% aqueous methylamine was added to 1.0 g (7 mmoles) 2-methylthio-4-thizzolinone in 15 ml ethanol. After 30 min, the precipitate formed was filtered off and crystallized from water to give 0.72 g (78%) product, mp 197-198°C (196-199°C [15]). Found: C 21.8; S 24.6%. Calculated for $C_4H_6N_2OS$: N 21.5; S 24.6%.

Samples of II and III were obtained as in our previous work [16] while samples of IV-VI were obtained by analogy to our previous procedure [13].

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*The aromatic proton signal in this case should correspond to the superposition of AA'BB'C and DD'EE'F systems [4] but these could not be resolved due to the approximation of these signals.

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SYNTHESIS OF ISOMERIC 4- AND 5-HYDROXYLAMINOTHIAZOLIDIN-2-THIONES

T. I. Orlova, S. P. Épshtein,
V. P. Tashchi, A. F. Rukasov,
L. Ya. Bogel'fer, and Yu. G. Putsykin

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Isomeric 4- and 5-hydroxylaminothiazolidin-2-thiones were synthesized by the reaction of 1,2-aminosubstituted oximes with CS_2, and of dimeric olefin nitrosochlorides with dithiocarbamate salts. These compounds react with aldehydes and ketones to form the respective nitrones. In contrast to the 5-derivatives, the 4-hydroxylamino derivatives hydrolyze to 4-hydorxythiazolidin-2-thiones.

We have previously reported the synthesis and reactivity of the 4-hydroxylaminoimidazolidin-2-ones [1, 2]. In continuation of our studies of heterocyclic systems that contain an exocyclic hydroxylamino group we have obtained the hitherto unknown 4- and 5-hydroxylaminothiazolidin-2-thiones.

By the reaction of 1,2-aminosubstituted oximes Ia-e with CS_2 we have synthesized the respective 5-hydroxylaminothiabzlidin-2-thiones, IIa-e. The N-(2-oximinoalkyl)dithiocarbamic acids A were separated as the cyclic form B, but treatment of, e.g., IIc with alkali by analogy with the properties of the 5-hydroxythiazolidin-2-thiones [3] gave salt III of linear structure. The ^{13}C NMR spectrum of the latter in H_2O is characterized by signals at 211.0 ($C_{(1)}$=S), 161.9 ($C_{(2)}$=N), 61.8 ($C_{(3)}$), 25.8 ($C_{(4,5)}$), and 11.1 ppm ($C_{(6)}$). Neutralization of the aqueous solution of III gives the starting hydroxylamine IIc, while methylation is accompanied by formation of the linear ester IV; the ^{13}C spectrum of the latter (DMSO) contains signals at 196.4 ($C_{(1)}$=S), 158.4 ($C_{(2)}$=N), 61.5 ($C_{(3)}$), 25.5 ($C_{(4,5)}$), 17.6 (S–CH_3), and 10.0 ppm ($C_{(6)}$). The locations of the carbon signals for compounds III and IV agree with the ^{13}C NMR spectra (C=S 193.5, C=N 153.5 ppm) for the authentic linear structure, viz., N,N-dimethyl-S-(3-oximino-2-methylprop-2-yl)dithiocarbamate synthesized according to [6].

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