^{1}H NMR Structural Study of 2-Phenylthiazolidine

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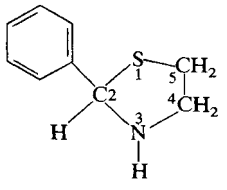
Deuteration of 2-phenylthiazolidine, and its complexation with the shift reagent tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium, have been used to study the signals and conformation of the heterocyclic protons and to interpret the ^{1}H NMR spectrum of this 2-substituted thiazolidine.

INTRODUCTION

2-Phenylthiazolidine (**1**) and many of its derivatives have radioprotective activity. The level of this activity depends, however, on the nature of the substituents.[1,2]



2-Phenylthiazolidine (**1**)

In an attempt to establish a relationship between the radioprotective property and the electronic character of variously substituted 2-phenylthiazolidines, an NMR study of **1**, has been carried out in order to assign the signals and determine the configuration of the heterocyclic protons.

RESULTS AND DISCUSSION

^{1}H NMR spectrum of 2-phenylthiazolidine (1) (Fig. 1)

The paramagnetic shift reagent tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium, $Eu(fod)_3$, was used to simplify the NMR spectrum of **1** in order to assign the signals and determine the configurations of the heterocyclic protons.

Assignment of signals to the heterocyclic protons

A plot of the chemical shifts (δ_{Eu}) of the heterocyclic protons at C-4 and C-5 as a function of the $Eu(fod)_3$ concentration revealed a linear relationship with a correlation coefficient of greater than 0.99 for all four protons. These results imply that there was only one site of complexation.

A plot of δ_{Eu} as a function of the molar ratio of $Eu(fod)_3$ to **1** also revealed a linear relationship with a correlation coefficient greater than 0.99. The values for the slope (the shift parameter) of each regression line and the intercept at the y axis (chemical shift in the absence of shift reagent) are given in Table 1.

Determination of the configuration of the heterocyclic protons

The separation of the signals of the different protons allowed a first-order analysis of all the spectra corresponding to 2-phenylthiazolidine complexed with $Eu(fod)_3$. The ^2J and ^3J coupling constants for H-A, H-B, H-C and H-D were determined from the spectrum in Fig. 1. The average coupling constants are listed in Table 2.

The results indicate that H-A and H-B are geminal, as are H-C and H-D. Furthermore, the ^{1}H NMR spectrum (not shown) of 2-phenylthiazolidine-5,5-d_2 showed an AB system for the 2 protons at C-4 with a coupling constant of 12.50 Hz. Consequently, H-A and H-B are situated at position 4 of the heterocycle; H-C and H-D ($^2J = 10$ Hz) are, therefore, bonded to C-5. Similar coupling constants for the geminal protons in 4- and 5-methylthiazolidines have been reported.[4]

The fact that H-A and H-B underwent the greatest shifts on addition of $Eu(fod)_3$ strongly suggests that

Table 1. Chemical shifts (δ) of 1 in the absence of $Eu(fod)_3$ and the europium shift parameter values s[a]

	H-2	H-A	H-B	H-C	H-D
δ	5.43	2.88	2.53	2.55	2.65
s	10.01	12.65	11.35	6.66	4.33

[a] s is proportional to the inverse square of the distance between the proton in question and the site of complexation.[3]

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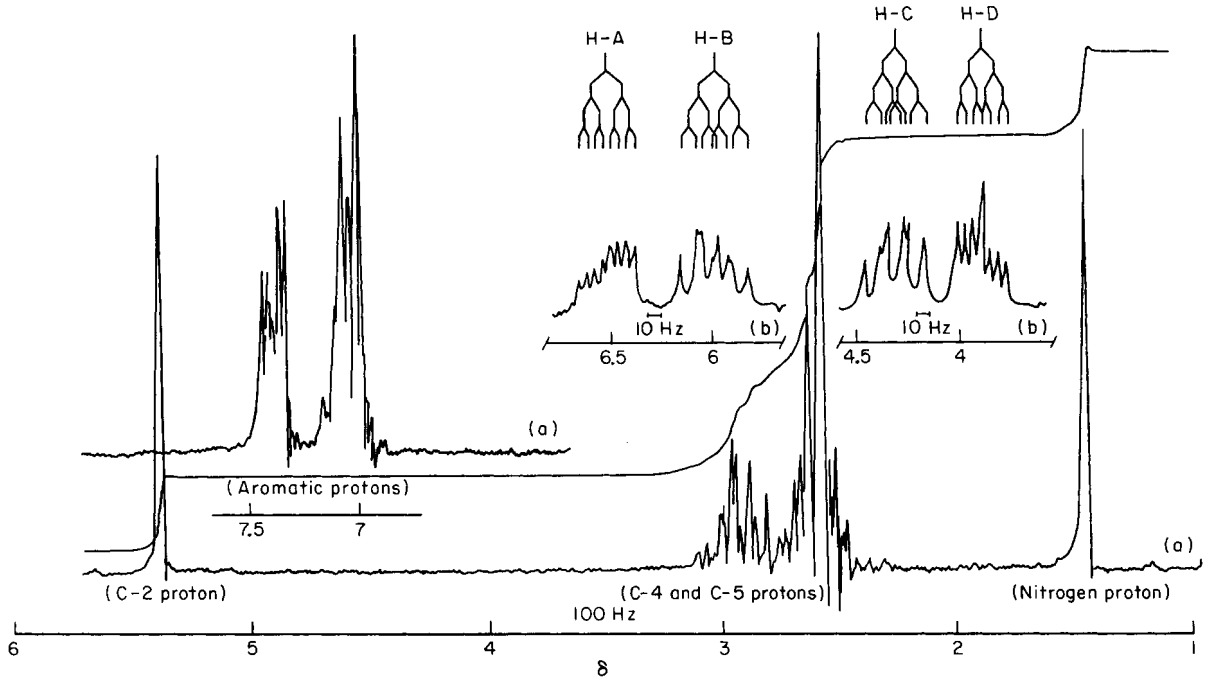
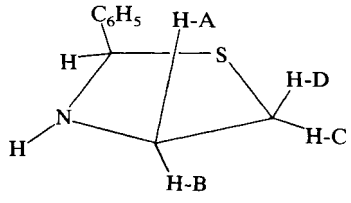


Figure 1. (a) The 100 MHz spectrum of 2-phenylthiazolidine in C_6D_6. The signal at $\delta = 5.40$ is absent in the spectrum of 2-phenylthiazolidine-2-d_1. (b) Spectrum of the heterocyclic protons at C-4 and C-5 of 2-phenylthiazolidine (41 mg) complexed with Eu(fod)$_3$ (70.5 mg) in C_6D_6.

the europium salt coordinated with nitrogen, which has been shown to be a preferred site of complexation for lanthanide shift reagents.[5]

Finally, it is logical to assume that H-A and H-D, which resonate at lower fields are in *cis* position with respect to the aromatic ring. In this position H-A and H-D are more strongly subjected to the paramagnetic effect of the aromatic ring than are H-B and H-C. The



corresponding coupling constants for the ethane fragment are listed in Table 3.

In general, our results do not agree with those of Wilson and Bazzone,[6] who studied 2-*tert*-butylthiazolidine. However, the $^3J(trans)$ coupling constant, J(H-B, H-D), of 6.60 Hz is in agreement with that found by Kulkarni and Govil[7] for 2,2-dimethylthiazolidine and for thiazolidine-4-carboxylic acid.

Table 2. Coupling constants for 1 complexed with Eu(fod)$_3$

	^2J	^3J	$^3J'$
H-A	12.30±0.20	6.25±0.25	3.30±0.20
H-B	12.30±0.20	8.10±0.10	6.55±0.20
H-C	10.00±0.00	8.30±0.20	6.20±0.05
H-D	10.00±0.00	6.60±0.30	3.30±0.20

Table 3. Coupling constants for the C-4 and C-5 protons

$^3J(cis)$	$^3J(trans)$
J(H-A, H-D) = 3.30	J(H-A, H-C) = 6.25
J(H-B, H-C) = 8.20	J(H-B, H-D) = 6.60

EXPERIMENTAL

The proton NMR spectra were recorded on a Varian XR 100 spectrometer. The solvent was C_6D_6 and the sample temperature was 20 °C. The sweep rate was 1 Hz s^{-1}. Chemical shifts are relative to internal TMS. The solutions of ligand–shift reagent complex were prepared by dissolving 41 mg of 2-phenylthiazolidine and 11.8 mg, 26.2 mg, 39.9 mg, 56.8 mg or 70.5 mg of Eu(fod)$_3$ in 0.5 ml of C_6D_6.

Synthesis of 2-phenylthiazolidine ($C_6H_5\overline{CHNHCH_2CH_2S}$)

Benzaldehyde (10.6 g, 0.1 mol) was condensed with cystamine (7.7 g, 0.1 mol) in 100 ml of anhydrous benzene. Recrystallization from anhydrous ethanol gave 11.7 g of product (70%), m.p. 108–109 °C (lit. value[2] 108 °C).

Synthesis of 2-phenylthiazolidine-2-d_1 ($C_6H_5\overline{CDNHCH_2CH_2S}$)

Isotopic benzyl alcohol ($C_6H_5CD_2OH$). The reduction of ethyl benzoate (12 g, 0.08 mol) in ether by lithium aluminium deuteride, $LiAlD_4$ (3.4 g, 0.08 mol) gave 6.5 g of benzyl alcohol-α-d_2 (74%), b.p. 105 °C/25 mm.

Isotopic benzyl chloride ($C_6H_5CD_2Cl$). The reaction of thionyl chloride (14.3 g, 0.12 mol) with isotopic benzyl alcohol (6.5 g, 0.06 mol) in benzene gave 5.5 g of benzyl chloride-α-d_2 (73%), b.p. 75 °C/25 mm.

Isotopic benzaldehyde (C_6H_5CDO). 2-Nitropropane (11.6 g, 0.13 mol) followed by isotopic benzyl chloride (5.5 g, 0.042 mol) were added dropwise to 100 ml of a 10% NaOH solution maintained under agitation. The reaction mixture was refluxed for 2 h, cooled, and then extracted with ether. The ether phase was washed with water, dried over Na_2SO_4, and evaporated. Vacuum distillation gave 1.3 g of benzaldehyde-α-d_1 (29%), b.p. 112 °C/25 mm.

2-Phenylthiazolidine-2-d_1. Isotopic benzaldehyde (1.23 g, 0.012 mol) was condensed with cystamine (0.8 g, 0.010 mol) in 15 ml of anhydrous benzene. Recrystallization from anhydrous ethanol gave 1 g of product (58%), m.p. 112 °C.

Anal. Calc. for $C_9H_{10}DNS$: C, 65.06; H, 6.02; N, 8.43. Found: C, 64.91; H, 6.23; N, 8.41.

Synthesis of 2-phenylthiazolidine-5,5-d_2 ($C_6H_5\overline{CHNHCH_2CD_2S}$)

Glycine ethyl ester ($H_2NCH_2COOC_2H_5$). Glycine ethyl ester hydrochloride (75.4 g, 0.54 mol) and silver oxide (60.3 g, 0.26 mol) were suspended under vigorous agitation in 500 ml of anhydrous ether.[8] Agitation was maintained for 30 min after the appearance of the silver chloride precipitate. The solution was then filtered and the ether phase was concentrated. Distillation gave 22 g of glycine ethyl ester (40%), b.p. 60 °C/25 mm and 65 °C/40 mm.

2-Hydroxyethylamine-2,2-d_2 ($HOCD_2CH_2NH_2$). This was synthesized according to the method of Kawer *et al.*[9] The reduction of glycine ethyl ester (21.6 g, 0.21 mol) by $LiAlD_4$ (10 g, 0.24 mol) gave 4.8 g of 2-hydroxyethylamine-2,2-d_2 (36%), b.p. 94 °C/16 mm.

2-Methyl-2Δ-thiazoline-5,5-d_2 ($CH_3\overline{C:NCH_2CD_2S}$). This product was synthesized according to the method of Roggero.[10] 2-Hydroxyethylamine-2,2-d_2 (4.6 g, 0.073 mol) was acetylated; treatment of the resulting product with P_2S_5 in mineral oil[11] gave 2.2 g (29%) of 2-methyl-2Δ-thiazoline-5,5-d_2, b.p. 61 °C/25 mm.

2-Aminoethanethiol-1,1-d_2. Acid hydrolysis of 1.7 g (0.0165 mol) of the thiazoline prepared in the previous step gave 600 mg (32%) of 2-aminoethanethiol hydrochloride-1,1-d_2, m.p. 70 °C.

2-Phenylthiazolidine-5,5-d_2. The hydrochloride salt (600 mg, 0.0052 mol) prepared in the previous step was condensed with benzaldehyde (550 mg, 0.0052 mol) according to the conditions described by Larice *et al.*[12] The conversion of the resulting product to the free base gave 750 mg of the final product (86%). m.p. 109 °C.

Anal. calc. for $C_9H_8D_2NS$: N 8.38. Found: 8.32.

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