LITERATURE CITED

1. F. Vögtle and U. Elben, Chem. Ber., 111, 1434 (1978).
2. U. Elben, H. Fuchs, K. Frensch, and F. Vögtle, Liebigs Ann. Chem., No. 8, 1102 (1979).
3. K. Takayama, N. Nambu, and T. Nagai, Chem. Pharm. Bull., 27, 715 (1979).

# 2-HYDROXYMETHYLAMINO-4-THIAZOLINONE.

CONFIRMATION AND CHELATE FORMATION

S. M. Ramsh

In DMSO-d_6 solution 2-hydroxymethylamino-4-thiazolinone, as well as its 5-methyl-congener, exists in the form of E- and Z-conformers relative to the exocyclic nitrogen-carbon bond; for each of these conformers, furthermore, both a transoid and cisoid orientation of the hydrogen and oxygen atoms, relative to the N–CH$_2$ bond, are possible. The transoid form is able to form a chelate derivative with intramolecular hydrogen bond formation. Both acids and bases catalyze transitions among the "open" forms, although chelate formation is only acid-catalyzed.

Heating 37% aqueous formaldehyde with 2-amino-4-thiazolinone (Ia) in ethanol at 70°C results in the formation of an adduct, namely, a monohydroxymethyl derivative. Tertiary amines accelerate the reaction, and hydroxymethylation occurs at room temperature in their presence. The adduct does not melt, even upon heating to 250°C, although its derivatograph (thermal gravimetric analysis) indicates that it loses one molecule of formaldehyde in the 140-160°C temperature range. The adduct gives only one spot with thiazolinone Ia on TLC, and its UV spectrum is identical [to that of thiazolinone Ia]. Because of its thermal lability, the adduct does not exhibit a molecular ion (M^+) peak in its mass spectrum, but does exhibit M^+ peaks due to compound Ia and formaldehyde.

We have previously demonstrated [1] that, for the hydroxymethylation of mesomeric anions, kinetic and thermodynamic regioselectivity overlap, as a result of which hydroxymethylation occurs on the "harder" site of an ambident anion, which, in this case, is the exocyclic nitrogen atom [2]. Hydroxymethylation of the neutral molecule takes place only at elevated temperatures, where addition to the carbonyl group carbon atom is reversible, and as a result, thermodynamic control of the product mixture leads to formation of the most stable hydroxymethylation derivative, whose structure in this case would correspond to the most stable tautomer of Ia, the aminotautomer [2]. Thus, the adduct should exhibit the structure of the 2-hydroxymethyl derivative IIa, regardless of whether it is the anionic form or neutral Ia which reacts. This expected hydroxymethylation pathway has been verified by NMR analysis of compound IIa.

a R=H; b R=CH$_3$
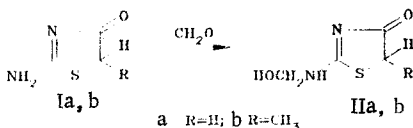
PMR Spectra. The PMR spectrum of compound IIa in DMSO-d_6 at an operating frequency of 270 MHz (Fig. 1a) is totally unexpected. It contains four signals due to the NH proton, one of which, the most downfield, broadened one at about 10 ppm, cannot always be discerned; there are also four triplets due to the hydroxyl proton, four multiplet signals arising from the methylene protons of the hydroxymethyl group, and three signals due to the methylene protons attached to the heterocycle, $C_{(5)}H_2$. This type of PMR spectrum can be rationalized on
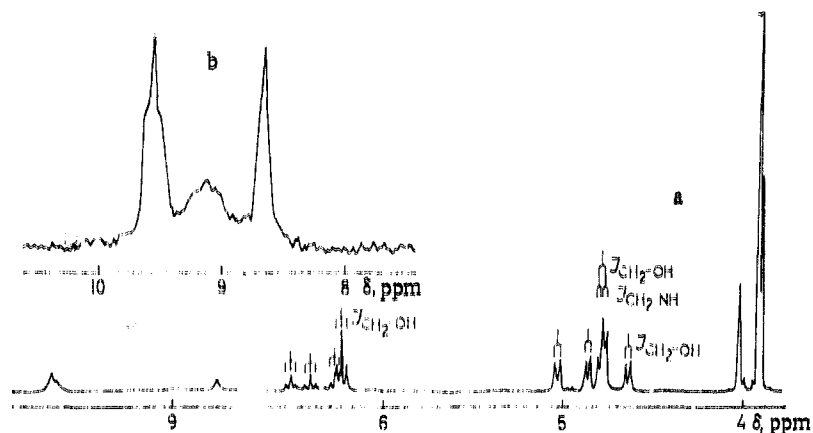
Fig. 1. PMR spectra of 2-hydroxymethylamino-4-thiazo-
linone (IIa): a) 270 MHz, concentration 200 mmole/
liter; b) 90 MHz, concentration 45 mmole/liter.

the basis of the presence in solution of an equilibrium mixture of conformers, IIa-E″ $\rightleftarrows$ IIa-E′ $\rightleftarrows$ IIa-E $\rightleftarrows$ IIa-Z $\rightleftarrows$ IIa-Z′ $\rightleftarrows$ IIa-Z″. The equilibrium between the open forms, IIa-E $\rightleftarrows$ IIa-Z, does not differ from the conformational equilibrium for 2-methylamino-4-thiazolinone [3], and may be attributed to partial sp^3-hybridization of the exocyclic nitrogen atom $N_{(2')}$. Conformer IIa-E is sterically the most favored isomer [at a concentration of 0.2 mole/liter, the ratio (IIa-E + IIa-E′)/(IIa-Z + IIa-Z′) is about 3:1]; it gives rise to the very strong triplet at 9.69 ppm for the NH group proton, which is deshielded by the oxygen atom in the cisoid orientation of the hydrogen and hydroxyl groups relative to the N–CH₂ bond, and thus is shifted to lower field relative to conformers IIa-E′ and IIa-E″.* The HOCH₂NH fragment of conformer IIa-E gives rise to vicinal spin-spin coupling, with a constant of J = 7.3 Hz, of the hydroxyl and methylene group protons, just as is observed for all of the other isomeric forms, but also exhibits vic-inal coupling due to the CH₂–NH protons, with a spin-spin coupling constant J = 4.6 Hz; the signals due to these protons thus appear as a multiplet centered at 4.78 ppm as a result of overlap of two doublets. Splitting of the methyl group proton signal by the vicinal NH group proton has been detected previously, in the case of the E-conformer of 2-methylamino-4-thiazo-linone [3]. A similar splitting pattern which is seen in secondary amides [4, 5], can be at-tributed to rate retardation of exchange of the amide proton as a consequence of partial pos-itive charge on the nitrogen atom; in our case, suppression of the exchange rate is due not only to the amide character of $N_{(2')}$, but also to the steric requirements of the exchange process.

The broadened signal at about 10 ppm and the triplet centered at 4.64 ppm correspond to the NH and NCH₂ group protons, respectively, in conformer IIa-Z. Just as was observed in the case of the corresponding protons in the Z-conformer of 2-methylamino-4-thiazolinone, these protons resonate either downfield (in the case of the NH proton) or upfield (in the case of the NCH₂ protons) relative to the same protons in the E-conformer [3]. The chemical shifts of the methylene group protons in the heterocycle, $C_{(5)}H_2$, in both of the open conformers, IIa-E and IIa-Z, are exactly the same as in 2-methylamino-4-thiazolinone [3], namely, 3.92 ppm for the E-conformer and 3.90 ppm for the Z-conformer. The triplets due to hydroxyl group protons, at 6.24 (IIa-E) and 6.27 ppm (IIa-Z), are superimposed on one another.

Examination of Stuart–Dreiding molecular models reveals the possibility of chelate structures, characterized by intramolecular hydrogen bonding, for IIa-E″ and IIa-Z″, without any significant changes in either bond angles or bond lengths. From a stereochemical view-point, chelate formation should be especially favorable in the case of an sp^3-hybridized exocyclic nitrogen atom. CNDO calculations [6] of 2-amino-4-thiazolinone (Ia) give a popu-lation density for the p^π_z orbital of $N_{(2')}$ of 1.757 (i.e., a π-change of +0.243), which is indicative of the significant sp^3 character of this nitrogen atom. Three-dimensional models also reveal that conformer IIa-E′ can form a "cyclic" hydrate, which is facilitated by the partial negative charge on $N_{(3)}$ [2], and that the Z-conformer can exist in a chelate form, IIa-Z′, with CH₂O···S contact. The feasibility of the existence of form IIa-Z′ is also sup-ported by the calculated degree of π=charge on the sulfur atom (+0.092) and by x-ray struc-

_____
*The methylene protons of the hydroxymethyl groups in the chelate forms IId-E″ and IIa-Z″ also experience downfield shifts for the same reason.

TABLE 1. ^{13}C-NMR Spectral Chemical Shifts for Compound IIa

δ, ppm	Assignment	
	atom	form
191,49	$C_{(4)}$	IIa-E'+IIa-E"
191,03	$C_{(4)}$	IIa-E
190,67	$C_{(4)}$	IIa-Z+IIa-Z'+IIa-Z"
186,59	$C_{(2)}$	IIa-Z+IIa-Z'+IIa-Z"
184,91	$C_{(2)}$	IIa-E+IIa-E'+IIa-E"
74,85	N—C	IIa-Z+IIa-Z'+IIa-Z"
71,11	N—C	IIa-E+IIa-E'+IIa-E"
43,50	$C_{(5)}$	IIa-Z+IIa-Z'+IIa-Z"
42,41	$C_{(5)}$	IIa-E+IIa-E'+IIa-E"

ture analysis of the almost isoteric compound, 2-amino-4-triazolinone-5-caboxylic acid [7] (S···O distance, 2.96 Å, compared to the sum of van der Waals raddi, 3.25 Å).
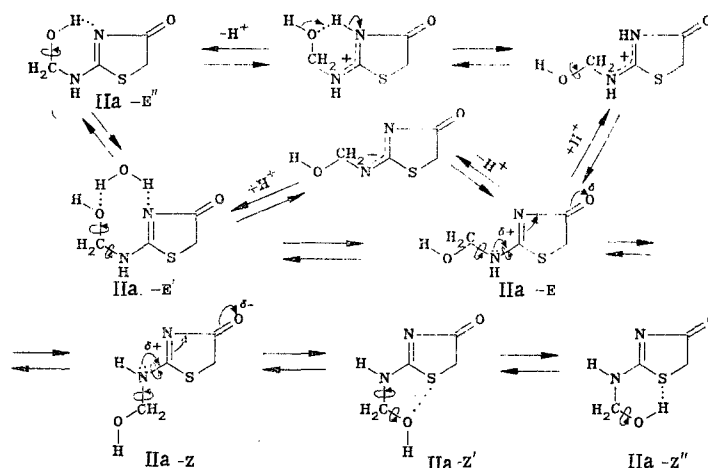
Form IIa-E" is characterized by a strong signal for the NH group proton at 8.78 ppm and by a doublet for the NCH₂ group protons at 5.02 ppm; form IIa-Z", on the other hand, exhibits the corresponding signals at 9.00 ppm (broad signal) and at 4.86 ppm (doublet). The chemical shifts of the NH group protons in these two forms are virtually identical to the chemical shift for 2-amino-4-thiazolinone (Ia), which is indicative of the absence of strain in the chelate structures. The signals due to the methylene protons of the heterocycle overlap for forms IIa-Z and IIa-Z", whereas the corresponding resonance for isomer IIa-E" occurs at 4.02 ppm. Upon protonation, i.e., complete transfer of a proton to $N_{(3)}$ [9], the $C_{(5)}H_2$ proton signal is shifted downfield [8]. At a concentration of 200 mmole/liter, the amounts of forms IIa-Z and IIa-Z', on one hand, and form IIa-Z", on the other hand, are approximately equivalent, while the ratio (IIa-E + IIa-E')/(IIa-E") is about 3:1.* Addition of D₂O results in the disappearance of the signal multiplicity for the NCH₂ group protons.

Changes in the concentration of compound IIa, within the range 0.9-620 mmole/liter, do not affect the signal positions for the mobile (active) NH and OH group protons. As the concentration is lowered, however, the amount of the chelate forms decreases; at a concentration of 0.9 mmole/liter, (IIa-E + IIa-E')/(IIa-E") is about 10:1, and (IIa-Z + IIa-Z')/(IIa-Z") is about 3:1, whereas the ratio of the "open" forms, (IIa-E + IIa-E')/(IIa-Z + IIa-Z'), equals about 2.7:1, which is almost unchanged. Decreasing the concentration of the chelate forms apparently does not result in diminution of the intensity of the high field components of the NH group proton signals. Thus, the (IIa-E + IIa-E')/(IIa-E") ratio changes from 3:1 to 5:1 as the concentration is lowered from 200 to 45 mmole/liter, but the intensity ratio for the 9.70 and 8.78 ppm signals remains unchanged at about 1.7 (see Fig. 1b). We attribute this observation to preferred solvation of the open forms IIa-E' and IIa-Z' by residual water present in the solvent, which is in excess compared to the small concentration of sample which is present in solution; specific solvation of the hydroxyl groups in chelates IIa-E" and IIa-Z" facilitates their cleavage and transition to the "open" forms IIa-E' and IIa-Z', which are characterized by transoid configurations of the N—H and CH₂—O bonds. The signals due to

*Estimated based on the relative signed intensities of the NCH₂ group methylene protons.
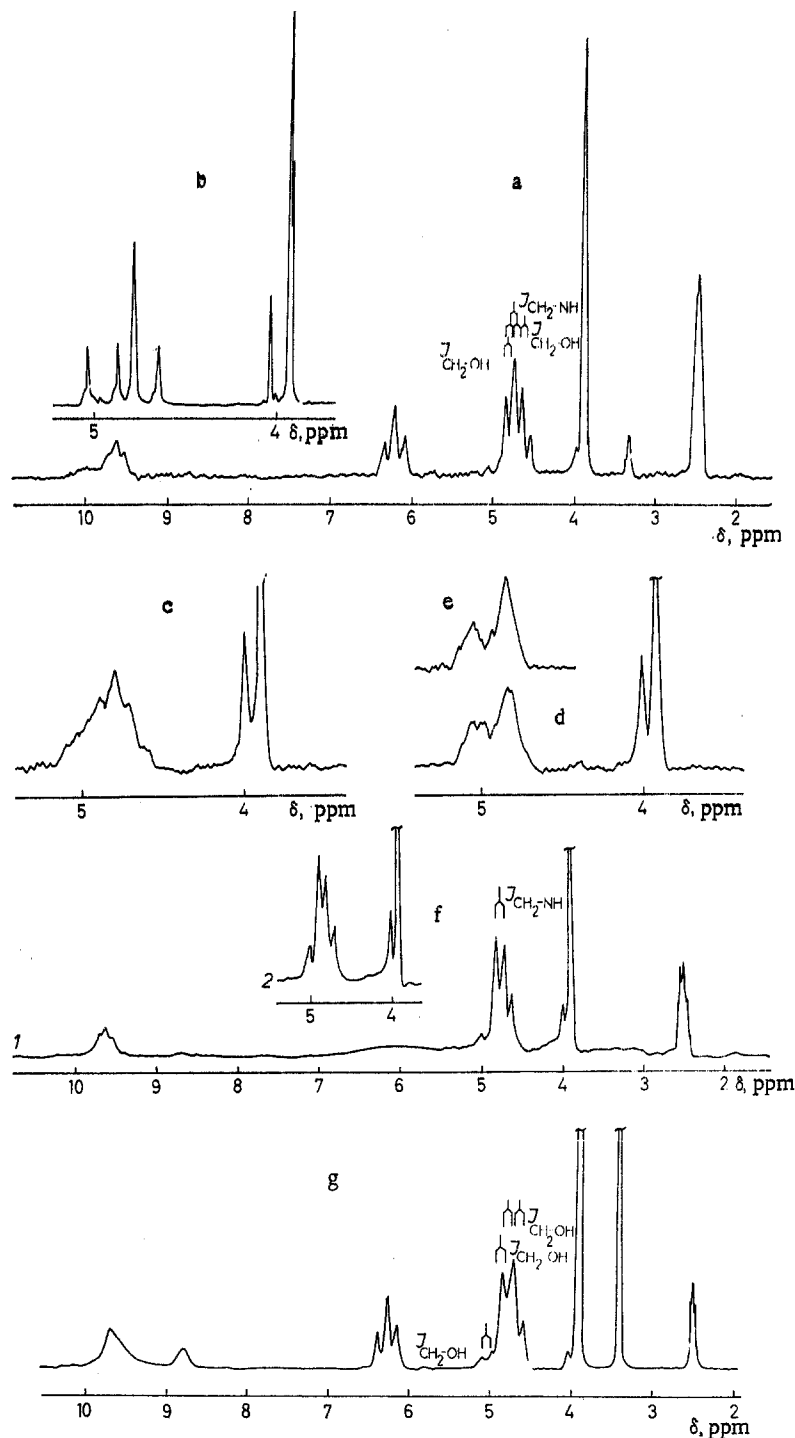
Fig. 2. PMR spectra of 2-hydroxymethylamino-4-thiazolinone
IIa: a) in purified and dried DMSO-d_6, 60 MHz, concentra-
tion 60 mmole/liter; b) same sample, after addition of D_2O
to the sample tube, 270 MHz; c) same sample at 47°C; d) same
sample at 83°C; e) same sample at 92°C; f) in DMSO-d_6 in the
presence of catalytic amounts of acetic acid, 60 MHz, concen-
tration 620 mole/liter , recorded immediately after dissolv-
ing (1), and 5 min after the first spectrum (2); g) same sam-
ple in the presence of catalytic amounts of dibutylaniline.

the OH and CH_2 group protons overlap in both forms IIa-E' and IIa-E", and IIa-Z' and IIa-Z";
these compounds differ only in the NH group proton signals, which are the same in forms IIa-
E' and IIa-E", and IIa-Z' and IIa-Z". The equilibrium shifts which accompany change in the
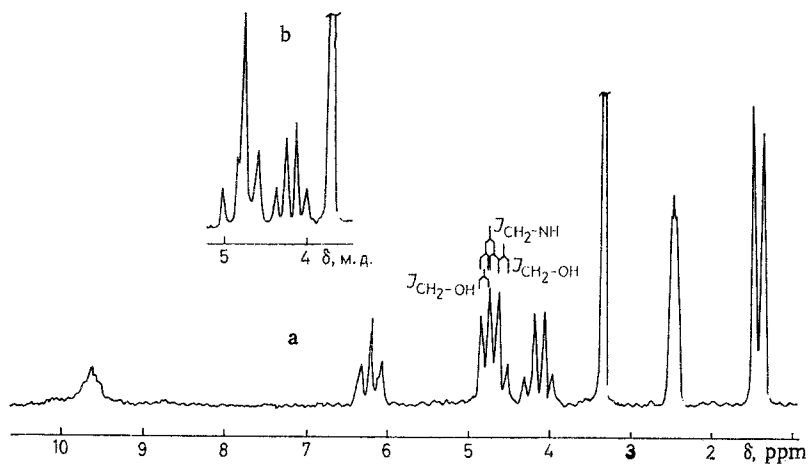concentration of IIa in DMSO-d_6 solution are thus due to varying amounts of different solvent

Fig. 3. PMR spectra of 5-methyl-2-hydroxymethylamino-4-
thiazolinone (IIb): a) in purified and dried DMSO-d_6 at
60 MHz and a concentration of 100 mmole/liter; b) same
sample after addition of D_2O to the sample tube.

complexes. Dimerization (self-association) schemes, although structurally possible for com-
pounds of similar structure [3], cannot explain the observed spectral changes, in particular,
the changes in signal intensities for the discrete forms of compound IIa, which accompany
concentration variations.

At a IIa concentration of 0.9 mmole/liter, the amount of excess water (relative to the
amount of dissolved substrate), and the presence of very small amounts of acidic impurities
therein, suppresses spin-spin coupling of the CH_2—OH group protons, although spin-spin coup-
ling of the CH_2—NH group protons in form IIa-E is retained. At this concentration, spin-
spin coupling of the CH_2—NH group protons is also observed in form IIa-Z" (δ_{CH_2} 4.86 ppm, J =
4.9 Hz). Apparently, specific solvation of the $N_{(3)}$ atom (calculated charge, —0.535 [2]) by
excess water results in steric conditions which favor exchange processes for the NH group
proton in form IIa-Z".

^{13}C-NMR Spectra. The recorded ^{13}C-NMR spectra of compound IIa allow us to rule out pro-
totropic tautomerism as the reason behind the complex PMR spectra; in particular, the $C_{(2)}$
and $C_{(4)}$ signals are in the same position as for the amino tautomer [3]. The N—C and $C_{(5)}$
methylene carbon atoms are sensitive to the E $\rightleftarrows$ Z conformational equilibrium about the $C_{(2)}$—
$N_{(2')}$ bond (the intensity ratio of the weak field and high field signals is about 1:2), but
apparently are not sensitive to chelation or to the orientation about the CH_2—N bond (see
Table 1). The $C_{(4)}$ carbon atom is sensitive not only to the E $\rightleftarrows$ Z equilibrium, but also to
chelate formation and formation of isomer IIa-E'.

Dynamics and Mechanism of Transitions. In several instances we observed PMR spectra of
compounds IIa and IIb in which the equilibria involving form II-E, on one side, and forms
II-E' and II-E", on the other side, had not yet been established. It appears that in high-
purity DMSO-d_6, which does not contain acidic or basic impurities which can catalyze inter-
conversion about the $N_{(2')}$—CH_2 bond (as might be expected, this is DMSO which is virtually
free of water), the rate of the II-E $\rightleftarrows$ II-E' transition is very low. The conversion barrier
is controlled by the degree of orbital overlap for the hydroxyl oxygen, $C_{(2)}$ carbon, and $N_{(3)}$
nitrogen atoms in the case of the IIE $\rightleftarrows$ IIE' equilibrium, and for the hydroxyl oxygen, $C_{(2)}$
carbon, and $S_{(1)}$ sulfur atoms in the case of the IIZ $\rightleftarrows$ IIZ' equilibrium. Either protonation
of $N_{(3)}$ [9] or deprotonation of $N_{(2')}$ changes the hybridization of the nitrogen atoms in such
a way that the geometry of the amide fragment permits a decrease in the barrier for rotation
about the $N_{(2')}$—CH_2 bond. It is assumed that the degree of sp^2-hybridization of the $N_{(2')}$
nitrogen atom increases upon both protonation [9] and deprotonation (the calculated π-orders
for the $N_{(2)}$—$C_{(2)}$ and $N_{(3)}$—$C_{(2)}$ bonds in the 2-methylamino-4-thiazolinone anion are 0.726
and 0.523, respectively). Examination of Stuart—Dreiding molecular models also reveals that
rotation about the $N_{(2')}$—CH_2 bond in the E-conformers is not hindered by sp^2-hybridization of
the $N_{(2')}$ atom, but is strained in the Z-conformers. We cannot propose any arguments to
account for the fact that the barrier for the IIZ $\rightleftarrows$ IIZ' conversion is so much lower than
that for the IIE $\rightleftarrows$ IIE' barrier, since we did not detect any catalytic effect which would in-
crease the rate of the IIZ $\rightleftarrows$ IIZ' transition.

Finally, the rate of the uncatalyzed partial proton transfer for the IIE' ⇄ IIE" conversion is also low, which may be explained in terms of hindered rotation about the CH_2-O bond as a result of overlap of the p-orbitals of the oxygen atom and both nitrogen atoms, as well as by the characteristics of the proton transfer reaction [10]. In any event, as can be seen in the PMR spectrum reproduced in Fig. 2a, the proton signals for form IIa-E" at 5.02 and 4.02 ppm are just barely discernible, whereas the signal at 8.76 ppm is totally missing. According to the relative intensities of the multiplet components for the N-CH₂ group protons, form IIa-Z" is present in solution in equilibrium amounts. Addition of D_2O* to the sample tube (Fig. 2b) or increasing the temperature (Fig. 2c) leads to an increase in the concentration of isomer IIa-E" up to its equilibrium value,† although in the latter case, higher temperatures are also accompanied by collapse of the spin-spin multiplets and coalescence of the signals due to the "open" conformers, and by collapse of the doublet due to form IIa-Z" (Fig. 2d); still higher temperatures lead to collapse of the spin-spin doublet of form IIa-E". Catalytic amounts of acetic acid impurity also increase the rate of both rotation and chelation, and repeated extractions allowed us to follow the increase in the concentration of form IIa-E" up to its equilibrium value (Fig. 2f); the presence of acids increases the rate of exchange of the hydroxylic protons and suppresses spin-spin interaction of the CH_2-OH groups, while preserving spin-spin coupling of the CH_2-NH group protons.

In contrast, catalytic amounts of dibutylaniline accelerate proton exchange of the NH groups, and thus suppress spin-spin coupling of the CH_2-NH groups while retaining spin-spin coupling of the CH_2-OH groups (Fig. 2g). Spectrum 2g is characterized by the almost complete disappearance of the methylene proton signals for form IIa-E" as well as by the intensity of the signal at 8.76 ppm due to the NH group proton. This demonstrates that in the presence of basic impurities the IIa-E ⇄ IIa-E' conversion proceeds very rapidly, and equilibrium is achieved between these two forms, whereas the rate of uncatalyzed chelation is very slow, and as a result the IIa-E' ⇄ IIa-E" equilibrium is achieved at a much slower rate.

Analogous spectral results were obtained for 5-methyl-2-hydroxymethylamino-4-thiazolinone (IIb). As an example, in neutral DMSO-d₆ which contains neither acidic nor basic impurities, form IIb-E" is scarcely detected (Fig. 3a) just as was observed in the case of compound IIa, but addition of D_2O results in a significant incrdase in its concentration (Fig. 3b).

EXPERIMENTAL

PMR spectra sere recorded on Tesla BS-467 (60 MHz), Bruker HX-270 (270 MHz), and Bruker HX-90 (90 MHz) spectrometers in DMSO-d₆ solution versus HMDS as internal standard. DMSO was purified as reported earlier [3]. The mass spectrum of compound IIa was obtained on an MX-1313 spectrometer using direct sample injection and an ionizing current of 70 eV at a source temperature of 100°C. The derivatograph of compound IIa was recorded on a derivatograph apparatus of F. Paulik, I. Paulik, and L. Erdey (Hungary).

2-Hydroxymethylamino-4-thiazolinone (IIa). A mixture of 4.6 g (40 mmoles) of compounds IIa and 16 ml (200 mmoles) formalin in 30 ml of ethanol was stirred for 5 min at 70°C, until all of the starting material precipitate had dissolved. The resulting precipitate of IIa which was obtained after cooling the reaction mixture was washed with ethanol and crystallized from idoxane. In the presence of equimolar amounts of either dimethylaniline or dibutylaniline compound IIa can be obtained at room temperature by stirring the reaction mixture for 30-40 min and filtering the resulting precipitate due to product. Yield 5.8 g (99%), mp 160°C. IR spectrum (Vaseline oil): 3300 (OH), 3250 (NH), 1675 (C=O), 1550-1570 (C=N). UV spectrum (in ethanol), λ_{max}, (log ε): 220 (4.22), 250 nm (3.90). Found: N 18.9; S 21.3%. $C_4H_6N_2O_2S$. Calculated: N 19.2; S 21.8%.

Compound IIb was prepared in a similar manner from 5-methyl-2-amino-4-thiazolinone (Ib). Yield 89%, mp 166°C. IR spectrum (vaseline oil): 3290 (OH), 3240 (NH), 1685 (C=O), 1550-1590 (C=N). UV spectrum (in ethanol), λ_{max} (log ε): 221 (4.21), 249 nm (3.88). Found: N 17.7; S 19.8%. $C_5H_8N_2O_2S$. Calculated: N 17.5; S 20.0%.

---

*The accelerating effect of D_2O can be attributed not only to an isotope effect 11 , but also to the fact that D_2O contains an acidic impourty which catalyzes rotation and proton transfer.
†Increasing the temperature also increases the concentration of the energetically unfavorable form IIa-E", which can be seen in Fig. 2c-f.

LITERATURE CITED

1. S. M. Ramsh, S. Yu. Solov'eva, and A. I. Ginak, Khim. Geterotsikl. Soedin., No. 7, 928 (1983).
2. Yu. G. Basova, Candidate's Dissertation, Chemical Science, Leningrad (1980).
3. S. M. Ramsh, N. A. Smorygo, E. S. Khrabrova, and A. I. Ginak, Khim. Geterotsikl. Soedin., No. 4, 544 (1986).
4. R. Baibl, Interpretation of Nuclear Magnetic Resonance Spectra, Atomizdat, Moscow (1969) p. 77.
5. A. I. Kol'tsov and G. M. Kheifets, Usp. Khim., 41, 875 (1972).
6. B. É. L'vovskii and G. B. Erusalimskii, Koord. Khim., 2, 1221 (1976).
7. V. Armithalingam and K. V. Muralidharan, Acta Cryst., 28B, 2417
8. S. M. Ramsh, n. A. Smorygo, and A. I. Ginak, Khim. Geterotsikl. Soedin., No. 8, 1066 (1984).
9. S. M. Ramsh, A. I. Ginak, N. A. Smorygo, Yu. G. Basova, and E. G. Sochilin, Zh. Org. Khim., 14, 1327 (1978).
10. I. P. Gregerov, V. K. Pogorelyi, and I. F. Franchuk, The Hydrogen Bond and Rapid Proton Exchange [in Russian], Naukova Dumka, Kiev (1978), p. 204.
11. R. V. Hoffmann, Mechanisms of Chemical Reactions [Russian translation], Khimiya, Moscow (1979), p. 258.

ACID DEUTERIUM EXCHANGE IN BENZAZOLES

I. F. Tupitsyn, N. N. Zatsepina,   UDC 547.72+546.11.02.2:541.127
A. I. Belyashova, and A. A. Kane

The kinetics of acid deuterium exchange in benzazoles carrying electron-donor substituents in the 5-, 6-, or 7-positions have been studied. Mass spectrometric studies have shown that exchange in 5-methoxy-1,2-dimethylbenzimidazole takes place exclusively at one position in the benzene ring, in 5-chloro-, 7-chloro-, 5-methoxy-2-methylbenzothiazole and 6-methoxy-2-methylbenzoxazole simultaneously in two positions, and in 6-methoxy-2-methylbenzothiazole the hydrogen at all three possible positions is exchangeable. Using quantum chemical reactivity indices (CNDO/2) in dynamic and state approximations, the orientational features of the reaction have been ascertained. The lack of agreement between the reactivities of the most reactive sites to exchange in heteroaromatic bicycles of similar structure and electrophilic localization energies is explained by differences in the energy profile of the reaction.

Continuing studies of proton-deuterium exchange (H–D exchange) in bicyclic heteroaromatic systems [1], we have measured the rate constants for the reactions of some substituted benzazoles. The acid-initiated H–D exchange reaction in condensed five- and six-membered aromatic heterocycles with two heteroatoms in the ring has received considerably less attention [2, 3] than, for example, in quinolines and isoquinolines [4-6], and no such studies have been carried out in benzazoles. However, for the elucidation of factors governing changes in electrophilic reactivity, such studies are of considerable interest for theoretical heterocyclic chemistry as a whole.

The π-electron deficient parent compounds of this series (benzothiazole N-methylbenzimidazole, and benzoxazole) appear to be totally inert to acid H–D exchange in the benzene ring. In order to facilitate the occurrence of exchange reactions we introduced into the benzene ring, as on a previous occasion [1], an activating substituent (chloro- or methoxy-) in the 5-, 6-, or 7-position of the benzazole nucleus. In addition, in order to be able to