N.m.r. spectra of cyclic amines. II—Factors influencing the chemical shifts of α-protons in aziridines

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N.m.r. Spectra of Cyclic Amines

II—Factors Influencing the Chemical Shifts of α-Protons in Aziridines

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Proton magnetic resonance spectra of *trans* and *cis*-2,3-diphenylaziridine (1 and 2) and their *N*-ethyl derivatives 3 and 4 were measured in carbon tetrachloride, chloroform, and benzene-d_6 at low temperatures (1 and 3) and in dry conditions (1 and 2). On the basis of these results it was concluded that an *N*-ethyl group exerts a shielding influence on a *cis* ring proton and a deshielding influence on a *trans* ring proton. From results obtained by measuring the ^{1}H n.m.r. spectra of 1–4 in deuterochloroform-trifluoroacetic acid it was derived that the lone pair of the aziridine nitrogen exerts a shielding influence on *cis* related ring hydrogens. In most *N*-alkylaziridines the effect of the *N*-alkyl group predominates.

The shielding of axial α-protons in saturated 6-membered nitrogen heterocycles is well documented.[1–4] This shielding is presumably caused by the anisotropy of the *trans* axial lone pair and that of the equatorial alkyl substituent, if present, on the nitrogen. Alternatively this phenomenon has also been viewed as deshielding of a proton by a skew or a *cis* related lone pair in acylic as well as cyclic systems.[5]

Previously we have studied *cis*- and *trans*-2,5-diphenylpyrrolidine and their *N*-methyl derivatives and we have shown that by comparison of the ^{1}H n.m.r. spectra of the free bases and those of their protonated species it is possible to estimate the contribution of the nitrogen lone pair and that of the *N*-methyl group to the chemical shift of the α-protons. It was found that α-protons in pyrrolidines are shielded when situated *trans* to a lone pair and *cis* to an *N*-methyl group. Furthermore it was suggested that the same treatment could be applied to assess the contribution of the lone pair and the *N*-alkyl group to the chemical shifts of α-protons in other saturated nitrogen heterocycles.[6]

In view of our current interest in the chemistry of aziridines,[7,8] we have chosen this system as the next subject for our studies.

Most aziridines have a nitrogen inversion barrier between the limits attained by dynamic n.m.r.[9,10] Exceptions are compounds substituted on the nitrogen by groups capable of conjugation with the nitrogen lone pair.[11–13] Consequently in the last decade a large number of papers dealing with various aspects of n.m.r. spectral properties of aziridines has been published. By means of the now well established various coupling constants,[14–16] and the use of ASIS[17,18] (aromatic solvent induced shifts) it is now easy to assign the signals belonging to various hydrogens in an aziridine molecule. It was observed by several workers[15,16,18–24] that in *N*-alkylaziridines (with the exception of *N*-*t*-butylaziridines[19b]) the ring protons *cis* to the magnetically anisotropic *N*-alkyl bond and *trans* to the lone pair are more shielded than protons *trans* to the *N*-alkyl group and *cis* to the lone pair. On the other hand, in *N*-unsubstituted aziridines hydrogens *cis* related to the lone pair were found to be the more shielded.[16,19,20,23] It seems therefore that the effect of the nitrogen lone pair on the chemical shift of a CH in the aziridine ring is reversed on passing from *N*-unsubstituted to *N*-alkylaziridines.

In an attempt to clarify this question and to estimate the magnitude and the sign of the influence of the nitrogen lone pair and of the *N*-alkyl group, we have undertaken to study the n.m.r. spectra of *cis*- and *trans*-2,3-diphenylaziridine and their *N*-ethyl derivatives.

RESULTS AND DISCUSSION

Throughout this section the terms *cis* and *trans* are used in their usual chemical sense. The terms *syn* and *anti* are used to designate the relationship between a hydrogen and the substituent attached to the nitrogen.

The n.m.r. data of aziridines **1–4**, measured at room temperature in three solvents, are listed in Table 1. Examination of these spectral data reveals that among the *N*-unsubstituted aziridines (**1** and **2**) the CH protons of the *cis* isomer absorb at lower field than those of the *trans* isomer. The reverse holds true for the *N*-alkylaziridines (**3** and **4**). Another interesting phenomenon is that *N*-alkylation causes an upfield shift in the *cis* series (**2**→**4**) but not in the *trans* series.

The n.m.r. spectrum of *trans*-2,3-diphenylaziridine (**1**) was measured recently by Lattes and coworkers,[26] who were able to show that in anhydrous conditions and at sufficiently low temperature the N—H hydrogen exchange and the nitrogen inversion is sufficiently slow, and a well resolved ABX type spectrum

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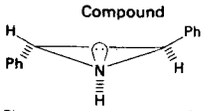
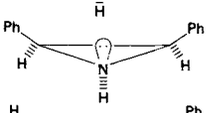
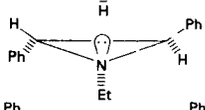
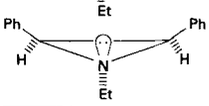
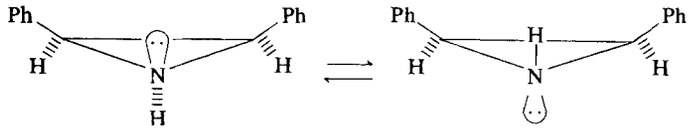
Table 1. N.m.r. spectra of aziridines 1–4[a]

Compound	Solvent	NH	NCH_2	CH	CH_3
	CCl_4	1.22		2.87 s	
1	$CDCl_3$	1.55		3.02 s	
	C_6D_6	1.10		2.79 s	
	CCl_4	1.32		3.39 s	
2	$CDCl_3$	1.56		3.50 s	
	C_6D_6	0.88		2.95 s	
	CCl_4		2.27 m[b]	2.97 br.s	1.01 t
3	$CDCl_3$		2.34 m[b]	3.15 br.s	1.06 t
	C_6D_6		2.26 m[b]	2.99 br.s	1.01 t
	CCl_4		2.60 q	2.69 s	1.26 t
4	$CDCl_3$		2.62 q	2.79 s	1.26 t
	C_6D_6		2.35 q	2.53 s	1.14 t

[a] s = singlet, m = multiplet, br.s = broad singlet; t = triplet.
[b] The CH_2 appears as a multiplet due to magnetic non-equivalence of the two CH_2 protons. Cf.: R. K. Hill and T. H. Chan, *Tetrahedron* **21**, 2015 (1965).

of **1** can be observed. We were also able to obtain a well resolved spectrum of **1** in dry carbon tetrachloride and deuterochloroform. These spectral data of *trans*-2,3-diphenylaziridine are summarized in Table 2.

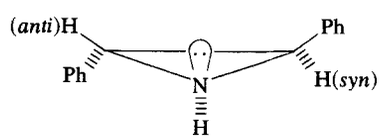
From the aromatic solvent induced shifts (*vide infra*) of aziridine **1** (Tables 2 and 4) it is clear that in this compound the proton *syn* (to N—H) appears at lower field. In contrast to this the *syn* ring proton of *N*-ethyl-*trans*-aziridine (**3**) appears at higher field, as indicated by the low temperature spectral results obtained for this compound. These results are listed in Table 3. *cis*-2,3-Diphenylaziridine (**2**) may exist as the two possible invertomers **2a** and **2b**. Following previous workers we have also found that the aziridine CH



2a **2b**

protons of **2** appear as a sharp singlet at $\delta = 3.39$ in carbon tetrachloride without any special precautions. The measuring of the n.m.r. spectrum under anhydrous conditions, however, gave rise to a doublet centered at $\delta = 3.39$. J(CH,NH) was found to be 9.3 Hz,

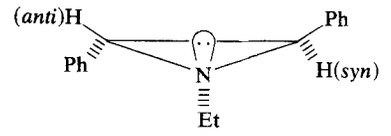
Table 2. N.m.r. spectral data of *trans*-2,3-diphenylaziridine (1) in dry solvents at low temperature



Solvent	temp (°C)	Chemical shift (δ ppm) H *syn*	H *anti*	HCCH	Coupling constant (*J*Hz) HNCH *syn*	HNCH *anti*	Ref.
CCl_4[a]	−23	2.95	2.65	2.3	9	8	26
CCl_4[b]	−25	3.02	2.72	2.3			This work
$CDCl_3$[b]	−37	3.19	2.90	2.3	9	8	This work
C_6H_6[a]	3–5	2.78	2.69	2.3			26

[a] aziridine concentration: 10% wt/vol.
[b] solution containing 0.04 mol fraction of **1**.

Table 3. N.m.r. spectral data of *trans*-1-ethyl-2,3-diphenylaziridine (3) at low temperatures.



Solvent	Temp (°C)	Chemical shift (δ) H *syn*	H *anti*	Coupling Constant (Hz) *J*(HCCH)
CCl_4	−20	2.84	3.08	3.5
$CDCl_3$	−13	2.98	3.36	3.5
C_6D_6	+7	2.79	3.11	3.5

which is in harmony with J(CH, NH) *cis* values found in *N*-unsubstituted aziridines.[26] Irradiation of the NH signal, or addition of D_2O, converted the CH doublet into a singlet. On the basis of this experiment and the large aromatic solvent shift found for **2** (0.44 ppm, see Table 4), we conclude that **2** exists as invertomer **2a**. The same conclusion was reached by Lattes and co-workers on the basis of infrared spectral studies.[27,28]

The n.m.r. spectra of *cis*-1-ethyl-2,3-diphenylaziridine (**4**) measured in all solvents (Table 1) gave sharp, well resolved signals. On the basis of the solvent shifts of **4**, energy considerations of the two possible conformers, and analogies from the literature,[20,29] we assume that **4** exists as the conformer in which the *N*-ethyl group is oriented away from the phenyl rings.

Table 4 summarizes the ASIS data for the aziridines studied. It is seen that the shifts for the *syn* protons are greatly affected by *N*-substitution (cf. **1–3** and **2–4**), whereas the shifts for the *anti* protons are negative both in **1** and **3**. It has been proposed that the benzene molecule is repelled by the nitrogen lone pair and therefore tends to approach solutes with oriented lone pairs from the side of the molecule that is away from the lone pair.[18] It is seen from Table 4 that the magnitude of the ASIS decreases with increasing substitution on the '*syn*' side (*trans* to the lone pair) of the aziridine molecule.

Comparison of the data obtained for the *trans*-aziridines (**1** and **3**) in carbon tetrachloride reveals that *N*-ethylation causes shielding of the *syn* protons ($\Delta\delta_{NEt-NH} = -0.18$ ppm), but deshielding of the *anti* protons ($\Delta\delta_{NEt-NH} = 0.36$ ppm). Much stronger shielding of the *syn* protons ($\Delta\delta_{NEt-NH} = -0.70$ ppm) is observed in the *cis* series (**2** and **4**).

It can also be seen from the data presented that aziridines **1–4** exhibited different solvent shifts when passing from CCl_4 to $CDCl_3$. Since such solvent shifts are usually caused by the formation of charge transfer

Table 4. Aromatic solvent induced shifts of aziridines 1–4

Compound	Δδ (ppm) CCl_4—C_6D_6 H *syn*	H *anti*
1	0.17	−0.04
2	0.44	—
3	0.05	−0.03
4	0.16	—

complexes between solute and solvent molecules, and that the stability of a charge transfer complex would be expected to vary with the basicity of the solute, it was of interest to determine the pK_a values of **1–4**, in order to seek some correlation between pK_a values and the magnitude of the solvent shifts. However, on the basis of the pK_a values obtained (**1**, 4.92; **2**, 4.67; **3**, 5.56; **4**, 4.34 at 25 °C[30]) no simple correlation could be found.

On the basis of the data so far presented, it is impossible to estimate the separate effects of the nitrogen lone pair and of the nitrogen substituent on the chemical shifts of the α-protons. Although the fact that the solvent shift for the *syn* H of compound **3**, $\Delta\delta_{CDCl_3-CCl_4} = 0.14$ ppm, as compared to that for the *anti* H, $\Delta\delta_{CDCl_3-CCl_4} = 0.28$ ppm, gives reason to suspect that neutralization of the lone pair is accompanied by stronger deshielding for the *anti* H (*cis* to the lone pair) than for the *syn* H, a more clear cut experiment was considered necessary.

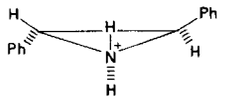
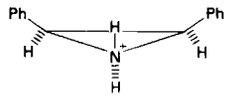
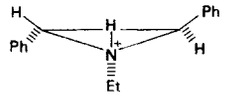
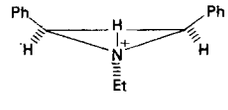
We have therefore recorded the n.m.r. spectra of aziridines **1–4** in deuterochloroform/trifluoroacetic acid (TFA).[31] Aziridines are known to undergo ring opening reactions under the influence of acids.[32] In all cases we have recovered the unchanged aziridine from the $CDCl_3$/TFA solution after measuring the spectra, to ensure that no ring opening occured during the experiment. The n.m.r. spectra of the protonated aziridines are listed in Table 5.

Examination of the data in Table 5 reveals that the chemical shifts of the CH protons of protonated **1** and **2** are quite close to each other ($\Delta\delta = 0.08$ ppm), as are the chemical shifts of the CH proton of protonated **4** and the *syn* proton of **3** ($\Delta\delta = 0.06$ ppm). This indicates that the steric relationship between the aziridine ring CH and the phenyl group located on the adjacent carbon has little influence on the chemical shift of that proton. However, the most significant result of the protonation experiments, in our view, is the large $\Delta\delta_{anti-syn}$ ($= 0.55$ ppm) obtained for protonated **3** as compared to 0.24 ppm (in CCl_4 see Table 3) for the free base. The 0.31 ppm difference between the values is attributed to the shielding exerted by the lone pair on a *cis* CH in an *N*-alkyl aziridine. It is in excellent agreement with the extent of shielding of a ring proton *cis* to a lone pair in *N*-unsubstituted aziridines which is found to be 0.30 ppm (Table 2) for **1** and 0.33 ppm for the parent ethylenimine.[23] While it is generally desirable to compare chemical shifts in the same solvent, the use of data obtained in carbon tetrachloride for the free bases seemed desirable because of lack of protonation in this solvent. On the other hand, the protonation experiments could not be carried out in carbon tetrachloride due to insolubility of the aziridinium salts. However, the data obtained for the free bases in chloroform show the same trends as those in carbon tetrachloride.

It has been pointed out in the introduction to this paper that the effect of the nitrogen lone pair on the chemical shifts of the aziridine ring proton seems to change unaccountably on passing from *N*-unsubstituted to *N*-alkylaziridines. It now seems possible to reconcile these seemingly conflicting results on the basis of our observations, if one assumes that a lone pair in an aziridine *always* exerts a shielding influence on a *cis* hydrogen, in *N*-unsubstituted as well as *N*-alkylaziridines. In *N*-unsubstituted aziridines the C—H *cis* to the lone pair indeed appears at higher field. In *N*-alkylaziridines the *N*-alkyl group (except *N*-*t*-butyl[19b]) exerts a shielding effect on the *syn* hydrogens (*trans* to the lone pair), but a deshielding effect on the *anti* hydrogens, shifting the *anti* hydrogens to lower field than the *syn* hydrogens.

This effect predominates to such an extent that it outweighs the deshielding influence of electron withdrawing groups α to the hydrogens. Recently we have observed[8] in a series of bicyclic aziridines with a bridgehead nitrogen that CH protons *cis* to the *N*-alkyl group, even when situated α to a cyano or carbethoxy group, appear at higher field than hydrogens without any adjacent deshielding group but that are situated *trans* to the *N*-alkyl group.

Table 5. Chemical shifts and coupling constants of the CH protons of protonated aziridines 1–4 in $CDCl_3$-TFA[a]

	Compound	Chemical shift (ppm)	Coupling constant (Hz)
1		4.80 broad	
2		4.72 dd	*J*(CH, NH)*cis* = 7.0, *J*(CH, NH)*trans* = 5.5
3		*anti*[b] 5.13 dd *syn*[b] 4.58 dd	*J*(CH, NH)*cis* = 7.0, *J*(CH, CH) = 7.0 *J*(CH, NH)*trans* = 5.0 *J*(CH, CH) = 7.0
4		4.52 d	*J*(CH, NH)*trans* = 5.5

[a] d = doublet; dd = double doublet.
[b] The assignment of these signals to *anti* and *syn* protons in protonated **3** is based on the *J*(CH, NH) values and chemical shifts, and on comparison with those of protonated **2** and **4**.

EXPERIMENTAL

N.m.r. spectra were measured by a JEOL C 60H spectrometer. Chemical shifts are given in ppm downfield from TMS which was used as internal standard. The high resolution mass spectra were measured by a MAT CH-5 spectrometer using a double focusing attachment. The pK_a values were measured by the use of a Radiometer pH meter 26.

trans-2,3-Diphenylaziridine (**1**) and *cis*-2,3-diphenylaziridine (**2**) were prepared according to Hassner and co-workers.[25]

trans-1-Ethyl-2,3-diphenylaziridine (**3**). A solution of 0.3 mmol triethyloxonium fluoroborate in 1 ml dry dichloromethane was injected into a solution of 98 mg (0.05 mmol) of *trans*-2,3-diphenylaziridine in 2 ml of dry dichloromethane placed, under nitrogen, in a small round bottomed flask equipped with an injection side arm covered with a serum cap. The reaction mixture was kept at 0 °C for 30 min. After removal of the solvent the residue was treated with ether. The residue from the ether extract was separated by preparative thick layer chromatography first on silica gel (benzene) followed by further purification of the product on alumina plates benzene–light petroleum 40–60 °C 1:1, producing an oily product. Mol. wt Calc. for $C_{16}H_{17}N$: 223.136. Found: 223.133 ± 0.004.

cis-1-Ethyl-2,3-diphenylaziridine (**4**) was prepared by treatment of **2** with triethyloxonium fluoroborate as described for the preparation of **3**. Separation of the reaction mixture by preparative thick layer chromatography on silica gel (benzene) yielded the product **4** in 80% yield, m.p. 75–76 °C from hexane. Mol. wt Calc. for $C_{16}H_{17}N$: 223.136. Found: 223.137 ± 0.004.

Preparation of samples for n.m.r. spectra

(a) All spectral data given in this work were determined using solutions containing 0.04 mol fraction of the aziridine, except where otherwise stated.

(b) The sample for the measurement of spectra under anhydrous conditions was prepared by using solvents which were predried over alumina, activity I, which was dried *in vacuo* at 150 °C for 1 day. After dissolution of the aziridine, the solution was further dried for 1 day over a fresh sample of alumina. The n.m.r. tubes were dried at 150 °C and were allowed to cool in a desiccator over phosphorus pentoxide.

(c) Samples for the protonation experiments were prepared by addition of 0.1 ml TFA (about two equivalents) to a cooled solution of the aziridine in deuterochloroform. The n.m.r. spectrum of the sample was then recorded. Further portions of 0.1 ml TFA were added until the addition of the last portion did not cause a change in the spectrum. The data given were recorded in the presence of approximately eight-fold excess of TFA over aziridine. After recording the spectra, the aziridines were recovered by basification of the solutions, followed by ether extraction and the usual workup.

Measurement of pK_a values of aziridines 1–4

Approximately 50 mmoles of the aziridine dissolved in 20 ml methanol and 12.5 ml water were introduced into a beaker fitted with a glass electrode, a calomel reference electrode, a stirrer and a rubber tube through which 0.1 N HCl was injected. The pH was read on a Radiometer pH meter 26 using an expanded scale. The meter was calibrated using a Radiometer pH 9.22 buffer. Titration was continued until approximately the calculated volume of acid was added. The experiments were carried out at 25 °C.

The pH was read after each round, the pK_a values were calculated at the end of rounds 4, 8, 12, 16, 20, 24, 28 and 32 by fitting the theoretical curve to the experimental values using an 'Olivetti programma 101' calculator. The pK_a obtained was a mean value of the pK_a's at rounds 8, 12, 16, 20 and 24. (1 round = $\frac{1}{64}$ ml 0.1 N HCl)

Correction of the pK_a for the presence of methanol was carried out as follows. The pH of a buffer 9.22/water 1:1 solution was found to be 9.185. The pH of a buffer 9.22/methanol/water 1:$\frac{8}{13}$:$\frac{5}{13}$ solution was found to be 9.340. Hence the corrected values (see discussion) were obtained by the subtraction of 0.155 (9.340–9.185) from the uncorrected mean pK_a values.

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