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AN NMR INVESTIGATION OF THE GEOMETRICAL ISOMERISM IN THE ANIONS OF AROMATIC AMINO COMPOUNDS†

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The nmr spectra of the anions of 2-, 6- and 8-aminopurines, 2- and 4-aminopyrimidines, 3- and 4-aminopyridazines, aminopyrazine, 2-aminopyridine, aniline and its p-methyl derivative in liquid ammonia containing potassium amide at low temperature show the presence of two geometrical isomers, due to restricted rotation of the deprotonated amino group. The occurrence of coalescence has been observed with aminopyrazine and p-methylaniline.

Introduction

The phenomenon of hindered rotation in N-substituted imines is known for many years; it even occurs in diphenyl ketimine, although only at very low temperature[1]. Recently, geometrical isomers of aromatic amines were found to exist at low temperatures[2-7]. This observation evidences the contribution of mesomeric structures in which the carbon-nitrogen bond has double bond character. Based on these results one has to expect the occurrence of geometrical isomerism in the anions of aromatic amines, since delocalization of the negative charge in the aromatic ring will enhance the double bond character of the carbon-nitrogen bond considerably. This has indeed been observed for the anion of N-methyl-2,4,6-trinitroaniline in dimethyl sulfoxide (as indicated by the non-equivalence of H-3 and H-5)[8], the anion of 2-(methylamino) pyrimidine (non-equivalence of H-4 and H-6)[9] and in the dianion of adenine (in which two different NH protons are present)[10].

However, ^1H nmr spectra of aminopyrazine[11], 2-aminopyridine[11] and several anilines[12] in liquid ammonia containing potassium amide do not indicate the existence of separate isomers. It is possible that in the strong basic medium a fast isomerization takes place, preventing the detection of the separate geometrical isomers. The non-equivalence of hydrogen atoms in a substituent has been found for the $CH_2^{\ominus}$ group in the dianion of 6-methylpurine[13] and in the anions of 4-methylpyrimidine[14], 4-methyl-5-bromopyrimidine[14], 2-methylpyridine[11] and methylpyrazine[11], generated in liquid ammonia containing potassium amide.

Results and Discussion

A. Aminopurines

The ^1H nmr spectrum of a solution of adenine in liquid ammonia containing potassium amide shows three sets of two signals (Table I) of which two sets are assigned to aromatic hydrogens and the set of two broad signals to the NH$^-$ group[10].

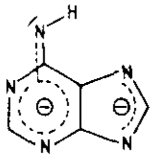
The assignments of two sets of aromatic hydrogens are made by comparison of the ^{1}H nmr spectrum with that of 8-deuterioadenine under identical conditions.

Table I. ^{1}H nmr data of the dianions of some aminopurines in liquid ammonia containing potassium amide at -50°C[a]

Dianion of	H-2	H-6	H-8	N-H	isomer distribution
adenine (1)	7.53	-	7.37	4.59	65%
	7.64	-	7.34	4.93	35%
8-chloroadenine (3)	7.42	-	-	4.49	65%
	7.53	-	-	4.75	35%
2-aminopurine (4)	-	7.94	7.38	3.83	75%
	-	8.00	7.38	3.69	25%
8-aminopurine (5)	7.18[b]	7.63[b]	-	3.90	-

[a] Chemical shifts in ppm relative to Me_4Si (δ= 0 ppm)

[b] These assignments can also be interchanged



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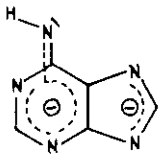

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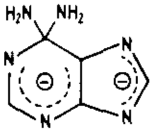

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The spectra can only be explained if one assumes the presence of dianion 1 (obtained by deprotonation of both the N^9- H and the NH_2 group) in two distinct geometrical isomers (structures 1a and 1b). Due to delocalization of the negative charge on the amino nitrogen atom over the purine ring the double bond character of the C_6- N bond is enhanced, resulting in restricted rotation and the formation of 1a and 1b. The presence of both isomers shows that in this basic medium the isomerization and proton exchange are slow (on the nmr time scale). From the ^{1}H nmr data it could be established that the two geometrical isomers 1a and 1b are present in the ratio 65:35. Which isomer is the more abundant one has not been determined. This ratio is found to be independent of the potassium amide concentration, ranging from 1.5 to 4 equivalents.

The existence of the two geometrical isomers 1a and 1b is confirmed by ^{13}C nmr spectroscopy (Table II). In the decoupled spectrum of a solution of adenine in KNH_2/NH_3 all signals except the ones for C-2 and C-8 appear double. All signals can be assigned unambiguously by comparison of the spectrum with that of deuterioadenine and with literature data.

Table II. ^{13}C nmr data of the dianion of adenine (1) in liquid ammonia containing potassium amide at -50°C[a]

Dianion of	C-2	C-4	C-5	C-6	C-8
adenine (1)	151.6	157.6[b]	123.4[b]	165.1[b]	146.4
	151.6	156.2	124.3	167.7	146.4

[a] Chemical shifts in ppm relative to Me_4Si (δ= 0 ppm)

[b] More abundant isomer

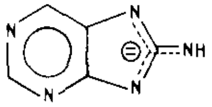
That the double signals for C-2 as well as for C-8 coincide is proven by selective decoupling. Since the ^1H nmr spectral data had shown the isomer ratio 65:35, the set of ^{13}C signals with the greater intensities is assigned to the more abundant isomer.

An attempt to confirm the geometrical isomerism by measuring the coalescence of the ^1H nmr signals with increasing temperature, failed. On allowing the temperature of the solution of the dianion to rise from -50°C up to 15°C in a sealed tube the signals are broadened and the isomer ratio (calculated from the ^1H nmr spectrum) changes from 65:35 to 50:50. We could not measure an average spectrum.

We have ascertained that the signals observed in the nmr spectra are not originated from the σ-adduct 2, possibly formed by attack of the amide ion on C-6 in the monoanion of adenine. Adduct formation in purines is known to occur at position 6[10,13] and adduct formation at a position already occupied by an amino group cannot be excluded either (for example the ring transformation of 4-amino-2-bromoquinoline into 4-amino-2-methylquinazoline[15]). Therefore we reacted adenine with ^{15}N labelled potassium amide. If adduct 2 should be formed, it would lead to incorporation of ^{15}N in recovered adenine. Since in our experiment no ^{15}N label could be found in the recovered adenine (mass spectrometry), we exclude the intermediacy of adduct 2.

The dianion of 8-chloroadenine (3) and that of 2-aminopurine (4) also show the presence of two isomers in the ^1H nmr spectrum (Table I). For 3 the isomer ratio (65:35) is the same as for adenine; for 4 a ratio of 75:25 was found. The signal assignment of 4 was based on comparison of the signals with those of 2-amino-8-deuteriopurine.

No double signals are detected in the ^{1}H nmr spectrum of the dianion of 8-aminopurine (5). That we are dealing with a dianion and not with a monoanion was shown by integration, indicating the presence of only one aminohydrogen. This result does not justify the conclusion that only one geometrical isomer is present, since the symmetry in the imidazole part of this dianion may lead to spectral coincidence of both isomers.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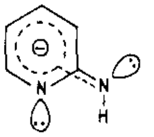
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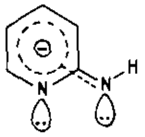
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B. Aminopyrazine, 2-aminopyridine, aminopyridazines and aminopyrimidines

The ^{1}H nmr spectra of the anion of aminopyrazine (6)as well as of 2-aminopyridine (7) in liquid ammonia containing potassium amide were previously reported without specifying the temperature at which the spectra were measured[11]. The occurrence of geometrical isomers was not mentioned. We observed, however, that when the ^{1}H nmr spectra of the anions of these amino compounds are measured at -50°C, the anion 6 exists as a mixture of two geometrical isomers in a ratio of 65:35.

Table III. ^{1}H nmr data of the anions of some monocyclic aromatic amines in liquid ammonia containing potassium amide at -50°C[a]

Anion of	H-2	H-3	H-4	H-5	H-6	N-H	isomer distribution
aminopyrazine (6)	-	7.25	-	6.57	7.17	4.47	65%
	-	7.14	-	6.63	7.31	4.25	35%
2-aminopyridine (7)	-	5.73	6.70	5.49	7.45	3.90	55%
	-	5.82	6.62	5.42	7.32	4.22	45%
3-amino-6-methyl-pyridazine (8)	-	-	6.12	6.40	-	4.30	70%
	-	-	6.09	6.42	-	3.72	30%
4-aminopyridazine (9)	-	7.76[b]	-	5.88[b]	7.62[b]	4.45	50%
	-	7.90[b]	-	5.72[b]	7.54[b]	4.45	50%
2-amino-4-phenyl-pyrimidine (10)	-	-	-	6.10	7.75	4.70	50%
	-	-	-	6.10	7.75	4.76	50%
4-aminopyrimidine (11)	7.67	-	-	5.81	7.24	4.80	70%
	7.82	-	-	5.78	7.24	4.74	30%
4-methylaniline (12)	5.80	6.40	-	6.32	5.94	2.92	c
2,4-dimethylaniline (13)	-	6.46	-	6.43	6.05	2.70	85%
	-	d	-	6.28	5.84	3.09	15%

[a] Chemical shifts in ppm relative to Me_4Si. (δ = 0 ppm)

[b] In these cases it cannot be decided which signals belong to one isomer.

[c] Symmetric molecule.

[d] Not observable.

Raising the temperature gradually changes this ratio to 50:50 at 0°C and finally results in incomplete coalescence at +20°C. Cooling to -50°C restores the 65:35 ratio, proving that the isomers are in thermodynamic equilibrium. Comparison of these results with those of adenine, where at room temperature no coalescence is observed for the dianion of adenine (1) (see section A), indicates that the stabilization of the negative charge in 6 is less than in 1.

The anion of 2-aminopyridine (7) is also present in two geometrical isomers at -50°C (ratio 55:45). The ratio is independent of the concentration of 7 (0.2-2mmol/ml) and of potassium amide (1.5-10 equivalents). As no isomerism was reported in the literature[11], it is clear that the ^{1}H nmr spectra must have been measured above the coalescence temperature. The almost equal concentration of both isomers shows that stabilization of the syn-isomer 7a via intramolecular hydrogen bonding[5] and destabilization of the anti-isomer 7b by repulsion between the two electron pairs[16] is unimportant.

The ^{1}H nmr spectrum of the anion of 3-amino-6-methylpyridazine (8) also shows the presence of two geometrical isomers in a ratio of 70:30; thus the preference for one isomer is slightly greater (Table III) than in 7. The methyl group appears as a singlet in each isomer and is therefore probably not deprotonated[11,13,14].

The anion of 4-aminopyridazine (9) is also present in two geometrical forms (Table III). The isomer distribution is 50:50, being the same as for the symmetrical anion of 4-aminopyridine. Thus, the ratio does not change, when a nitrogen atom is introduced in the meta position of the anion of 4-aminopyridine.

As already indicated in the introduction, geometrical isomerism has been observed for the anion of 2-(methylamino) pyrimidine[1]. In the present study we find indications for the occurrence of two isomers for the anion of 2-amino-4-phenylpyrimidine (10)(Table III). The spectrum shows two separate NH signals, and two different signals for H-5 (not for H-6). The isomer distribution is 50:50. The results in Table III show further that also for the anion of 4-aminopyrimidine (11) geometrical isomerism exists; the ratio is 70:30.

C. Anilines

The anions of aniline and methylanilines lack the stabilizing ring nitrogens, and therefore may be expected to have a lower rotation barrier, due to a decreased double bond character of the carbon-nitrogen bond. Hence, the coalescence temperature should be lower than in the case of aminopyrazine. In the literature no indication is available for the occurrence of geometrical isomers in the spectra of aniline and methylanilines in liquid ammonia containg potassium amide at +31°C [12].

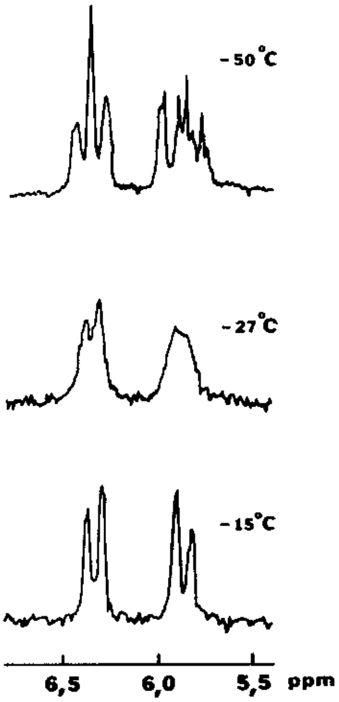

Figure. Part of the ^{1}H nmr spectrum of 12 at different temperatures

However, in our study we find that at -50°C the anions of aniline and 4-methylaniline (12) show the presence of geometrical isomers (Table III). As both compounds are symmetric, restricted rotation will be reflected in the non-equivalence of H-2 and H-6 and of H-3 and H-5, but not in the N-H signal. For 12 these different signals for all four ring hydrogen atoms are clearly observed. The simplicity of the spectrum makes this compound suitable for an attempt to measure coalescence.

Indeed, on raising the temperature from -50°C to -27°C coalescence takes place, and at -15°C the spectrum consists of two doublets, representing both equivalent ortho and meta hydrogens (Figure).

The aromatic signals in the spectrum of the anion of aniline at -50°C cannot be simply interpreted, but their complexity suggests non-equivalence of both the ortho and the meta-hydrogen atoms, and hence restricted rotation of the carbon-nitrogen bond.

The anion of 2,4-dimethylaniline (13) too is found to exist in two isomers, in a ratio of 85:15. This indicates that introduction of a methyl group ortho to the amino function has a strong influence on the isomer ratio.

These data show that even in aniline anions, in which no stabilizing substituents or ring nitrogen atoms are present, geometrical isomerism can be observed at -50°C.

Experimental Section

^{13}C and ^{1}H nmr spectra were obtained with a Varian XL-100-15 spectrometer, equipped with a Varian 620/L16K computer. When measuring in $CDCl_3$, internal Me_4Si was used as standard. When measuring in liquid ammonia the sample temperature was ca.-50°C. Some samples were also measured at higher temperature in sealed tubes. For ^{1}H nmr spectra NH_3 was used as standard. The spectra were converted to the Me_4Si scale by adding 0.95 ppm. For ^{13}C nmr spectra Me_3N was used as internal standard. Adding 47.5 ppm converts these spectra to the Me_4Si scale.

Typical ^{13}C nmr spectral parameters were as follows : spectral width 5120 Hz, acquisition time 0.8 s, pulse delay 0-1.2 s, pulse width 10 μs.

Both ^{1}H and ^{13}C nmr spectra were usually measured on solutions of 0.4-0.6 mmol/ml with 4 equivalents of potassium amide. Isomer ratios were determined by integration of appropriate signals. Mass spectra and ^{15}N contents were determined on an AEI MS-902 mass spectrometer.

6-Amino-8-chloropurine[17], 8-aminopurine[18], 3-amino-6-methylpyridazine[19], 4-aminopyridazine[20], 2-amino-4-phenylpyrimidine[21] and 4-aminopyrimidine[22] were prepared according to the literature. All other compounds were purchased.

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References

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