Nuclear Magnetic Resonance Investigation of Geometrical Isomerism in the Anions of (Methylamino)pyridines. Assignment of the Syn and Anti Isomers

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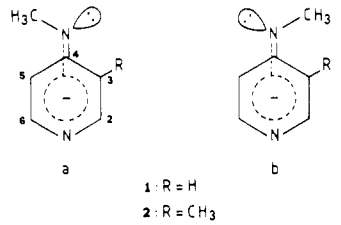
The ^1H and ^{13}C NMR spectra of the anions of 4-, 3-, and 2-(methylamino)pyridine and some of their *o*-methyl-substituted derivatives in liquid ammonia containing potassium amide at -50 °C are measured and assigned to the syn and anti isomers. The position of the signals of the *o*-hydrogen and carbon atoms is discussed.

In the literature the ^1H NMR spectra of the anions of aminopyrazine,[1] 2-aminopyridine,[1] and several anilines[2] at 25–31 °C are reported. In these studies the existence of geometrical isomers was not mentioned. However, geometrical isomerism has been noticed in the anion of 2,4,6-trinitroaniline,[3] and in our own studies evidence for the occurrence of syn and anti isomers of the anions of amino aza aromatics (2-aminopyridine, 2- and 4-aminopyrimidines, aminopyrazine, 3- and 4-aminopyridazine, and 2-, 6-, and 8-aminopurines) has also been obtained.[4-6]

This phenomenon has been ascribed to an enhanced double bond character of the exocyclic carbon–nitrogen bond, leading to restricted rotation.[4,5] In aniline and methylanilines restricted rotation has been found at -50 °C.[4] It has been reported that the anion of 2-(methylamino)pyrimidine also shows geometrical isomerism, as appears by the nonequivalency of H-4 and H-6.[5] In order to investigate the generality of this phenomenon in (methylamino)aza heteroarenes we measured ^1H and ^{13}C NMR spectra of the anions of 4-, 3-, and 2-(methylamino)-pyridine. Since the presence of a methyl substituent ortho to the methylamino group has an important influence upon the syn–anti ratio, which can provide us with an important clue to syn–anti assignment, we included in our study the NMR spectroscopy of the anions of 3-methyl-4-(methylamino)-, 4-methyl-3-(methylamino)-, and 3-methyl-2-(methylamino)pyridine.

Results and Discussion

(A) 4-(Methylamino)pyridines. The ^1H NMR spectrum of the anion of 4-(methylamino)pyridine (1) measured in liquid ammonia containing potassium amide at -50 °C shows, just as the neutral compound,[7] geometrical isomerism. This phenomenon is revealed by the appearance of separate signals for H-3 and H-5 and for H-2 and H-6, showing that these hydrogens are not identical.



The ^{13}C NMR spectrum also shows separate signals for both C-3 and C-5 and for C-2 and C-6 carbon atoms. In order to be able to assign the ^1H NMR signals to the respective atoms in each of the isomers **a** and **b**, we prepared the anion of 3-methyl-4-(methylamino)pyridine (**2**) and compared the spectra of **1** and **2**. We observed that the ^1H NMR spectrum of **2** consists only of a singlet (H-2) and two doublets (H-5 and H-6, Table I); there is no indication for the existence of two isomeric forms. It can be questioned whether this is due to the fact that this spectrum is an average of the two structures, isomerizing fast on the NMR time scale. We feel, however, that this is not probable on the following grounds: (i) in 3-methyl-4-(dimethylamino)pyridine the mesomeric interaction between the pyridine ring and the dimethylamino group is not seriously hindered by an *o*-methyl substituent;[8] (ii) the related compound 2-methyl-4-nitro-*N*-methylaniline is present in only *one* form at temperatures between -150 and -50 °C[7]; (iii) 4-(methylamino)pyridine (thus not the anion) undergoes coalescence at about -60 °C.

Since in our study we are dealing with anions, we have to expect higher coalescence temperatures; therefore, the two isomeric forms **2a** and **2b** should be observable at the temperature we used (-50 °C). In fact, the temperature range between -80 and +10 °C showed only one set of NMR signals. This leads to the conclusion that the spectrum of anion **2** measured under these conditions can only be explained by the presence of *one* isomer, i.e., the one in which the methyl of the methylamino group and the *o*-methyl are directed away from each other, due to repulsion (structure **2a**).

In the ^1H NMR spectrum of anion **1** the signals of H-3 and H-5 are well separated (δ 5.89 and 5.60 relative to Me_4Si, Table I), and the chemical shift of one of these is very close to that of H-5 in anion **2a** (5.62 ppm). The chemical shifts of the two signals of H-2 and H-6 of **1** (7.22 and 7.43 ppm) are also very similar to those of H-2 and H-6 of **2a** (7.25 annd 7.47 ppm). These close resemblances make it evident to assign the signals in the spectrum of **1** as indicated in Table I. From this result it appears that the *o*-hydrogen atom syn oriented to the nitrogen lone pair (H-3) resonates more downfield than the *anti*-hydrogen (H-5). It should be noted that we have represented the formulas throughout this paper with an sp^2 lone pair, with

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Table I. ^{1}H NMR Data of the Anions of *N*-(Methylamino)pyridines in Liquid Ammonia Containing Potassium Amide at −50 °C[a,b]

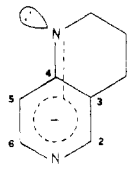
anion of	no.	chemical shift H-2	H-3	H-4	H-5	H-6	NCH_3	isomer distr, %
4-(methylamino)pyridine	1a	7.22	5.89		5.60	7.43	2.54	50:50
3-methyl-4-(methylamino)pyridine[c]	2a	7.25			5.62	7.47	2.66	100
3-(methylamino)pyridine	4a	7.50		5.76	d	d	2.50	80
	4b	7.03		d	d	6.84	2.60	20
4-methyl-3-(methylamino)pyridine[e]	5b	6.95			6.47	6.84	2.70	100
2-(methylamino)pyridine	6a		5.81	6.57	5.35	7.50	2.62	40[g]
	6b		5.58	6.96	5.57	7.57	2.54	60[g]
3-methyl-2-(methylamino)pyridine[f]	7a			6.50	5.35	7.43	2.71	100

[a] Chemical shifts are in parts per million relative to Me_4Si (δ 0). [b] Coupling constants: $J_{2,3}$ = 6 Hz, $J_{2,4}$ = 3 Hz, $J_{3,4}$ = 8-8.5 Hz, $J_{3,5}$ = 1.5-2.5 Hz, $J_{4,5}$ = 6-8 Hz, $J_{4,6}$ = 1.5-2.5 Hz, $J_{5,6}$ = 4-6 Hz. [c] The methyl group at C-3 is found at 1.81 ppm. [d] Present as a complex signal between 6.4 and 6.7 ppm. [e] The methyl group at C-4 is found at 1.87 ppm. [f] The methyl group at C-3 is found at 1.76 ppm. [g] Ratio after equilibration at 25 °C.

a p orbital in conjugation with the pyridine ring. We realize that this is only an approximation of the two electron pairs on the nitrogen, since the negative charge is not fully delocalized in the aromatic ring.

With the assignments of the ^{1}H NMR spectra of **1** and **2a** we are able to interpret the ^{13}C NMR spectra of anion **1** by selective decoupling experiments. The results are that the *o*-hydrogen resonating at lower field (H-3) is bound to the *o*-carbon atom at lower field (C-3) and that the hydrogen at higher field (H-5) is bound to the carbon at higher field (C-5). The same relationship is found for the H-2 and H-6 hydrogens, and the C-2 and C-6 carbon atoms. These results lead to the assignment as given in Table II.

This ^{13}C assignment of anion **1** is confirmed by the spectrum of the anion of the tetrahydro-1,6-naphthyridine **3**,[9] which may be regarded as a model for anion **2b** of

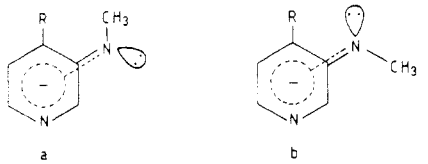


3

3-methyl-4-(methylamino)pyridine in which the *o*-hydrogen (H-5) and the lone pair are in the syn orientation and the methyl groups are directed toward each other. The *o*-carbon atom C-5 in anion **3**, being in a syn orientation to the lone pair, exhibits a downfield shift compared to that in the neutral compound. A downfield shift is also found for C-3 in anion **1a**, being in syn position relative to the nitrogen lone pair.

All results indicate that in anion **1** the *o*-carbon atom in the syn position relative to the lone pair resonates at a lower field than the *o*-carbon in the anti position. Thus, this is in analogy to what has been found for the *o*-hydrogen atoms.

(B) 3-(Methylamino)pyridines. In the ^{1}H NMR spectrum of the anion of 3-(methylamino)pyridine (**4**) H-2



a b

4: R = H
5: R = CH_3

(9) In order to make it easier to compare the data with the other compounds, the numbering of the atoms is chosen as shown in structure 3.

Table II. ^{13}C NMR Data of *N*-(Methylamino)pyridines in $CDCl_3$ at 35 °C and of Their Anions in Liquid Ammonia Containing Potassium Amide at −50 °C[a]

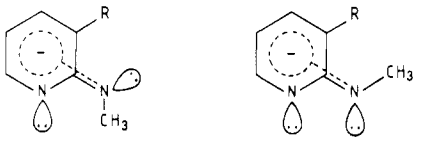
compd	chemical shift C-2	C-3	C-4	C-5	C-6	NCH_3
4-(Methylamino)pyridine						
neutral	149.8	107.3	154.9	107.3	149.8	29.2
anion **1a**	146.1	115.0	163.0	102.6	149.5	36.5
1,2,3,4-Tetrahydro-1,6-naphthyridine[9]						
neutral	137.7[b]	117.7	156.8	108.6	137.3[b]	
anion **3**	146.0	c	c	110.6	146.0	
3-(Methylamino)pyridine						
neutral	135.5	146.0	118.1	124.0	137.7	30.0
anion **4a**	143.6	159.2	107.4	124.8	122.6	37.3
anion **4b**	129.5	c	123.0[b]	122.3[b]	125.1[b]	37.3
4-Methyl-3-(methylamino)pyridine						
neutral[d]	130.0	144.7	132.2	125.1	137.3	30.4
anion **5b**[e]	127.0	156.3	130.2	122.7	124.5	37.1
2-(Methylamino)pyridine						
neutral	160.0	106.3	137.6	112.7	148.2	29.0
anion **6a**	166.7	114.5	132.2	99.1	149.1	35.5
anion **6b**	168.6	102.0	136.2	100.1	149.6	36.6

[a] Chemical shifts in parts per million relative to Me_4Si (δ 0). [b] These signals may also be interchanged. [c] These signals could not be observed. [d] The methyl group at C-4 is found at 17.2 ppm. [e] The methyl group at C-4 is found at 19.2 ppm.

appears as two well-separated signals (7.50 and 7.03 ppm, Table I); only one distinct signal for H-4 is observed at 5.76 ppm. Integration shows that this signal belongs to the same isomer as the H-2 signal at 7.50 ppm. This isomer comprises 80% of the mixture (calculated from the H-2 signals), and the percentage is independent of the temperature (varied from −50 to +20 °C). Unfortunately, we could not assign the signals in the spectrum between 6.4 and 6.7 ppm due to its complexity. Combined with the data from the spectrum of the anion of 4-methyl-3-(methylamino)pyridine (**5**), being present only in conformation **5b** (for the same reasons as mentioned in section A for anion **2**), we were able to assign the observed signals of **4**. The chemical shifts of the H-2 and H-6 signals of **5b** (6.95 and 6.84 ppm, respectively) are very close to the corresponding signals of the minor isomer of **4** (7.03 and 6.84 ppm, Table I). Hence the less abundant isomer should have structure **4b**. This means that *o*-hydrogen H-2 in anion **4a**, being in a syn orientation with respect to the nitrogen lone pair, is less shielded than H-2 in **4b** (anti); also, H-4 in a syn orientation is found more downfield (between 6.4 and 6.7 ppm, anion **4b**) than H-4 in **4a**. This is in accordance with the results in section A for anion **1**.

In the ^{13}C NMR spectra the resonance line of C-2 in anion **5b** at 127.0 ppm is close to that of C-2 in **4b** (129.5 ppm). From selective decoupling experiments with **4** it became clear that the lower field *o*-hydrogens (H-2 in **4a** and H-4 in **4b**) are bound to the downfield *o*-carbons C-2 and C-4, respectively. Thus, the *o*-carbon atom C-2 which is in the syn position to the nitrogen lone pair resonates at lower field than C-2 in the anti position; for C-4 the same relationship is found. These results are in agreement with those found for anion **1** (see section A).

(C) 2-(Methylamino)pyridines. In the NMR spectra of the anion of 2-(methylamino)pyridine (**6**) again two



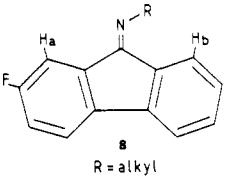
isomers can be observed. The ratio of these isomers is found to vary between 60:40 and 40:60 at −50 °C. When the temperature was allowed to rise from −50 to +25 °C (followed by measurement of the NMR spectrum at −45 °C), a reproducible ratio was found (40:60). Apparently we are dealing with a change from a kinetic distribution to the thermodynamic equilibrium.

For the assignment of the spectra of the thermodynamically controlled mixture we applied the same criteria as applied in sections A and B. The ^1H NMR spectrum of the minor isomer is similar to that of the anion of 3-methyl-2-(methylamino)pyridine (**7**, Table I), being expected to exist in conformation **7a** only. Thus, the minor isomer has conformation **6a**, and the more favored structure is **6b**. The predominance of **6b** is unexpected since repulsion of the electron pairs on the NCH_3^- group and on the ring nitrogen would favor the formation of isomer **6a**. The preference for **6** to be present in conformation **6b** may be caused by complex formation between the potassium cation and the electron pairs of **6b**. In order to establish whether complexation is operative, we added 18-crown-6 ether, which is effective in complexation of potassium cations, to the solution. With an increasing concentration of crown ether the signals of **6b** decrease and even disappear in favor of those for **6a**. Furthermore, when instead of potassium amide cesium amide is used as base, a change of the isomeric ratio from 40:60 to 55:45 in favor of conformer **6a** has been observed. These results suggest that the complexation of **6b** with the potassium cation is the dominating factor in determining the isomer distribution. The larger size of the cesium ion makes this complexation less efficient. The preferred formation of **6a** under kinetic control is not due to a preference of the neutral compound for a conformation like **6a**, because a solution of 2-(methylamino)pyridine in methanol does not show isomerism on being cooled to −110 °C.

In the major isomer **6b**, H-3 (anti to the lone pair) is more shielded than in **6a**. As concluded from selective decoupling experiments in the ^{13}C NMR spectrum, the resonance of C-3 syn to the lone pair (**6a**) is at lower field (114.5 ppm) than that in the anti position (102.0 ppm). This is in agreement with the results obtained with anions **1** and **4** (see sections A and B).

Conclusion

In the foregoing we demonstrated that in all three isomeric *N*-(methylamino)pyridine anions the *o*-hydrogen syn oriented to the amino lone pair is less shielded than that in the anti position. The *syn*-hydrogen is thus found at a lower field than the *anti*-hydrogen. The same effect has been reported for aromatic hydrogens in arylketimines[10,11] and in fluorene derivatives **8**.[12] In the latter



compounds assignments were based on the H–F coupling. The difference between the chemical shifts of H_a and H_b in **8** can be as large as 1.3 ppm, with H_a more downfield.[12] Also in all three *N*-(methylamino)pyridine anions the *o*-carbon in the anti orientation relative to the lone pair resonates at higher field. This upfield shift may be due to steric compression by the *N*-methyl group.[11,13,14] These experimental results confirm the theoretical calculations which Lunazzi et al. used to assign the *o*-carbon atoms in *N*-methylaniline.[15] This neutral compound exists in two isomeric forms at −130 °C. For the *m*-carbon atoms was found that the carbon on the *same* side of the molecule as the *N*-methyl group was associated with the lower field absorption. This was confirmed by our experiments.

Experimental Section

The procedures followed to obtain the ^1H and ^{13}C NMR spectra have been described previously.[4] All compounds were synthesized according to known procedures [4-(methylamino)pyridine,[16] 3-methyl-4-(methylamino)pyridine,[17] 1,2,3,4-tetrahydro-1,6-naphthyridine,[18] 3-(methylamino)pyridine,[19] 4-methyl-3-(methylamino)pyridine,[20] 2-(methylamino)pyridine,[16] and 3-methyl-2-(methylamino)pyridine[21]].

Acknowledgment. We are indebted to all those who synthesized the compounds used in this study, to Dr. M. J. A. de Bie (State University Utrecht) and Dr. J. F. J. Engbersen for helpful discussions, and to Mr. M. van Dijk for his assistance.

Registry No. 1a, 77862-17-0; **2a**, 77862-18-1; **3**, 77862-19-2; **4a/4b**, 77862-20-5; **5b**, 77862-21-6; **6a/6b**, 77862-22-7; **7a**, 77862-23-8; 4-(methylamino)pyridine, 1121-58-0; 1,2,3,4-tetrahydro-1,6-naphthyridine, 13623-84-2; 3-(methylamino)pyridine, 18364-47-1; 4-methyl-3-(methylamino)pyridine, 77862-24-9; 2-(methylamino)-pyridine, 4597-87-9.

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