voor mijn vader en moeder

Promotor: dr.H.C.van der Plas, hoogleraar in de organische scheikunde

J. BREUKER

THE CHICHIBABIN AMINATION OF DIAZINES
GEOMETRICAL ISOMERISM IN ANIONS OF AROMATIC AMINES

Proefschrift
ter verkrijging van de graad van
doctor in de landbouwwetenschappen,
op gezag van de rector magnificus,
dr.C.C.Oosterlee,
hoogleraar in de veeteeltwetenschap,
in het openbaar te verdedigen
op woensdag 28 april 1982
des namiddags te vier uur in de aula
van de Landbouwhogeschool
te Wageningen.

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STELLINGEN

1 In tegenstelling tot wat Pileni beweert vormen de spectrometrische resultaten van Gribble en Bousquet geen bewijs voor het optreden van een intramoleculaire waterstofbrug in *o*-acetylaceetanilide tussen de amide substituent en een aromatisch proton.

M.P.Pileni, Bull.Soc.Chim.Fr. II, 545 (1980)
G.W.Gribble en F.P.Bousquet, Tetrahedron 27, 3785 (1971)

2 De vorming van 2,4-diamino-1,6-naftyridine uit 2,4-dibroom-1,6-naftyridine verloopt niet noodzakelijkerwijze via 2-amino-4-broom-1,6-naftyridine.

W.Czuba, T.Kowalska en P.Kowalski, Pol.J.Chem. 52, 2369 (1978)

3 Tosa en medewerkers suggereren ten onrechte dat de stabiliteit van enkele geïmmobiliseerde microorganismen met carrageen als drager groter is dan met polyacrylamide gel.

T.Tosa et al., Biotechnol.Bioeng. 21, 1697 (1979)

4 Het is onjuist de resonantieintegralen tussen de reactanten in de overgangstoestand van nucleofiele substitutiereacties aan azaaromaten op verschillende posities van het substraat gelijk te stellen.

M.Hirota et al., Bull.Chem.Soc.Japan 52, 1498 (1979)

5 Het optreden van het dieenamine, voorgesteld door Orsini c.s. als tussenproduct in de synthese van methyl 2-oxo-2,3,4,4a,5,6,7,8-octahydronaftaleen-1-carboxylaat uit 1-pyrrolidinylcyclohexeen en Nazarov's reagens, is niet bewezen.

F.Orsini, F.Pelizzoni en R.Destro, Gazz.Chim.It. 108, 693 (1978)

6 De bewering van Desideri c.s., dat *p*-nitrofenyl 2-aminofuro(3,2-b)-pyridine-3-carboxylaat uitsluitend voorkomt in de trieenamine vorm, wordt niet gesteund door de NMR gegevens.

N.Desideri, F.Manna en M.L.Stein, J.Heterocyclic Chem. 18, 1085 (1981)

7 Het is merkwaardig dat Ohno en medewerkers bij de bereiding van 4,4-dideutero-1,4-dihydro-1-propylnicotinamide geen gebruik maken van de door hen zelf aangeprezen methode.

A.Ohno, H.Yamamoto en S.Oka, J.Am.Chem.Soc. 103, 2041 (1981)
T.Okamoto, A.Ohno en S.Oka, Bull.Chem.Soc.Japan 53, 330 (1980)
K.Nakamura, A.Ohno, S.Yasui en S.Oka, Tetrahedron Lett. 4815 (1978)

8 In de huidige problematiek van vuilstortplaatsen getuigt het van een actieve instelling het hoofd in het zand te steken.

9 Het valt te betreuren dat de afmetingen van het toekomstige, grotere model girobetaalkaart debet zal zijn aan vermindering van het gebruikscomfort.

J.Breuker Wageningen, 28 april 1982

The Chichibabin amination of diazines. Geometrical isomerism in anions of aromatic amines.

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Ontwerp omslag: Els Louwerens

CONTENTS

Chapters 2, 5 and 6 have been published in the literature:

Chapter 2: J.Org.Chem. 44, 4677 (1979)
Chapter 5: Heterocycles 15, 1041 (1981)
Chapter 6: J.Org.Chem. 46, 3509 (1981)

Chapter 7 is in the press (J.Org.Chem.)

1 INTRODUCTION

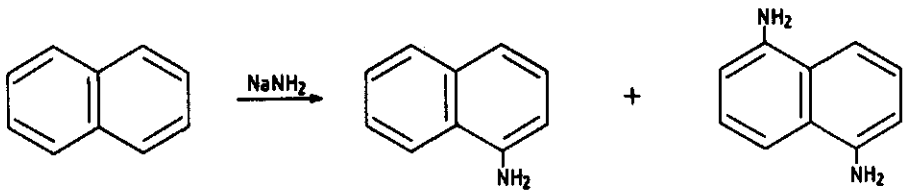
General

The behaviour of aza- and polyazaaromatics in nucleophilic substitution reactions receives considerable attention in the laboratory of Organic Chemistry in Wageningen and elsewhere. Many different reaction pathways for nucleophilic displacements at *ipso*, *cine* and *tele* positions have been discovered, depending on the structure of the substrate and the nature of the attacking nucleophile[1]. Complicated mechanisms are frequently operative in these substitutions, especially if the nucleophile attacks a position different from the one on which the leaving group is present[2]. Ring opening may occur, leading to an acylic intermediate which is able to undergo a recyclization either to the same heterocyclic ring system as present in the starting material[3] or to a different ring system[1]. A ring transformation has then taken place.
In virtually all these studies on nucleophilic substitution to date substrates were involved in which a substituent with obvious leaving group character was present. An investigation on the possible occurrence of a ringopening reaction during replacement of hydrogen in a heteroaromatic system by a nucleophilic group has never been undertaken. In our laboratory the amide anion is commonly used as nitrogen nucleophile in aromatic substitutions and it was therefore decided to focus attention on the mechanism of the replacement of hydrogen by amide. This reaction is known as the Chichibabin amination.

In the course of this investigation we came across the interesting phenomenon that some anions of aromatic amino compounds, present in liquid ammonia containing potassium amide, show geometrical isomerism[4].
In the first part of this introduction a survey is presented of the most important aspects of the Chichibabin amination. In the second part relevant literature on the geometrical isomerism in aryl and heteroarylamines is discussed.

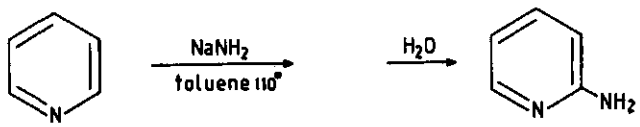
The Chichibabin amination[5]

In 1906 Sachs reported for the first time that hydrogen in an aromatic system can be replaced by an amino group if the aromatic substrate is melted with solid sodamide (Scheme 1.1)[6].



Scheme 1.1

Eight years later the Russian chemist Chichibabin (or Tschitschibabin) found that milder conditions could be applied for the amination of a heteroaromatic compound as demonstrated by the preparation of 2-aminopyridine by refluxing pyridine with sodamide in toluene (Scheme 1.2)[7].



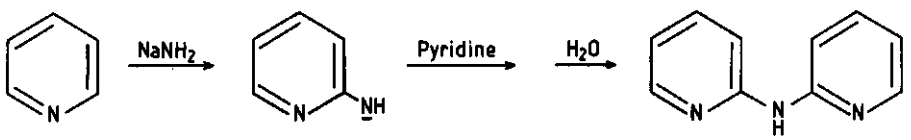
Scheme 1.2

The substitution of a hydrogen atom in an aromatic heterocycle by an amino group is widely known as the Chichibabin amination. Since its discovery this reaction has attracted the attention of many chemists, and reviews have appeared dealing with the preparative aspects, the mechanism, the kinetics etc.[5,8,9]. In this short introduction we pay attention to those principles of this substitution reaction which are relevant to our own work.

Two main methods are known to perform the amination: *i.* heating of the substrate with a metal amide in an inert solvent, such as toluene, xylene, decaline and N,N-dimethylaniline[8]; *ii.* reaction of the aromatic compound with liquid ammonia containing amide anions[10].
These two methods will be discussed separately. We restrict ourselves to the discussion of the amination of six-membered azaaromatics, although many other aromatic compounds are known to undergo this reaction[5].

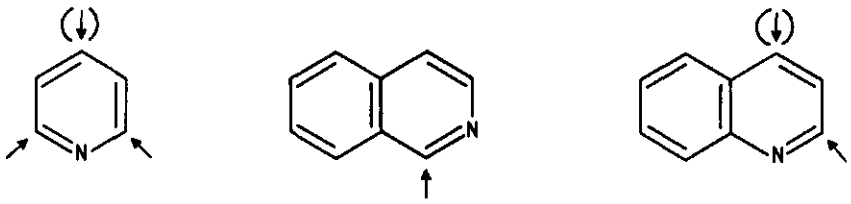
A. Chichibabin amination in an inert solvent

The original method used by Chichibabin for the preparation of 2-aminopyridine features the use of high temperatures. During the reaction the evolution of hydrogen gas is observed[8]. The fact that this hydrogen production is continuous suggests a gradual proceeding of the reaction. Hence both starting material and product are present at the same time. The product will exist as an anion in this strongly basic medium and as such is able to react as a nucleophile with unreacted pyridine. This leads to the formation of the secondary amine, that is observed as side-product (Scheme 1.3)[11].



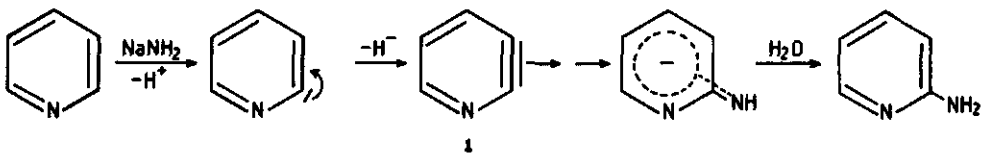
Scheme 1.3

Another important feature of the Chichibabin amination is the regioselectivity, *i.e.* that the substition specifically takes place on only those carbon atoms in the heterocyclic nucleus which have a low electron density. For instance, pyridine is aminated at position 2(6)[12,13] and not at position 3. The isoquinoline system is aminated at C-1[14] and quinoline at C-2 and to a lesser extent at C-4 (Scheme 1.4)[15].



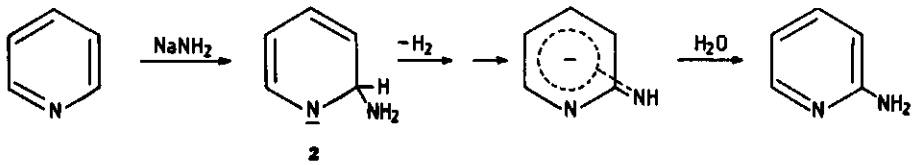
Scheme 1.4

The discussion about the mechanism of the Chichibabin amination of pyridine and its derivatives was focussed on the occurrence of either the elimination-addition mechanism $\left[S_N(EA)\right]$, or the addition-elimination mechanism $\left[S_N(AE)\right]$. In the former pathway the proton at C-2 is eliminated under the influence of the strong base, yielding the pyridyl-2 anion, which by elimination of a hydride ion leads to the unstable didehydropyridine 1 (2,3-pyridyne, scheme 1.5). This intermediate 1 undergoes exclusive addition of ammonia or sodamide to C-2[16].



Scheme 1.5 The $S_N(EA)$ mechanism

The $S_N(AE)$ mechanism comprises the initial formation of the unstable σ-adduct 1,2-dihydropyridinide ion (2)[17] which aromatizes on elimination of hydrogen (Scheme 1.6). This aromatization step may proceed *via* different pathways[18,19], as will be shown further on.



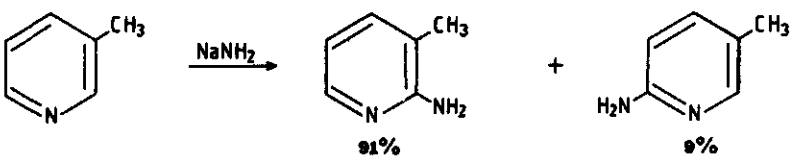
Scheme 1.6 The $S_N(AE)$mechanism

More recent experiments have shown that the hetaryne mechanism is not operative in the Chichibabin amination. This rejection is mainly based on the following grounds:

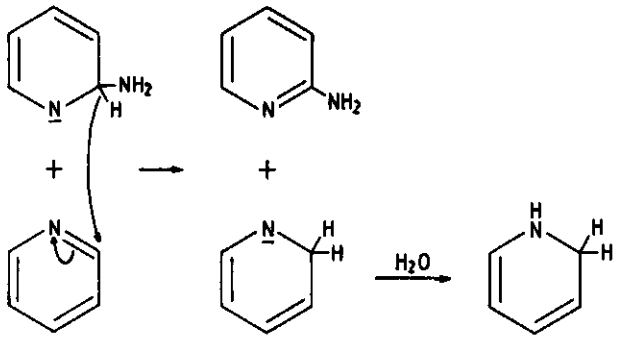
i. Proton exchange experiments show that in pyridine H-4 is more acidic than H-2. This leads to the conclusion that deprotonation of the pyridine ring should preferably result in a pyridyl-4 anion from which 3,4-pyridyne arises. A mixture of 3- and 4-aminopyridine, and not 2-aminopyridine, must then finally be obtained[20,21]. This argument is supported by the formation of the dimer 4,4'-dipyridyl by attack of deprotonated pyridine on the starting material[11,17].

ii. 2,3-pyridyne is not stabilized by delocalization of the extra lobes with the lone electron pair of the ring nitrogen atom, as has been advocated[22]. Recently calculations have shown that this orbital overlap actually leads to destabilization[23]. This implies that 2,3-pyridyne is less stable than 3,4-pyridyne.

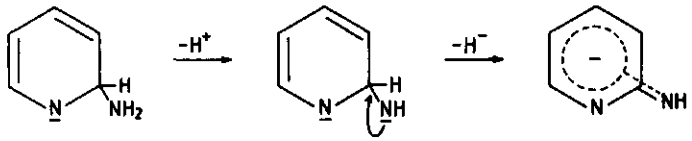
iii. No isotope effect has been observed in the amination of 3-deuteropyridine[19,24], indicating that elimination of H-3 as a hydride ion is *not* the rate-determining step.



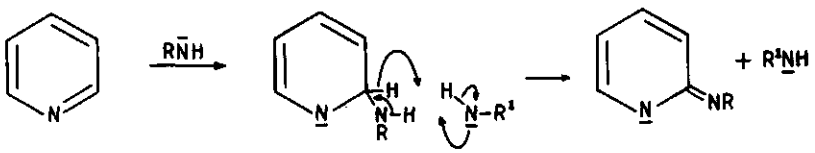
Scheme 1.7



Scheme 1.10



Scheme 1.11



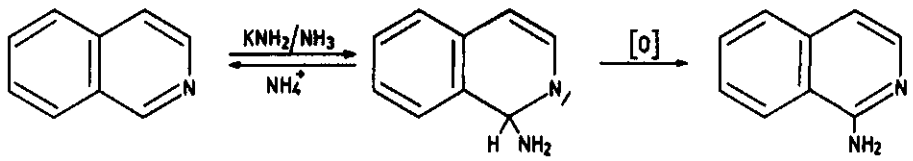
Scheme 1.12

addition of the sodium salt of the product causes the lag period in the hydrogen production to disappear[45].
Furthermore the Chichibabin reaction can be carried out with sodium alkylamides as nucleophile[49], but not with sodium salts of secondary amines which do not possess an acidic proton[45,50].

Finally the possibility of a radical anion intermediate has to be mentioned. The colour developed during the amination reaction is suggested to be due to the formation of the σ-adduct. In the presence of oxygen however neither the appearance of colour nor the evolution of hydrogen gas is observed[45]. This effect is reversible. Addition of radical inhibitors such as trinitrobenzene and azobenzene leads to the same result. Electron transfer from the amide anion to the heterocyclic compound, followed by recombination of the amide radical with the radical anion of the substrate, yielding the adduct, is proposed as the most feasible pathway[45]. This idea is confirmed by the occurrence of dimerization of the substrate as a side reaction[9,15,51].

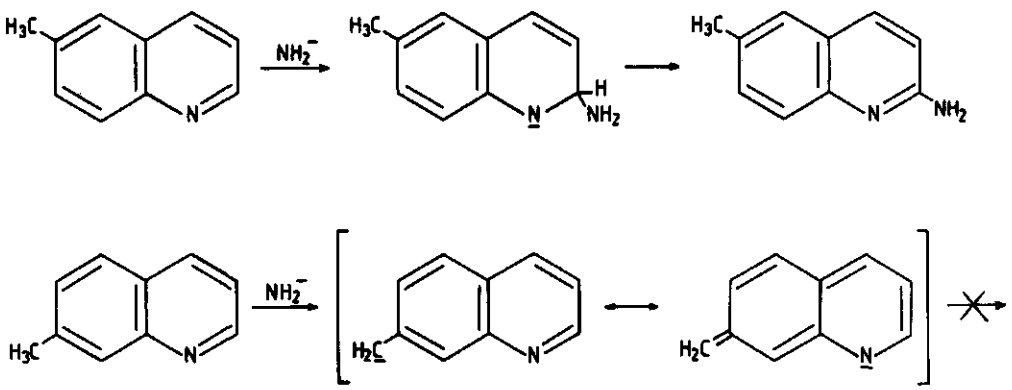
B. Chichibabin amination in liquid ammonia

In the 1930's Bergstrom used liquid ammonia as a solvent for Chichibabin amination reactions[10,52]. In this solvent potassium amide is preferred to sodamide because of its better solubility; so the reaction is a homogeneous one. The occurrence of possible mechanistic differences between the heterogeneous reaction in inert solvent and the homogeneous amination in liquid ammonia is hardly recognized in early literature[53].
Addition of the heterocyclic substrate to the KNH_2/NH_3-system causes the immediate development of an intense colour, which is ascribed to the formation of a covalent σ-adduct. Isoquinoline for instance forms the σ-adduct on C-1 (Scheme 1.13)[52].
On addition of an ammonium salt to the solution of the adduct the starting material was recovered quantitatively, whereas a high yield of 1-aminoisoquinoline was obtained if potassium nitrate was added to the solution as oxidant[52]. So, a σ-adduct is probably the intermediate, just as in the amination with sodamide in toluene.
Further evidence for the intermediacy of σ-adducts between heteroaromatic compounds and amide ions was not furnished until 1972, when their existence was established by application of ^1H as well as ^{13}C NMR spectroscopy[54-60].



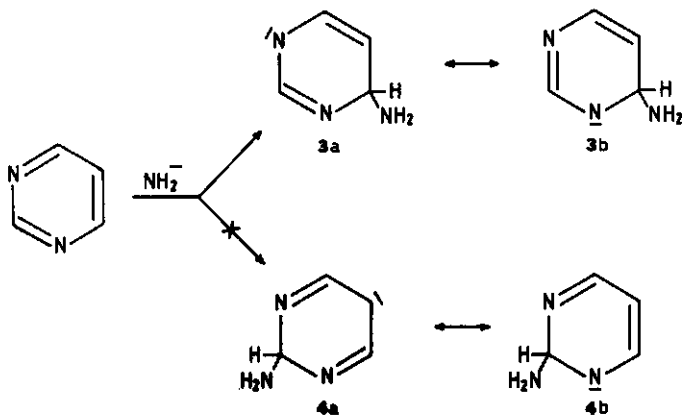
Scheme 1.13

If the aromatic compound is electron deficient adduct formation is usually fast and the position of attack is the carbon atom with the largest electron deficiency. The strongly basic character of the amide ion, however, has to be recognized and taken into consideration. Numerous studies have shown that amination does not take place if a substituent which can easily be deprotonated is present in the substrate. Deprotonation leads to a resonance-stabilized anion with part of its negative charge on the ring nitrogen atom. For instance, 2-methylpyridine and 2-methylquinoline are deprotonated in KNH_2/NH_3[61], as well as 2- and 4-methyl-1,8-naphthyridines (Scheme 1.14). On the other hand 3-methyl-1,8-naphthyridine is converted into the 2-adduct[62].



Scheme 1.14

The rapid and facile formation of the σ-adducts and their stability in liquid ammonia may have important consequences for the mechanism of the Chichibabin amination. The initially formed adduct, determined by the charge distribution in the substrate, is not necessarily the most stable one. This may lead to an interesting balance between a kinetically favoured and a thermodynamically favoured adduct. For instance, the C-2 carbon atom in pyrimidine is more electron deficient than C-4[37-39] but nevertheless the amide ion attacks C-4. This yields the dihydropyrimidinide 3, in which the favourable para-quinoid resonance structure 3a[63,64] stabilizes anion 3 more than the comparable para-quinoid structure 4a stabilizes the C-2 adduct (4, Scheme 1.15).

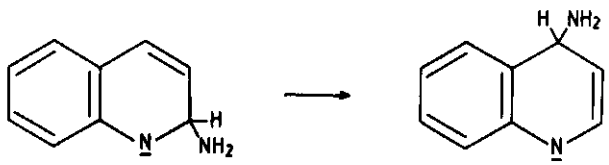


Scheme 1.15

Whether the electron distribution in the substrate or the stability of the adduct actually determines the position of attack depends on the degree of interaction and bond formation between the substrate and the nucleophile in the transition state. When this interaction is weak the transition state will bear close resemblance to the substrate and the adduct formation is charge controlled.

A transition state in which the bond between the carbon atom and the amide ion is formed to some extent is more 'adduct-like'. It has slightly less aromatic character than the charge controlled transition state and therefore

has a somewhat higher energy content. The result is that a higher activation energy is required for the formation of the more stable adduct than for the less stable charge controlled one. Due to this difference in activation energy the latter adduct is kinetically favoured.
Nevertheless, in an attempt to predict the site of attack the energy of the transition state is considered to be the determining factor[65-67]. The relative energies of the transition states of adduct formation at all positions of quinoline[65,66], isoquinoline and the naphthyridines[67] were calculated and compared. In these calculations the resonance integral, representing the interaction between the attacked carbon atom and the nucleophile, is regarded to be constant in all cases. The foregoing discussion concerning kinetic versus thermodynamic control makes it obvious that this simplification is not justified.
If the difference in rate of formation of the kinetically and thermodynamically determined adducts is sufficiently small, it should be possible to find both adducts together. This is in fact reported for quinoline in KNH_2/NH_3. The initially observed C-2 adduct finally isomerizes into the C-4 adduct, as seen by NMR spectroscopy (Scheme 1.16)[55].

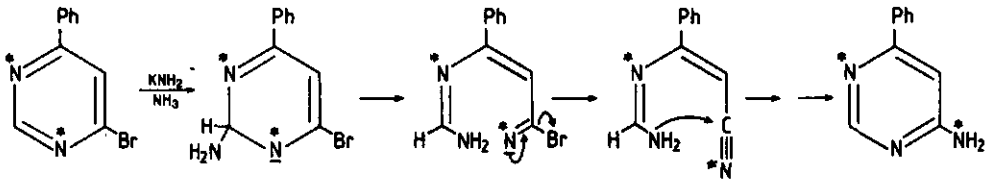


Scheme 1.16

This result is in accordance with the experimental fact that the ratio of the reaction products 2-aminoquinoline and 4-aminoquinoline is time-dependent[68]. A similar behaviour in adduct formation has also been observed with a number of 1,X-naphthyridines (X=5,6 or 7)[69].

In all the foregoing reactions it is assumed that the site of substitution and the site of addition in a Chichibabin amination of a heteroaromatic compound are one and the same. The generality of this assumption is open to question. Research in this laboratory has demonstrated that in many nucleo-

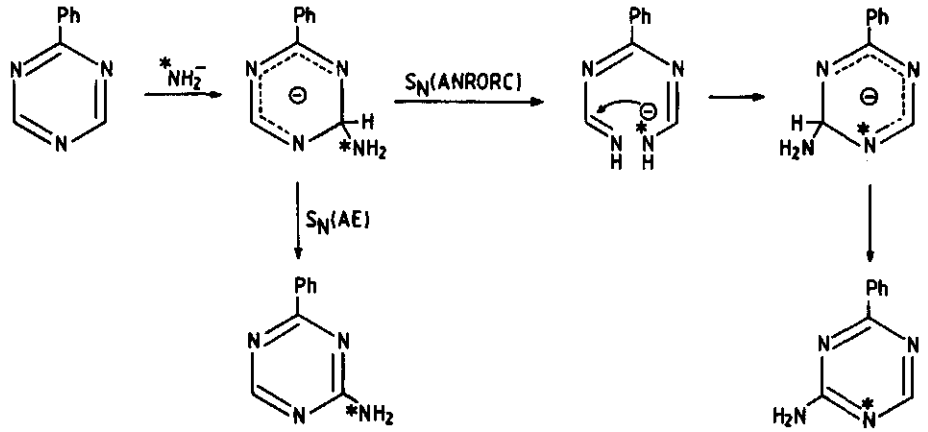
philic substitutions in azaaromatic compounds a leaving group is replaced by a nucleophile in such a way that the initial site of attack is *not* the carbon atom bearing the leaving group. Many of these reactions are accompanied by a so-called degenerate ring transformation, *i.e.* the aromatic ring in the final product is the same as in the starting material, but does not consist of the same atoms. Ring opening is an essential part of the mechanism. In the amination of 4-bromo-6-phenylpyrimidine [1(3)^{15}N] by KNH_2/NH_3 for instance the ring of the product 4-amino-6-phenylpyrimidine has partly lost its ^{15}N-label[70]. The inevitable conclusion is that the mechanism consists of a series of reactions, involving an Addition of the Nucleophile, Ring Opening and Ring Closure (Scheme 1.17). This reaction pathway, known as the S_N(ANRORC)-mechanism, appears to operate frequently in nucleophilic aromatic substitutions[3].



Scheme 1.17

What about aromatic compounds without a leaving group? One example is known in which the Chichibabin amination partially takes place according to an S_N(ANRORC) mechanism. Phenyl-1,3,5-triazine on treatment with $^{15}KNH_2/^{15}NH_3$ yields as product 2-amino-4-phenyl-1,3,5-triazine. 55% of this product contains ^{15}N label in the ring and must therefore be formed according to the ring opening/closure pathway (Scheme 1.18)[71].

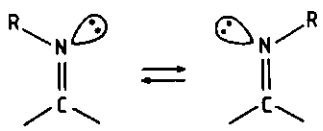
In the light of this result we became interested in studying the mechanism of the Chichibabin amination of some diazines, in which *a priori* an S_N(ANRORC) mechanism is possible. In chapter 2 of this thesis the results of the amination of 4-phenylpyrimidine are reported. An extension of this work to the amination of 4-*t*-butyl-pyrimidine and 5-phenylpyrimidine along with more detailed information on the mechanism of the reaction is given in chapter 3. The adduct formation and Chichibabin amination of phenylpyrazine is discussed in chapter 4.



Scheme 1.18

Geometrical isomerism in the anions of aromatic amines

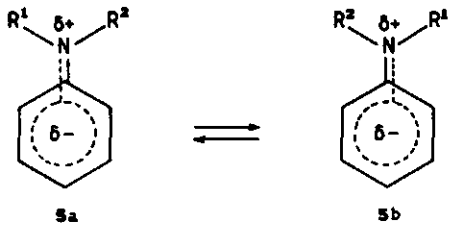
Many compounds containing a carbon-nitrogen double bond occur in two geometrical isomers (Scheme 1.19). This has been recognized for oximes, hydrazones, semicarbazones[72] etc. At low temperature even *s*-butyl-phenylketimine shows such a behaviour[73].



R = H, OH, NH_2, alkyl etc.

Scheme 1.19

This phenomenon is also observed in anilines, since in these systems delocalization of the nitrogen lone electron pair is possible, inducing a partial double bond (Scheme 1.20)[74,75]. The conjugation brings the substituents R^1 and R^2 in the plane of the aromatic ring.



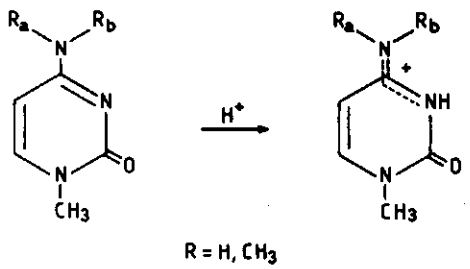
Scheme 1.20

In aniline both *ortho* as well as both *meta* hydrogen and carbon atoms are equivalent. When R^1 and R^2 are different however, the restricted rotation around the aryl-nitrogen bond in 5a ⇄ 5b causes the loss of this equivalency. Consequently these atoms may be observed separately by NMR spectroscopy provided that the isomerization rate is rather slow on the NMR timescale; if not, an average spectrum is expected to be the result. In fact, NMR is found to be a suitable method for the observation of the two geometrical isomers. The rotational barrier must be sufficiently high at the temperature used. In other words the temperature must be below that of coalescence.

The rotational barriers are usually calculated from dynamic NMR measurements[76], and this method has proven to be more reliable than a procedure based on ^{15}N chemical shifts[77]. The coalescence temperature of aromatic amines varies considerably, ranging from -120°C for N-methylanilines[78] to above +20°C for 9-substituted 6-(methylamino)purines[79]. Steric hindrance and intramolecular hydrogen bonding between the amino group and neighbouring substituents are important in determining the isomer ratio and the height of the rotational barrier[79-81].

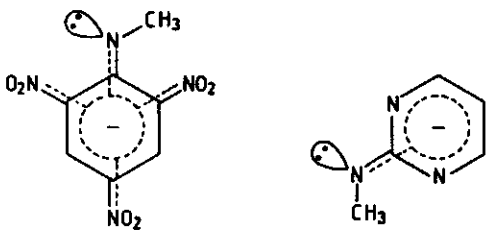
It is also obvious that the rotational barrier and the coalescence temperature are reduced by electron donating substituents[82], and increased by electron accepting groups[75,78,80,81,83,84]. A similar effect is found for

ring nitrogen atoms in *ortho*- or *para*-position[85]. Mesomeric effects are also important as shown by the lower rotational barrier for 3-(dimethylamino)-pyridine compared with that of the 4-isomer[76].
Geometrical isomerism of N-unsubstituted aryl amines can be observed, provided there is no rapid exchange of the amino hydrogen atoms. It is remarkable that this condition can be met not only in various organic solvents[86,87], but also in protic solvents as water[88]. Adenosine and 4-amino-1-methylpyrimidin-2-one are reported to show two different amino hydrogens in the NMR spectra[88,89] in slightly acidic medium. Protonation of a ring nitrogen in these systems even increases the rotational barrier (Scheme 1.21)[86,90].



Scheme 1.21

Likewise, geometrical isomerism may be expected in the anions of aromatic amino compounds because delocalization of the negative charge over the aromatic ring will enhance the double bond character of the aryl-nitrogen bond considerably. This isomerism is in fact used as an explanation for the non-equivalency of H-3 and H-5 in the NMR spectrum of N-methyl-2,4,6-trinitroaniline (6) in dimethyl sulfoxide containing sodium methoxide[91-93].



The same reasoning has been put forward to explain the non-equivalency of C-4 and C-6 in the ^{13}C NMR spectrum of the anion of 2-(methylamino)pyrimidine (7) in liquid ammonia containing potassium amide at -50°C[56].
Although geometrical isomerism is not uncommon, this phenomenon is not reported for a number of amino compounds in strongly basic aprotic media such as tetrahydrofuran, hexamethylphosphoramide, N,N,N',N',-tetramethylethylenediamine and 1,2-dimethoxyethane containing butyllithium[94].
Likewise the NMR spectra of the anions of aminopyrazine[95], 2-aminopyridine[95] and several anilines[96] in liquid ammonia containing potassium amide are reported without mentioning the occurrence of geometrical isomerism.
It seems reasonable to suggest that these NMR spectra were measured above the coalescence temperature, thus preventing the observation of two isomeric structures. This idea is confirmed in the second part of this thesis. Chapter 5 shows that aminopyrazine, adenine and some anilines indeed form two isomeric anions in KNH_2/NH_3 at low temperature. The NMR signals of the anions of N-methylaminopyridines can be assigned to the separate isomers, as described in chapter 6. Evidence that the 'effective size' of the amino lone pair is larger than the amino hydrogen atom in aminopyridines is presented in chapter 7. Furthermore the criteria for the assignment of ^{13}C NMR signals in aminopyridines and (methylamino)pyridines have been found to be different.

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2 OCCURRENCE OF AN S_N(ANRORC) MECHANISM IN THE CHICHIBABIN AMINATION OF 4-PHENYLPYRIMIDINE

J.Breuker and H.C.van der Plas

Introduction

During the last decade the amination of azaaromatics containing groups with a considerable leaving character, is a subject of continuous interest; special attention is paid to the use of potassium amide in liquid ammonia as aminating reagent. Sound proof is obtained - based on application of ^{15}N labeled compounds and NMR spectroscopy - that in an overwhelming number of cases the replacement of the leaving group by the amino group takes place for the greater part according to a so-called S_N(ANRORC) mechanism, describing a reaction sequence involving an Addition of the Nucleophile to the heterocycle, Ring Opening and Ring Closure reaction[1].

As extension of these studies we became interested whether the Chichibabin amination of azaaromatics by potassium amide (*i.e.* the replacement of a hydrogen by an amino group) would also occur according to an S_N(ANRORC) mechanism. Up to now only one example of a Chichibabin reaction has been reported in which the S_N(ANRORC) mechanism partly operates, *i.e.* in the amination of phenyl-s-triazine into amino-phenyl-s-triazine by potassium amide in liquid ammonia[2].

Since pyrimidines were found to be very appropriate systems to undergo S_N(ANRORC) substitutions[1] we started an investigation on the Chichibabin amination of 4-phenylpyrimidine (1). The choice of 4-phenylpyrimidine instead of the parent substance pyrimidine was mainly based on the fact that in introductory experiments the amination of pyrimidine by potassium amide led to a more complex mixture of compounds.

These different routes of formation of both amino products can reasonably be explained if we assume an initial attack of the ^{15}N labeled amide ion on position 6 of the starting material 1, yielding the 6-amino-1(or 3), 6-dihydropyrimidinide ion (6^*) (Scheme 2.2). The 4(6) position in pyrimidine is the preferred position for nucleophilic attack[3,4,5]. Adduct 6^* can aromatize into the 6-amino compound 4^* having its ^{15}N in the amino group. In an alternative route 6^* may undergo a ring opening into the resonance-stabilized species $8a^* \leftrightarrow 8b^*$. Ring closure into the 2-amino-1(or 3), 2-dihydropyrimidinide (9^*), followed by aromatization, yields the 2-amino compound 2^* with the label incorporated in the ring.

In order to substantiate this mechanism we investigated by ^1H and ^{13}C NMR spectroscopy whether one or more of these suggested intermediates could be detected. Therefore we measured the NMR spectra of 1 in the KNH_2/NH_3 system. The data are collected in tables 2.2 and 2.3.

In the ^1H NMR spectrum no signal of unreacted 1 was detected. A doublet at 4.71 ppm and a doublet at 4.92 ppm were observed, which are ascribed to the protons at positions 6 and 5, respectively, in 6. This assignment is based on comparison with the spectrum of 6-D-4-phenylpyrimidine in KNH_2/NH_3, showing the absence of a signal at 4.71 ppm, and at the same time disappearance of the coupling in the signal at 4.92 ppm. The signal for H-2 in 6 lies under the phenyl multiplet of the *meta*- and *para*-hydrogens at 7.2 ppm as indicated by the integral. The large upfield shift of 8.69 - 4.71 = 3.98 ppm for H-6, observed on comparison of the spectrum of 1 in KNH_2/NH_3 with that of 1 in deuterated chloroform, confirms the presence of an 1:1 anionic σ-adduct formed by attack of the amide ion on the C-6 of the pyrimidine ring.

In addition in the region 4-5.5 ppm two small signals were also observed: a doublet at 5.43 and a somewhat broadened singlet at 4.26 ppm. These signals are ascribed to H-5 and H-2 respectively in the 2-amino-1(or 3), 2-dihydropyrimidinide ion (7) (figure 2.1).

These assignments could be made by measuring the spectra of the deuterated compounds 6-D-4-phenylpyrimidine and 2-D-4-phenylpyrimidine in KNH_2/NH_3. The spectrum of 6-D-4-phenylpyrimidine shows a singlet at 5.43 ppm (besides the signal at 4.92 ppm as discussed before); the spectrum of 2-D-4-phenylpyrimidine has no peak at 4.26 ppm. The signal for H-6 in 7 probably lies under the phenyl multiplet. The upfield shift for H-2, observed on the formation of adduct 7 amounts to 9.22 - 4.26 = 4.96 ppm.

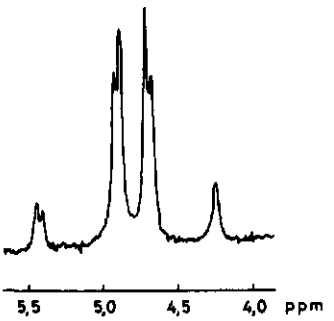
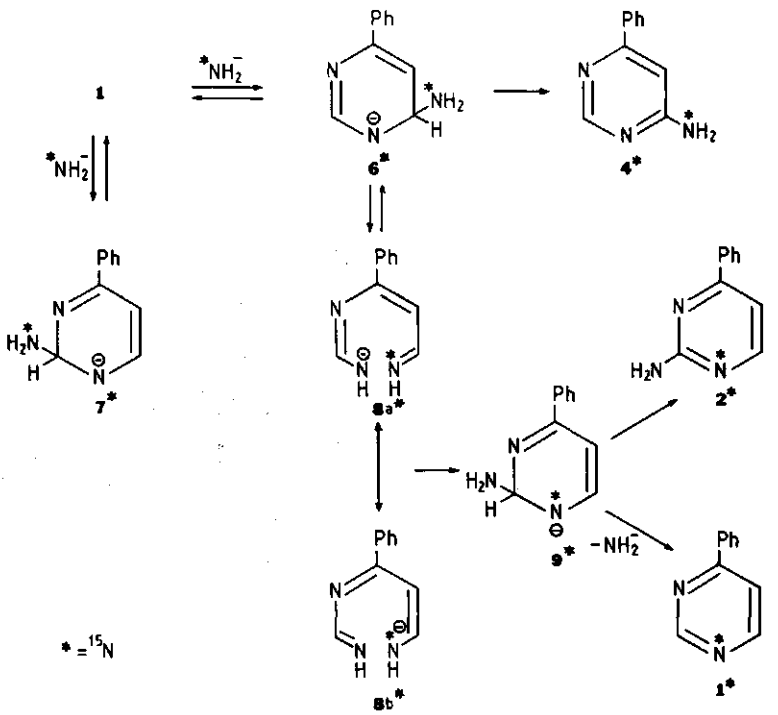


Figure 2.1 Part of the ^{1}H NMR spectrum, 20 minutes after dissolving 1 in KNH_2/NH_3, at -50°C.



Scheme 2.2

The ratio of the adducts 6 and 7, 20 min after dissolving 1 in KNH_2/NH_3, is about 80:20. It is evident that adduct 7 cannot act as an intermediate in the formation of 2 (in that case no ring opening is involved), since the ^{15}N labeling experiments show that about 95% of 2 has been formed according to an S_N(ANRORC) process. We found however that on standing of the reaction mixture for several hours, the amount of 7 diminishes and finally disappears. Apparently we are dealing with the kinetically favoured formation of 7, which slowly converts *via* 1 into the more stable adduct 6. A somewhat similar result has been found on dissolving quinoline in KNH_2/NH_3[6]: the adduct at position 2 slowly converts into the adduct at position 4.

Table 2.3 *^{13}C NMR data of 4-phenylpyrimidine and its σ-adducts*

	compound				
atom	1[a]	6[b]	Δ[c]	7	Δ[c]
	Chemical shifts[d]				
C-2	159.3	156.8	2.5	84.6	74.7
C-4	164.0	146.3	17.7		
C-5	117.2	93.4	23.8	88.2	29.1
C-6	157.5	63.7	93.8	155.6	1.9
C-1'	138.4	143.0			
C-2',6'	127.3	125.4			
C-3',5'	129.1	127.9			
C-4'	131.2	126.3			
	$^1J_{CH}$ coupling constants in Hz				
C-2H	199	176		149	
C-5H	170	157		158	
C-6H	179	149		168	

[a] in $CDCl_3$

[b] in KNH_2/NH_3

[c] upfield shift relative to 1

[d] relative to Me_4Si (δ=0 ppm)

^{13}C NMR spectroscopy of the solution of 1 in KNH_2/NH_3 confirms the formation of the two adducts 6 and 7. The assignment of the signals, based upon selected proton-decoupling, is given in Table 2.3. The large upfield shifts of C-6 in 6 (157.5 - 63.7 = 93.8 ppm) and of C-2 in 7 (159.3 - 84.6 = 74.7 ppm) and the decrease in ^{13}C-H coupling constants (from 179 to 149 Hz and from 199 to 149 Hz) are characteristic, indicating the decrease in s-character of the carbon-hydrogen bonding orbital on the site of amide attack compared with 1 in $CDCl_3$ as a solvent.

All NMR data are in agreement with our assumption concerning 6 as intermediate in the amination reaction. The result is the first example of the formation of an amino-diazine formed by a Chichibabin reaction *via* an S_N(ANRORC) mechanism.

As seen in scheme 2.2 the formation of 2^* from 6^* proceeds *via* intermediate 9^*. This intermediate is quite analogous to adduct 7^*, however with the important difference of the position of the ^{15}N label. Since 7^* is in equilibrium with 1, 9^* must be in equilibrium with 1^*, the starting material 1 in which ^{15}N is incorporated. Checking the recovered starting material on the presence of ^{15}N, we actually found that about 35-40% of ^{15}N was incorporated into 1. This result gives additional evidence for the occurrence of 9 as intermediate in the reaction course.

It is of interest to mention that we found no double labeling in the mass spectra of 2^* and 4^*. Therefore 1^* and 9^* cannot be present in the liquid ammonia containing the potassium amide. If this had been the case it should have led to the 2- and 6-amino compounds being *doubly* labeled. Since this is not found we reach the conclusion that the formation of 4^*, 2^* and 1^* takes place after the addition of the ammonium salt (neutralizing the amide ions) and that in KNH_2/NH_3 only 6^* is present. A similar result has been found before[7].

Experimental section

Melting points are uncorrected. The ^1H NMR spectra of solutions in $CDCl_3$ were recorded on a Hitachi-Perkin Elmer R-24B spectrometer, using tetramethylsilane (δ=0) as internal standard. The ^1H NMR spectra of the solutions in liquid ammonia containing potassium amide and all ^{13}C NMR spectra were

recorded on a Varian XL-100-15. In liquid ammonia the chemical shifts of the protons were measured against the ammonia signal (δ=0.95 ppm) as standard. In the ^{13}C NMR spectra trimethylamine (δ=47.5 ppm) was used as reference compound. All these values are converted to the Me_4Si scale by adding the indicated values. Typical spectral parameters for ^{13}C NMR spectra were as follows: spectral width 5120 Hz (1.25 Hz/point), acquisition time 0.8 s, pulse delay 1.2 s, puls width 10 - 20 μs.
Column chromatography was carried out over Merck Silica gel 60 (70-230 mesh ASTM).
The excess of ^{15}N in the compounds investigated was calculated from the (M+1)/M ratio, measured on an AEI MS-902 mass spectrometer.

Preparation of 6-deutero-4-phenylpyrimidine. A suspension of 4-hydrazino-6-phenylpyrimidine in D_2O was refluxed for 90 min. After evaporation of the solvent NMR spectroscopy of the residue revealed a complete exchange of the protons of the hydrazino group. This product was subsequently heated with D_2O and silver acetate according to procedures, previously described in the literature for similar conversions[8,9]. The resulting crude material was purified by preparative TLC using silica gel and chloroform with 2% of methanol as eluent. Yield 38%.

2-D-4-phenylpyrimidine was prepared in an analogous way as 6-D-4-phenylpyrimidine, starting from 2-hydrazino-4-phenylpyrimidine.

Amination. The amination reaction was performed as decribed before[10], however 10 mol % potassium nitrate was added[11]. After 70 h the potassium amide was destroyed by the addition of ammonium chloride. The ammonia was evaporated and ether/methanol was added to the residue. The mixture was separated into its components by column chromatography. Elution with petroleum-ether (b.r. 60-80°)/chloroform 1:1 and chloroform gave the starting material 1 and 2-amino-4-phenylpyrimidine (2), m.p. 165-166°C from petroleum ether, b.r. 60-80°. Yield 60% (average of 3 experiments). Further elution with 4% methanol in chloroform gave 6-amino-4-phenylpyrimidine (4), m.r. 222-225°C from benzene/ethanol 50/50. Yield 15%.

Hydrolysis of the amino compounds. 10 mg of 2- or 6-amino-4-phenylpyrimidine were heated with concentrated hydrochloric acid in a Carius tube (150°C during 15h). After neutralisation the 4-phenylpyrimidones were purified by column chromatography, using chloroform with 3% methanol as eluent.

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3 THE CHICHIBABIN AMINATION OF 4- AND 5-PHENYLPYRIMIDINE AND 4-*t*-BUTYLPYRIMIDINE

Introduction

The occurrence of ring opening and ring closure reactions in nucleophilic substitutions of azaaromatic compounds (the so-called S_N(ANRORC) mechanism) has emerged as rather common with substrates in which a good leaving group (*e.g.* halogen, thiomethyl) is present[1]. This mechanism is frequently encountered when potassium amide in liquid ammonia is used as reagent. Aminations in which an aromatic hydrogen is replaced by an amino group (the Chichibabin amination) can also occur according to this mechanism, as has been proven in the aminations of 2-phenyl-1,3,5-triazine[2] and 4-phenylpyrimidine (1)[3].
A detailed study of the amination of 1 disclosed that two σ-adducts are formed immediately on dissolving this compound in liquid ammonia containing potassium amide. Both are shown by ^{1}H as well as ^{13}C NMR spectroscopy, *i.e.* the thermodynamically stable C-6 adduct 3 and the kinetically favoured C-2 adduct 2. The latter slowly isomerizes into 3, from which the products are obtained, 6-amino-4-phenylpyrimidine (5) according to an addition-elimination mechanism (S_N(AE)) and 2-amino-4-phenylpyrimidine (8) *via* an acyclic intermediate (S_N(ANRORC)).
In order to clarify the reaction mechanism of the amination of 1 in further detail additional data on the structure of the intermediates which undergo the ring opening, and of the acyclic intermediates obtained after ring opening are presented in this paper. New results on the amination of 5-phenylpyrimidine and 4-*t*-butylpyrimidine are also given.

Results and discussion

A. 4-Phenylpyrimidine

The 6-amino-4-phenylpyrimidinide anion 3, proved as an intermediate in the Chichibabin amination of 1 by NMR spectroscopy[3], is stable under the applied reaction conditions (KNH_2/NH_3, -33°C). On standing for several days at room temperature the spectrum remains unchanged. Addition of ammonium chloride, however, leads to immediate evolution of hydrogen gas and conversion of 3 into the aminoproducts 5 and 8, which can be isolated after evaporation of the solvent. Previous studies with ^{15}N labeled potassium amide have shown that the percentage of S_N(ANRORC) mechanism is especially high in the formation of 8 (92%[3], Table 3.1). The profound effect of the ammonium ion on the

Table 3.1 Average yields and percentages of S_N(ANRORC) mechanism in the amination of 4-phenylpyrimidine (1).

reaction conditions[a]	compounds		
	1	5	8
	Yields (%)[b]		
I[3]	25	15	60
II	10	75	15
III	20	15	65
IV	5	35	55
	S_N(ANRORC) (%)[c]		
I[3]	38	5	92
II	6	12	52
III	3	5	24
IV	5	13	21

[a] I: Standard conditions[22] with quenching by ammonium chloride
II: Standard conditions[22] without quenching by ammonium chloride
III: Concentrated KNH_2/NH_3 (± 3.5M) with quenching after 20 minutes
IV: In KNH_2/*m*-xylene at 90-100°C during 1 hour

[b] Variation in yields up to 8%

[c] ± 5%

proceeding of the amination raises the question which role this cation plays in the occurrence of the S_N(ANRORC) mechanism in the formation of 8.
We therefore performed the amination without quenching the reaction mixture with ammonium chloride prior to work-up. When 1 is treated with KNH_2/NH_3 for 20 hours, the residue obtained after evaporation of the ammonia contains the same compounds 1, 5 and 8 as present in the product mixture found in the ammonium-quenched reaction I. The yields are different, however, namely 10% of 1, 75% of 5 and 15% of 8 (reaction II in Table 3.1). The increase in yield of 5 from 15% to 75% and the decrease in yield of 8 from 60% to 15% are especially remarkable.
When the amination without quenching is carried out in ^{15}N labeled KNH_2/NH_3 and the degree of labeling in the various positions of 1, 5 and 8 is determined, it appears that the incorporation of ^{15}N in the pyrimidine nucleus of 8 has decreased to about half of the value found for reaction I. So, not only is the yield of 8 lower, but also the fraction of 8 which is formed according to the S_N(ANRORC) mechanism. The total amount of products obtained *via* the S_N(ANRORC) pathway is about 66% in the ammonium-quenched reaction I (0.38 x 25% = 9.5% for 1, 0.05 x 15% = 0.8% for 5 and 0.92 x 60% = 55.2% for 8) and about 17% in reaction II (0.06 x 10% = 0.6% for 1, 0.12 x 75% = 9% for 5 and 0.52 x 15% = 7.8% for 8)[§].
These results justify the conclusion that quenching of the amination by the ammonium salt is an important factor in determining the degree in which the S_N(ANRORC) mechanism operates. Its role can be understood as follows.
The ammonium cation, a strong acid in this medium, not only neutralizes the amide anion, but also protonates the ring nitrogen atom of 3*. The resulting uncharged 6-amino-4-phenyl-1,6-dihydropyrimidine (4*) eliminates either hydrogen or ammonia leading to product 5* or starting material 1 (Scheme 3.1). Since 4* is more inclined to open its ring than the anionic species 3* a larger fraction can be expected to form the acyclic intermediate 6a* $\rightleftharpoons$ 6b*, which on recyclization gives 2-amino-4-phenyl-1,2-dihydropyrimidine (7*) and subsequently the 2-amino product 8* and labeled starting material 1*.
We tried to detect the intermediates 4, 6 and 7 by recording the NMR spectra during stepwise addition of ammonium chloride to the mixture of 2 and 3 in

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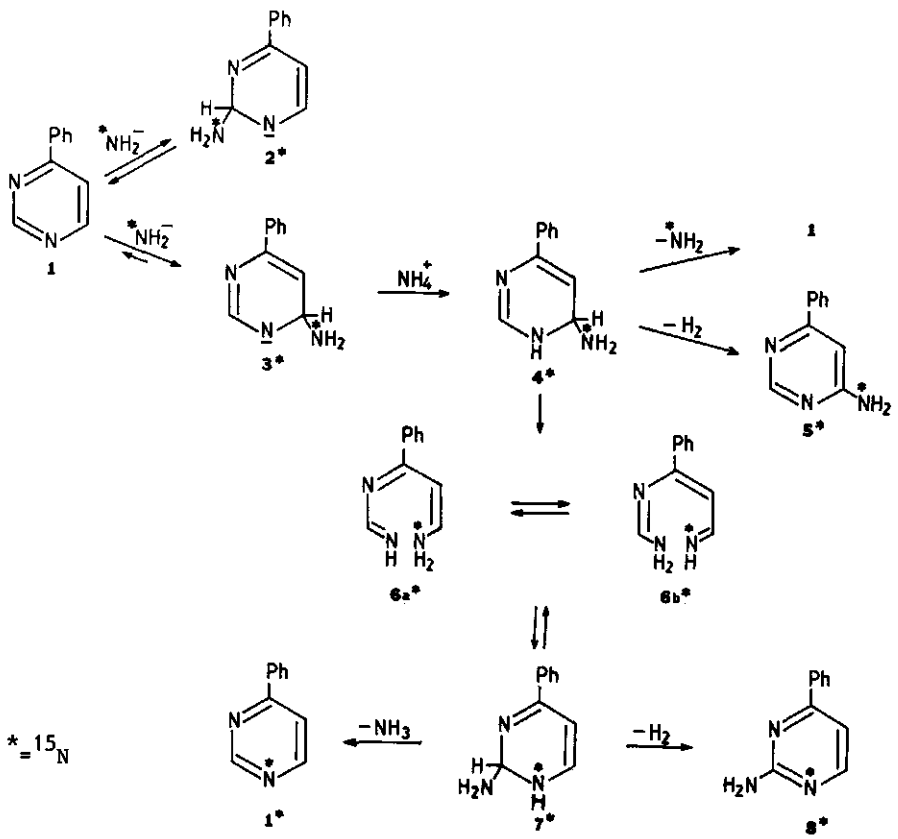
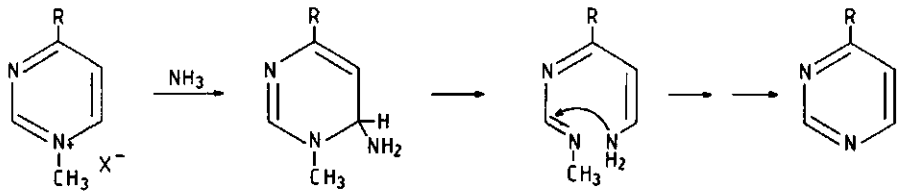
[§]These figures are not very accurate since some scrambling of ^{15}N label in heteroaromatic aminocompounds due to the treatment with strong acid under severe conditions cannot be excluded[4].

KNH_2/NH_3. The hydrogens in the exocyclic amino group of 2 and 3 are not observed due to a very rapid exchange in this basic medium. In consequence the H-2 signal of 2 is present as a singlet and the H-6 signal of 3 is only coupled with H-5 ($J_{5,6}$ = 5 Hz[3]). We found that after adding ammonium chloride to the reaction mixture these two signals have respectively turned into a triplet and a double triplet. Apparently the hydrogen exchange is now very slow and coupling with the hydrogens of the amino group can easily take place (J = 7 Hz). The solvent signal becomes a broad triplet. Further addition of the ammonium salt clouds the solution, the signals start to shift and become unclear. Detection of intermediate 6 is therefore not possible by this method.



Scheme 3.1

Although the NMR data do not give convincing evidence for the intermediacy of 4 and 6 we state that *the ring opening occurs mainly in uncharged 4 and not* as has been proposed previously[3] *in anion 3*. The facile ring opening of the pyrimidine nucleus in the dihydrocompound 4 is in agreement with the behaviour of N-methylpyrimidinium salts, which undergo demethylation with liquid ammonia. It has been proven that 1-methylpyrimidinium methylsulfate (9a, $X^- = CH_3OSO_3^-$) readily forms an uncharged σ-adduct 10a when dissolved in liquid ammonia (Scheme 3.2). This species undergoes a ring opening-ring closure sequence of reactions with elimination of methylamine, leading to pyrimidine, as proven by ^{15}N labeling[5]. The demethylation reaction in liquid



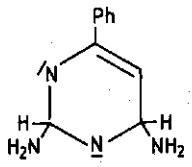
Scheme 3.2

ammonia has also been studied with 1-methyl-4-phenylpyrimidinium iodide (9b, $X^- = I^-$). When subjected to treatment with ^{15}N labeled ammonia, 4-phenylpyrimidine (1*) is mainly obtained *via* a ring opening-ring closure pathway (90%) in a fast reaction. Attempts to detect the intermediate 6-amino-1-methyl-4-phenyl-1,6-dihydropyrimidine (10b) failed. This C-6 adduct, and not the isomeric adduct on C-2, is regarded to be the main intermediate because adduct formation on C-6 is more favourable than on C-2 (see section C). Since 10b reacts very rapidly the assumption is justified that 1,6-dihydropyrimidine intermediates are inclined to readily open the ring. Based on these experiences we feel that the uncharged species 4 and not anion 3 is the most likely intermediate in the S_N(ANRORC) mechanism of the amination of 1.

B. The adduct mixture

As stated above in section A adduct 2 slowly isomerizes into the thermodynamically stable adduct 3. It has been reported that σ-adducts, formed from diazines[6] and tetrazines[7] with potassium amide and/or liquid ammonia, are easily oxidized to the corresponding amino products by potassium permanganate. We applied this method to oxidize the mixture of 2 and 3 into 8 and 5 respectively, and used this amination-oxidation procedure to establish the time-dependency of the composition of the adduct mixture by measuring the ratio in which the amino products 8 and 5 are formed. With this aim we added potassium permanganate to solutions of 1 in KNH_2/NH_3 one minute and two hours after dissolving. The product mixtures were analyzed by gas chromatography and were found to consist of 55% of 8 and 42% of 5 when the oxidant was added after one minute, and of 19% of 8 and 72% of 5 on addition after two hours. This result reflects the rearrangement of adduct 2 into 3 over an extended period of time.

The isomeration 2 →3 is assumed to proceed *via* 1, although the intermediacy of the 2,6-diadduct 11 is not excluded[3]. Resonance signals of neither 1 nor 11 are observed in the NMR spectra, hence the formation of 1 or 11 is the rate-determining step in the conversion of 2 into 3. NMR spectroscopy shows further that the isomerization rate is retarded when high amide concentrations are used (3.5 M instead of the usual 0.8 M). This result suggests 1, and not 11, as key intermediate in this isomerization process, since the intermediacy of 11 is expected to lead to an increase of the isomerization rate with an increasing amide concentration.



11

The ability to slow down the isomerization of 2 provides us with a method to check whether this C-2 adduct can give product 5 *via* an S_N(ANRORC) process. The reaction was carried out in a concentrated solution of labeled $K^{15}NH_2/^{15}NH_3$ (± 3.5 M). Ammonium chloride was added while an appreciable amount of 2* was still present in the reaction mixture (reaction III). After work-up the composition of the product mixture does not differ very much from the one obtained under standard conditions (compare with reaction I in Table 3.1). The percentage of 8 which is formed according to the S_N(ANRORC) mechanism, however, is lowered dramatically (from 92% to 24%) and virtually no

label (5%) is found in the nucleus of 5. Apparently 2 is not prone to ring opening-ring closure sequence. We suggest that this behaviour in not due to the impossibility for 2 to undergo ring opening. Rather, a strong preference exists in the acyclic intermediate 6 - formed after ring opening - for ring closure in such a way that 7 is formed due to the more electrophilic character of C-2 compared to C-6. This also explains the relatively high yield of 8 under the reaction conditions, indicated as I.

C. The acyclic intermediate

The foregoing sections emphasize that the uncharged dihydropyrimidine 4 undergoes a fast ring opening and ring closure in liquid ammonia, and that it was not possible to observe the open chain intermediate 6, due to the rapidity of the ring closure. We tried to get indirect NMR spectroscopic evidence for the intermediary existence of 6 by preventing the recyclization.
On dissolving 1 in liquid methylamine containing potassium methylamide an adduct on C-6 is formed (12, NMR data in Table 3.2). That only the stable

Table 3.2 *^1H NMR data of the ring protons in 12, 14, 15, 16 and 17*[a]

	compounds					
hydrogen	12[b]	Δδ[c]	14[d]	15[d]	16[d]	17[e]
H-2	7 3	1.9	f	f	f	8.01
H-5	4.94(d)[g]	2.70	5.50(d)[h]	4.87(d)[h]	4.91(d)[i]	5.46(d)[j]
H-6	4.85(d)[g]	3.84	5.01(d)[h]	f	7.52(d)[i]	7.28(d)[j]
phenyl	7.2 7.5		7.2-7.4 7.7-7.9	7.2-7.4 7.5-7.7	7.4	7.4-7.6

[a] Chemical shifts relative to Me_4Si (δ = 0 ppm)
[b] In CH_3NHK/CH_3NH_2
[c] Upfield shifts relative to 1
[d] In n-$C_3H_7NH_2$
[e] In CH_3NH_2/D_2O
[f] These signals lie under the phenyl signal
[g] $J_{5,6}$ = 4.5 Hz
[h] $J_{5,6}$ = 5.0 Hz
[i] $J_{5,6}$ = 7.5 Hz
[j] $J_{5,6}$ = 11.7 Hz

The yields are the same as in the amination of 1 without quenching. Moreover, when the reaction is carried out in labeled $K^{15}NH_2/^{15}NH_3$ and azobenzene is added before ammonium chloride, none of the products has a label incorporated in the pyrimidine ring. All these results lead to the conclusion that the S_N(ANRORC) mechanism does *not* occur in the presence of azobenzene. Obviously no effect is observed when azobenzene is added after quenching, since ring opening and closure have already taken place.

E. Amination in m-xylene as solvent

The stability of the anionic σ-adducts in KNH_2/NH_3 is of great significance in the mechanism of the Chichibabin amination as presented in the preceding sections. When the reaction is performed in the classical way, *i.e.* in apolar solvents like N,N-dimethylaniline, xylene or toluene[14], this adduct is far less stable due to the lack of solvating power of the solvent. As a result the adduct formation is the rate-determining step which requires a higher activation energy. Elevated temperatures are necessary to achieve amination.

The Chichibabin amination of 1 was carried out with 4 eq. potassium amide in *m*-xylene as solvent at a temperature of 90°C (reaction IV). After a reaction time of one hour little starting material is left, 35% of 5 is formed and the main product is 8 in 55% yield (Table 3.1). Use of ^{15}N labeled KNH_2 revealed whether the products were formed by an S_N(ANRORC) mechanism. The label was mainly found in the exocyclic amino group of 5 and 8 and this result leads to the conclusion that addition-elimination (S_N(AE)) accounts for virtually all products.

The difference between the results of this reaction IV and those of reaction I is rationalized as follows. The rate-determining step in *m*-xylene as solvent is considered to be the initial nucleophilic attack on C-2 as well as on C-6[14]. After formation of the adducts they immediately react further into the respective amino products with hydrogen evolution. Thus, C-2 adduct 2 cannot isomerize into 3, as it does in liquid ammonia.

The amino products are formed as such in KNH_2/*m*-xylene and undergo an additional amination on prolonged heating, especially at higher temperatures, leading to 2,6-diamino-4-phenylpyrimidine. A similar disubstitution has also been found in the Chichibabin amination of 4-methylpyrimidine[15].

F. 5-Phenylpyrimidine

Dissolving 5-phenylpyrimidine (18) in KNH_2/NH_3 leads to immediate formation of a σ-adduct. The ^1H NMR spectrum of the solution shows one isolated sharp singlet at 4.98 ppm, and all other signals are gathered in a complex region between 7.0 and 7.5 ppm (Table 3.3). This spectrum can be assigned to either C-2 adduct 19 or C-4 adduct 20. The latter assignment appears to be the correct one as proven by comparison of this spectrum with that of its 4-deuterio derivative in KNH_2/NH_3. If adduct formation were to have taken place at C-2 the ratio between the high field singlet at 4.98 ppm and the low field multiplet at 7.0-7.5 ppm would be 1:6 in the deuterated compound. In case 20 is formed and if we neglect any possible effect of the deuterium isotope on the adduct formation, 50% of the molecules of 20 would have a deuterium atom on the sp^3 hybridized C-4 and 50% a hydrogen atom. The ratio of the singlet and the multiplet would then be 1:13. Since the actual ratio found is 1:13.8, it strongly proves the presence of 20.

The ^{13}C NMR data are in good agreement with the formation of C-4 adduct 20 (the upfield shift for C-4 is 90.1 ppm and J_{C4-H} decreases from 181 to 148 Hz, Table 3.4). The data are also quite similar to those obtained when 4-phenylpyrimidine (1) is dissolved in KNH_2/NH_3[3].

Oxidation of the solution of σ-adduct 20 with potassium permanganate, five minutes after dissolving 18 in KNH_2/NH_3, gave 4-amino-5-phenylpyrimidine 22 as the main product (75%), and a small amount (2%) of 2-amino-5-phenylpyrimidine (21). Quenching the solution of 20 in KNH_2/NH_3 with ammonium chloride after 20 hours and work-up of the reaction mixture gave the two amino compounds 21 and 22, both in a yield of about 20% (reaction I in Table 3.5).

Since almost no C-2 adduct 19 has been observed and considering that an amount of 21 is still formed, it was of interest to investigate whether 21 was obtained in an S_N(ANRORC) process from C-4 adduct 20. The amination of 18 was carried out with ^{15}N labeled KNH_2/NH_3 and quenched with ammonium salt. The usual procedures[3] revealed that no label was incorporated in the pyrimidine ring of either the recovered starting material 18 or the 4-amino compound 22*. The 2-amino compound 21*, however, did contain ^{15}N label in the pyrimidine ring and consequently must be formed according to the S_N(ANRORC) process from 20* (Scheme 3.5). The part of the molecules that reacts *via* this mechanism is found to be 80% (reaction I in Table 3.5).

Table 3.3 ^{1}H *NMR data of 5-phenylpyrimidine (18) and its σ-adduct 20*[a]

	compounds		
hydrogen	18[b]	20[c]	Δδ[d]
H-2	9.15	e	
H-4	8.90	4.98	3.92
H-6	8.90	e	
phenyl	7.4-7.6	7.0-7.5	

Table 3.4 ^{13}C *NMR data of 5-phenylpyrimidine (18) and its σ-adduct 20*

	compounds		
atom	18[b]	20[c]	Δδ[d]
	chemical shifts[a]		
C-2	156.8	155.6	1.2
C-4	154.0	63.9	90.1
C-5	133.5[f]	105.5	28.0
C-6	154.0	138.6	15.4
C-1'	133.3[f]	142.1	
C-2',6'	126.2	122.7	
C-3',5'	128.6	128.2	
C-4'	128.2	122.1	
	coupling constant $^{1}J_{C-H}$ in Hz		
C2-H	204	174	
C4-H	181	148	
C6-H	181	159	

Notes to Tables 3.3 and 3.4:

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

[b] In $CDCl_3$

[c] In KNH_2/NH_3

[d] Upfield shifts relative to 18

[e] These signals lie under the phenyl multiplet

[f] These signals may be interchanged

Table 3.5 Average yields and percentages of S_N(ANRORC) mechanism in the amination of 5-phenylpyrimidine (18).

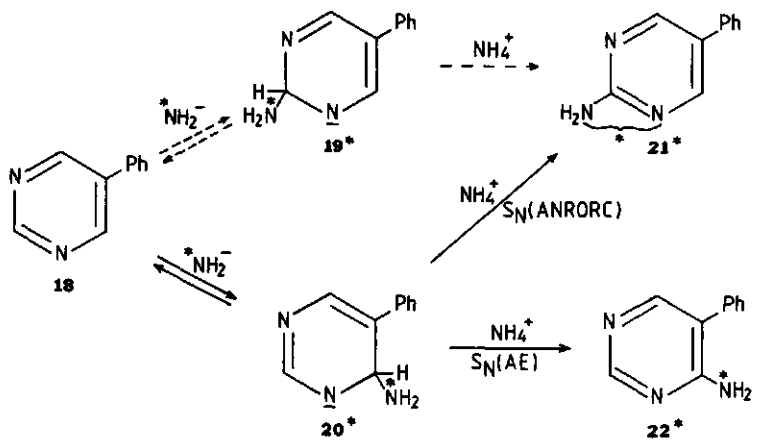
reaction conditions[a]	compounds		
	18	21	22
	yields (%)[b]		
I	60	20	20
II	60	20	20
	S_N(ANRORC) (%)[c]		
I	2	80	6
II	0	63	0

[a] I: standard conditions[22] with quenching by NH_4Cl
II: standard conditions[22] without quenching by NH_4Cl

[b] variation in yields up to 10%

[c] ±5%

Performing the amination without quenching by the ammonium salt does not cause a significant difference in the result: the yield of 22 is 20% and no ^{15}N is incorporated in the ring. Thus, 22 is only formed by an S_N(AE) pathway. The yield of 21 is also about the same and 63% of 21 was found to be formed by the S_N(ANRORC) mechanism (reaction II in Table 3.5).



Scheme 3.5

G. 4-t-butylpyrimidine

Dissolving 4-*t*-butylpyrimidine (23) in KNH_2/NH_3 immediately leads to the formation of both the C-2 adduct 24 and the C-6 adduct 25 as proven by NMR spectroscopy. The ratio 24:25 is 1:9 as measured from the integrals of appropriate signals, again illustrating the greater preference for addition on C-6. The ^1H NMR spectrum shows large upfield shifts of the hydrogen atoms on the sp^3 hybridized carbons of the ring: 3.98 ppm for H-6 in 25 and 5.14 ppm for H-2 in 24 (Table 3.6). The signal assignment of 4.14 ppm to H-5 in 25 is based upon the *para*-coupling of H-5 (a double doublet) with H-2, and upon comparison with the spectrum of partially 5-deuterated 4-*t*-butylpyrimidine in KNH_2/NH_3. In the latter spectrum the signal at 4.14 ppm is smaller and H-6 at 4.63 ppm is shown as a triplet signal. The same features are observed for the H-5 and H-6 signal of 24.

These results are confirmed by ^{13}C NMR spectroscopy. The carbon atoms attacked by the amide ion are characterized by a large upfield shift and a strong decrease in the coupling constant $^1J_{C-H}$ (Table 3.7).

After evaporation of ammonia the reaction mixture contains 2-amino-4-*t*-butylpyrimidine (26) and 6-amino-4-*t*-butylpyrimidine (27) in 25% and 40% yield respectively (reaction II in Table 3.8). Neither these products nor the retrieved starting material have followed the S_N(ANRORC) mechanism to an appreciable extent, as determined in the usual way by experiments with ^{15}N labeled KNH_2/NH_3 (Table 3.8).

No considerable differences in yields of products are found if the reaction mixture is quenched with ammonium chloride before evaporation of the solvent. 26 remains the minor product (25% yield). When the reaction is performed with labeled KNH_2/NH_3 26 and 27 do not contain ^{15}N in the nucleus (Scheme 3.6). This result is in striking contrast with the occurrence of the S_N(ANRORC) mechanism in the amination of 4-phenylpyrimidine (1) and 5-phenylpyrimidine (18). There are more examples, however, of ring opening-ring closure reactions which are not followed by 4-*t*-butylpyrimidine derivatives, *i.e.* the non-occurrence of a Dimroth rearrangement of 4-*t*-butyl-1,2-dihydro-2-imino-1-methylpyrimidine in aqueous base[16]. Furthermore we established that only a few percent of 4-*t*-butyl-1-methylpyrimidinium iodide in liquid ammonia is demethylated whereas the corresponding reactions with 1-methylpyrimidinium methylsulfate (9a) and 1-methyl-4-phenylpyrimidinium iodide (9b) readily proceed along the S_N(ANRORC) pathway (see section A).

Table 3.6 ^{1}H *NMR data of the ring protons of 4-t-butylpyrimidine (23) and its σ-adducts 24 and 25*[a]

	compounds				
hydrogen	23[b]	24[c]	Δδ[d]	25[c]	Δδ[d]
H-2	9.12(d)[e]	3.98	5.14	7.05(d)[e]	2.07
H-5	7.30(dd)[e,f]	4.89(d)[g]	2.41	4.14(dd)[e,g]	3.16
H-6	8.61(d)[f]	6.95(d)[g]	1.66	4.63(d)[g]	3.98

Table 3.7 ^{13}C *NMR data of 4-t-butylpyrimidine (23) and its σ-adducts 24 and and 25*

	compounds				
atom	23[b]	24[c]	Δδ[d]	25[c]	Δδ[d]
	chemical shifts[a]				
C-2	158.1	86.3	71.8	156.7	1.4
C-5	116.8	84.4	32.4	90.0	26.8
C-6	156.7	155.4	1.3	64.2	92.5
C-1'	37.4	35.4		34.5	
C-2'	29.2	30.1		29.3	
	coupling constant $^{1}J_{C-H}$ in Hz				
C2-H	202	152		178	
C5-H	165	155		155	
C6-H	181			144	

Notes to Tables 3.6 and 3.7:

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

[b] In $CDCl_3$

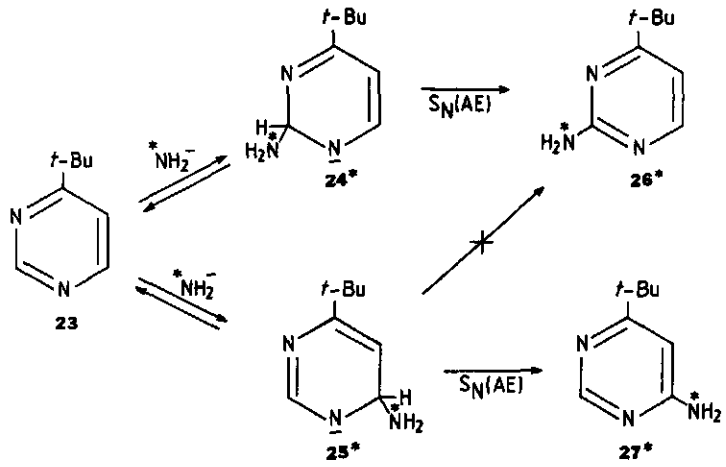
[c] In KNH_2/NH_3

[d] Relevant upfield shifts relative to 23

[e] $J_{2,5}$ = 1.0 Hz

[f] $J_{5,6}$ = 5.5 Hz

[g] $J_{5,6}$ = 4.0 Hz



Scheme 3.6

Table 3.8 Average yields and percentages of S_N(ANRORC) mechanism in the amination of 4-t-butylpyrimidine (23)

	compounds		
reaction conditions[a]	23	26	27
	yields (%)[b]		
I	45	25	30
II	35	25	40
	S_N(ANRORC) (%)[c]		
I	2	15	7
II	0	10	4

[a] I: Standard conditions[22] with quenching by NH_4Cl
II: Standard conditions[22] without quenching by NH_4Cl

[b] Variation in yields up to 10%

[c] ± 5%

Experimental section

The ^{1}H NMR spectra were recorded on a Varian EM 390 spectrometer equipped with a Varian EM 3940 variable temperature controller or on a Varian XL-100-15 spectrometer, using tetramethylsilane as internal standard (δ = 0 ppm). In liquid ammonia the chemical shifts were measured against the solvent signal (δ = 0.95 ppm). The ^{13}C NMR spectra were recorded on a Bruker CXP 300 spectrometer. Acetone (δ = 29.8 ppm) or $CDCl_3$ (δ = 77.0 ppm) was used as the reference compound. Typical spectral parameters were as follows: spectral width 15,000 Hz (3.7 Hz/point), acquisition time 0.275 s, pulse delay 2 s. The excess of ^{15}N in the compounds investigated was calculated from the (M+1)/M ratio, as determined on an AEI MS 902 mass spectrometer equipped with a VG ZAB console.

Gas chromatography was carried out using a Varian 3700 apparatus and a glass column (length 200 cm, o.d. 6 mm) filled with 3% of SP 2250 on Chromosorb W-HP 100/120 mesh, operating at various temperatures (130-200°C). The 5-phenylpyrimidine derivatives were analyzed on 6% OV-275 on Chromosorb as stationary phase at 225°C.

5-phenylpyrimidine (18)[17], *4-t-butylpyrimidine (23)*[18] and *1-methyl-4-phenylpyrimidinium iodide (9b)*[19] were synthesized as described in the literature. *4-deuterio-5-phenylpyrimidine* and *4-t-butyl-1-methylpyrimidinium iodide* were prepared by processes described for 6-deuterio-5-bromo-4-*t*-butylpyrimidine[20] and 9b[19] respectively.

Preparation of 5-deuterio-4-t-butylpyrimidine. 4-*t*-butyl-2-thioxopyrimidin-6-one[21] was refluxed in a mixture of D_2O, dioxane and D_2SO_4 (40:20:1) for 3.5 hours. The 5-deuterio-4-*t*-butyl-2-thioxopyrimidin-6one obtained after evaporation was converted into 5-deuterio-4-*t*-butylpyrimidine according to the procedures described for 5-bromo-4- -butylpyrimidine[21].

The amination procedure. The standard method applied for the amination is described in the literature[22], using ammonium chloride for quenching the reaction.

Methylamination was performed in the same way. The reagent $KNHCH_3/CH_3NH_2$ was prepared by condensing methylamine over solid potassium amide and stirring for half an hour.

The yields were determined by gas chromatographic analysis of the reaction

mixture. The products, obtained after column chromatography over silica gel, were identified by comparison with reference compounds.

Hydrolysis of the amino compounds. A few mg of the amino compound were heated with concentrated hydrochloric acid in a sealed Carius tube (160°C for 18 hours). After neutralization the pyrimidinones were extracted with ether and purified by preparative TLC using chloroform/methanol as eluent.

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4 THE CHICHIBABIN AMINATION OF PYRAZINE AND PHENYLPYRAZINE

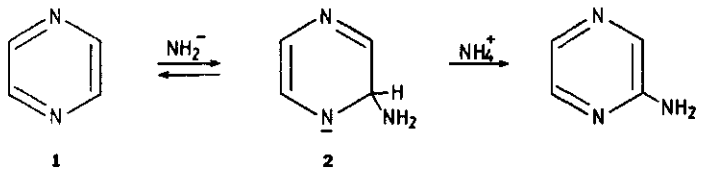
Introduction

A ring opening-ring closure sequence is quite common as mechanism in amino-dehalogenations of azaaromatic compounds by KNH_2/NH_3[1]. The reactions of 2-phenyl-1,3,5-triazine[2], 4-phenyl- and 5-phenylpyrimidine[3] demonstrate that even the replacement of an aromatic hydrogen by an amino group (the Chichibabin amination) proceeds partially according to this pathway (the so-called S_N(ANRORC) mechanism). Chloropyrazine is aminated completely *via* an acyclic intermediate on treatment with KNH_2/NH_3[4], and pteridines[5,6,7] as well as pyrido(2,3-b)pyrazine[8] also undergo ring opening in the pyrazine part of the molecule on use of the same reagent. These results induced us to study whether the S_N(ANRORC) mechanism is also involved in the Chichibabin amination of pyrazine and phenylpyrazine.

Results and discussion

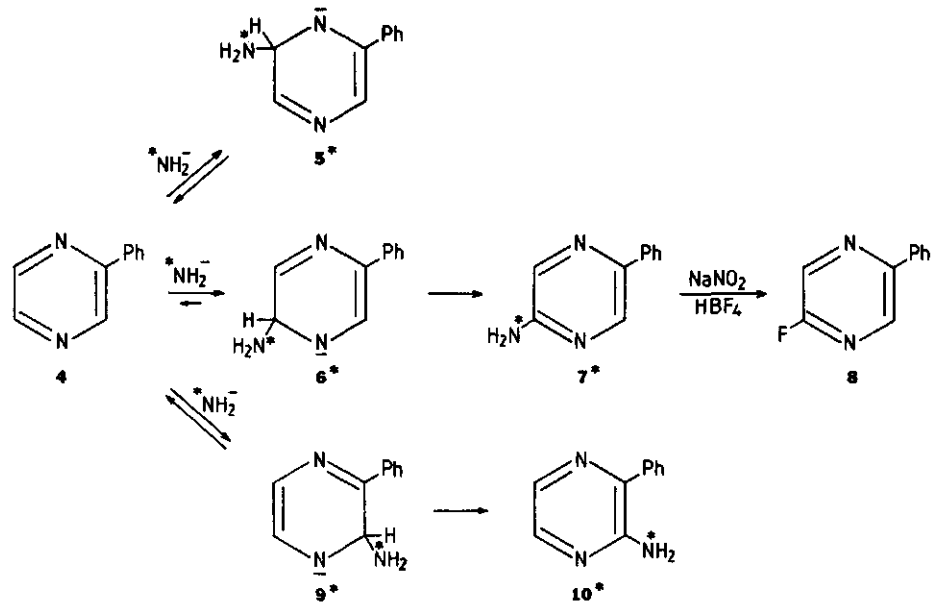
Pyrazine (1) forms σ-adduct 2 in liquid ammonia containing potassium amide[9]. Addition of ammonium chloride to this solution and evaporation of the solvent gives a mixture of starting material (50-55%) and aminopyrazine (3, 30-35%). When the reaction is performed in ^{15}N labeled KNH_2/NH_3 and the labeled amino compound converted into pyrazinone, this compound does not contain ^{15}N, indicating that - in contrast to the amination of chloropyrazine - the Chichibabin amination of 1 does *not* proceed according to an S_N(ANRORC) mechanism, but *via* the more classical addition-elimination pathway (Scheme 4.1).

Amination of phenylpyrazine (4) following the same procedure, gives two products which are identified by comparison with reference compounds as 5-amino-2-phenylpyrazine (7, 35-40% yield) and 3-amino-2-phenylpyrazine (10, 5-10%).



Scheme 4.1

The ^{1}H and ^{13}C NMR spectra of the solution of 4 in KNH_2/NH_3 at -60°C were recorded. The ^{1}H NMR spectrum is complex, suggesting the presence of more than one species. Starting material 4 is not observed. Three different σ-adducts can actually be identified based on comparison of this spectrum with those of 5- and 6-deuterio-2-phenylpyrazine in KNH_2/NH_3 (Table 4.1). The three doublets at 4.33, 5.93 and 6.03 ppm are ascribed to H-6 in the σ-adducts 5, 6 and 9 respectively (Scheme 4.2), and the three doublets at 4.16, 5.70 and 6.76 ppm to H-5 in 6, 5 and 9. The hydrogen atom attached to the sp^3 hybridized carbon atom in 5 and in 6 is found as a doublet at 4.33



Scheme 4.2

Table 4.1 *^{1}H NMR data of phenylpyrazine (4) and its σ-adducts 5, 6 and 9*[a]

hydrogen	compounds						
	4[b]	5[c]	Δδ[d]	6[c]	Δδ[d]	9[c]	Δδ[d]
H-3	8.81(d)[f]	e		e		5.35	3.46
H-5	8.25(d)[g]	5.70(d)[h]	2.55	4.16(d)[h]	4.09	6.76(d)[h]	1.49
H-6	8.40(dd)[f,g]	4.33(d)[h]	4.07	5.93(d)[h]	2.47	6.03(d)[h]	2.37

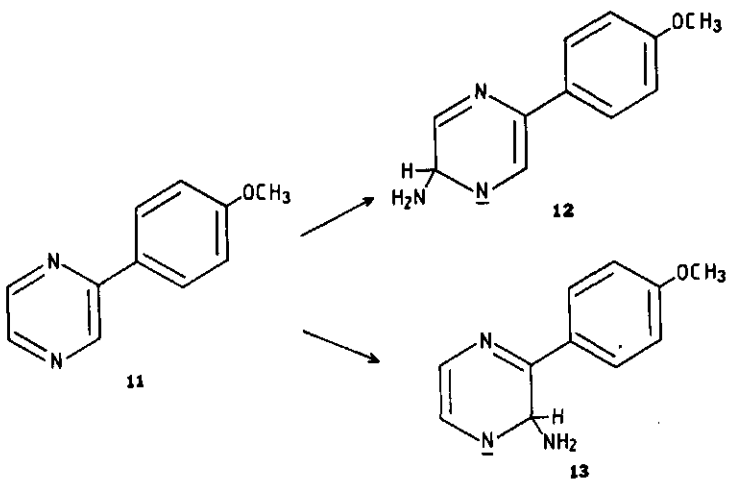
[a] Chemical shifts relative to Me_4Si (δ = 0 ppm)
[b] In $CDCl_3$
[c] In KNH_2/NH_3
[d] Upfield shifts relative to 4
[e] These signals lie under the phenyl multiplets
[f] $J_{3,6}$ = 1.5 Hz
[g] $J_{5,6}$ = 3.0 Hz
[h] $J_{5,6}$ = 2.5 Hz

Table 4.2 *^{1}H NMR data of (p-methoxyphenyl)pyrazine (11) and its σ-adducts 12 and 13*[a]

hydrogen	compounds				
	11[b]	12[c]	Δδ[d]	13[c]	Δδ[d]
H-3	8.87(d)[e]	7.07	1.80	5.34	3.53
H-5	8.33(d)[f]	4.20(d)[g]	4.13	6.73(d)[g]	1.60
H-6	8.46(dd)[e,f]	5.85(d)[g,i]	2.61	5.99(d)[g,i]	2.47
OCH_3	3.82	3.81		3.76	
phenyl	7.90[h] 6.93[h]	6.75, 6.86, 7.32 and 7.70[h]			

[a] Chemical shifts relative to Me_4Si (δ = 0 ppm)
[b] In $CDCl_3$
[c] In KNH_2/NH_3
[d] Upfield shifts relative to 11
[e] $J_{3,6}$ = 1.5 Hz
[f] $J_{5,6}$ = 3.0 Hz
[g] $J_{5,6}$ = 2.7 Hz
[h] J = 9 Hz
[i] These signals may be interchanged

and 4.16 ppm respectively, and in 9 as a singlet at 5.35 ppm. The upfield shifts $\Delta\delta$ lie between 3.4 and 4.1 ppm and are of the usually observed magnitude. The rather low field resonance of H-3 in 4 and 9 is due to the deshielding effect of the neighbouring phenyl substituent. For the same reason the H-3 signals of 5 and 6 are expected to lie in the complex region of the phenyl multiplets.
In order to simplify this complex picture we measured the NMR spectrum of (*p*-methoxyphenyl)pyrazine (11), since the introduction of the *para* methoxy substituent reduces the phenyl multiplet to two doublets. In KNH_2/NH_3 11 gives two adducts, *i.e.* the C-5 adduct 12 and the C-3 adduct 13 (Scheme 4.3).



Scheme 4.3

All hydrogens of the pyrazine ring in both adducts are visible and can be assigned alongside four sharp doublets of the phenyl groups (Table 4.2). The upfield shifts are very close to those observed for 6 and 9.
The ^{13}C NMR spectrum of 4 in KNH_2/NH_3 shows only the presence of the adducts 6 and 9; adduct 5 cannot be detected due to its low concentration. The assignment of the carbon atoms in 6 and 9 is based on comparison with the spectra of 5-deuterio-2-phenylpyrazine and of 3,5-dideuterio-2-phenylpyrazine (Table 4.3).

Table 4.3 ^{13}C *NMR data of phenylpyrazine (4) and its σ-adducts 6 and 9*

	compounds				
atom	4[a]	6[b]	Δδ[c]	9[b]	Δδ[c]
	Chemical shifts[d]				
C-3	142.3	141.4	0.9	62.1	80.2
C-5	143.0	64.6	78.4	142.5	0.5
C-6	144.3	126.2	18.1	110.5	33.8
	Coupling constants $^1J_{C-H}$ (Hz)				
C3-H	181	172		150	
C5-H	184	152		164	
C6-H	181	160		174	

[a] In $CDCl_3$
[b] In KNH_2/NH_3
[c] Upfield shifts relative to 4
[d] Relative to Me_4Si (δ = 0 ppm)

The ratio of 5, 6 and 9 calculated from the ^1H NMR spectrum is 1:3:6, and this ratio does not change much when the mixture is left to stand for 20 hours at -60°C. At a temperature of -40°C adduct 5 disappears within 1.5 hours, and the ratio 6:9 becomes 45:55. After keeping the solution overnight at room temperature in a sealed tube the C-5 adduct 6 is the only species observed (also some decomposition has taken place). All these results show that the adducts 5 and 9 are kinetically favoured, and that 6 is thermodynamically the most stable one.

The formation of both 6 and 9 suggests the possibility that the two amino products 7 and 10 are formed *via* an S_N(ANRORC) process. In order to determine the possible contribution of this process we carried out the amination of 4 in ^{15}N labeled KNH_2/NH_3. The main product 7* was diazotized in tetrafluoroboric acid (40%) yielding 5-fluoro-2-phenylpyrazine (8), which was found to contain *no* ^{15}N. A ring opening-ring closure pathway is therefore excluded in the formation of 7 (Scheme 4.2). We did not succeed, however, in locating the ^{15}N-label in product 10*, because hydrolysis (acidic and basic)

as well as diazotization (in hydrochloric acid, acetic acid, tetrafluoroboric acid and sulphuric acid) failed.
Nevertheless we obtained some evidence that the 3-amino product 10 is not formed from adduct 6. A solution of 4 in KNH_2/NH_3 in a sealed Carius tube was kept overnight at room temperature. As shown above, at this temperature only C-5 adduct 6 is then present. Cooling and quenching with ammonium chloride yielded only one product, namely 7. No trace of 10 was discovered. This result excludes the operation of an S_N(ANRORC) mechanism in the formation of 10. This is confirmed by the fact that on addition of azobenzene, which has been found to prevent the S_N(ANRORC) mechanism in the amination of 4-phenylpyrimidine[3], product 10 is still formed.
A similar temperature dependency of the product of a Chichibabin amination has been demonstrated for 1,5-naphthyridine[10].
This temperature effect also explains the result of the reaction of 4 in liquid methylamine (b.p. -6°C) containing potassium methylamide: when quenched after 3 hours, 5-methylamino-2-phenylpyrazine is formed in considerable yield (60%), whereas no 3-methylamino-2-phenylpyrazine is detected. The preference for substitution at C-5 is due to the higher reaction temperature so that the thermodynamically most stable adduct is formed.

Experimental section

^1H NMR spectra in $CDCl_3$ were recorded on a Hitachi-Perkin Elmer R-24B or on a Varian EM 390 spectrometer, using Me_4Si as standard (δ = 0 ppm). The latter apparatus, equipped with a Varian EM 3940 variable temperature controller, or a Varian XL-100-15 spectrometer was used for the spectra in liquid ammonia. The solvent peak served as standard (δ = 0.95 ppm). The ^{13}C NMR spectra were recorded on the Varian XL-100-15 with trimethylamine added as reference compound (δ = 47.5 ppm). Typical parameters were: spectral width 5120 Hz (1.25 Hz/point), acquisition time 0.8 s, pulse delay 1.2 s, pulse width 10-20 μs.
The excess of ^{15}N was calculated from the (M+1)/M ratio, determined on an AEI MS 902 mass spectrometer equipped with a VG ZAB console. Gas chromatographic analyses were performed on a Varian 3700 apparatus using a glass column (200 cm, o.d. 6 mm) filled with 3% SP 2250 on Chromosorb W-HP 100/120

mesh, operating at 100-200°C.
Column chromatography was carried out over Merck silica gel 60 (70-230 mesh ASTM) using chloroform/methanol mixtures as eluent.

Phenylpyrazine (4) was prepared according to the literature[11]. The same procedure, starting from 1.0 g pyrazine and 1.4 equivalents *p*-methoxyphenyllithium, was used to prepare *(p-methoxyphenyl)pyrazine* (11). After recrystallization from petroleum-ether (b.r. 40-60°C) 1.2 g of 11 was obtained (52%), m.p. 86.5-87.5°C. Analysis: calculated for $C_{11}H_{10}N_2O$ (186.21): C 70.95, H 5.41; found: C 71.24, H 5.70.
5-deuterio- and *6-deuterio-2-phenylpyrazine* were synthesized according to the procedure described before[12].

2,6-dideuterio-3-phenylpyrazine-1-oxide was prepared as follows. 4 was oxidized with a 1:1 mixture of glacial acetic acid and 30% hydrogen peroxide[13] at room temperature. After several days the conversion was complete. The solution was basified with ammonia and extracted with ether. Drying over $MgSO_4$ and evaporation yielded the solid 3-phenylpyrazine-1-oxide. Selective exchange of H-2 and H-6 was achieved in a 0.5 N NaOH solution in a 1:1 mixture of D_2O and CD_3OD[14] at 40°C in 6 hours, followed by extraction with ether. Yield 80%.

Reduction of 2,6-dideuterio-3-phenylpyrazine-1-oxide. Several attempts were made to reduce the N-oxide. Neither the procedure using powdered iron or zinc in acetic acid[15] nor the reaction with phosphorylchloride in dimethylformamide[16] or tetrahydrofuran[17] was successful. We found that reduction with sodium dithionite[17] gave the desired *3,5-dideuterio-2-phenylpyrazine* in 57% yield.

Amination. The amination procedure in liquid ammonia and in methylamine were carried out as described before[3,18]. The products were purified by column chromatography.
5-methylamino-2-phenylpyrazine was recrystallized from petroleum-ether b.r. 40-60°C. ^1H NMR ($CDCl_3$): δ = 8.42 ppm (1H, d, J = 1.5 Hz), δ = 7.8-7.9 ppm (3H, m), δ = 7.2-7.5 ppm (4H, m), δ = 4.93 ppm (1H, NH), δ =2.95 ppm (3H, d, J = 5 Hz). Analysis: calculated for $C_{11}H_{11}N_3$ (185.22): C 71.32, H 5.99; found: C 71.04, H 5.71.

Conversion of the amino products. Aminopyrazine (3) was converted into pyrazinone according to the literature[19].
5-Amino-2-phenylpyrazine (7) was dissolved in 40% tetrafluoroboric acid and diazotized at -5 - 0°C by adding solid sodium nitrite. After stirring 0.5 hour at 0°C and subsequently at room temperature the solution was neutralized by sodiumcarbonate and extracted with ether. The resulting 5-fluoro-2-phenylpyrazine (8) was purified by preparative TLC.

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

N.J.Kos, J.Breuker, H.C.van der Plas and A.van Veldhuizen

Introduction

The phenomenon of hindered rotation in N-substituted imines is known for many years; it even occurs in phenylbutyl 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 dimethylsulfoxide (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]. On the other hand, ^{1}H 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 strongly 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^- 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 ^{1}H NMR spectrum of a solution of adenine in liquid ammonia containing potassium amide shows three sets of two signals (Table 5.1) of which two sets are assigned to aromatic hydrogens and the set of two broad signals to the NH^- group[10]. The assignments of the aromatic hydrogens are made by comparison of the ^{1}H NMR spectrum with that of 8-deuterioadenine under identical conditions.

Table 5.1 ^{1}H NMR data of the dianions of some aminopurines in liquid ammonia containing potassium amide at -50°C[a]

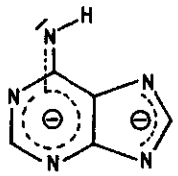
Dianion of	H-2	H-6	H-8	N-H	isomer distribution
adenine (1)	7.53	-	7.37	4.59	65%
	7.64	-	7.34	4.93	35%
8-chloroadenine (3)	7.42	-	-	4.49	65%
	7.53	-	-	4.75	35%
2-aminopurine (4)	-	7.94	7.38	3.83	75%
	-	8.00	7.38	3.69	25%
8-aminopurine (5)	7.18[b]	7.63[b]	-	3.90	-

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

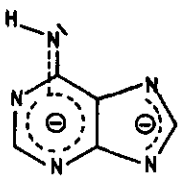
[b] These assignments may also be interchanged

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 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). It could be estabilised from the ^{1}H NMR data that the two geome-

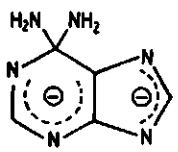
trical isomers 1a and 1b are present in the ratio 65:35. Which isomer is the more abundant one has not been determined. This ratio is found to be independent of the potassium amide concentration, ranging from 1.5 to 4 equivalents.



1a



1b



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The existence of the two geometrical isomers 1a and 1b is confirmed by ^{13}C NMR spectroscopy (Table 5.2). 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 twice. All signals can be assigned unambiguously by comparison of the spectrum with that of deuterioadenine and with literature data.

Table 5.2 ^{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

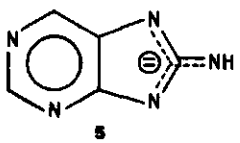
That the double signals for C-2 as well as for C-8 coincide is proven by selective decoupling. Since the ^1H NMR spectral data had shown the isomer ratio 65:35, the set of ^{13}C signals with the greater intensities is assigned to the more abundant isomer.

An attempt to confirm the geometrical isomerism by measuring the coalescence of the ^{1}H 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 ^{1}H 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 do not originate 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]). We therefore reacted adenine with ^{15}N labeled 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 by 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 ^{1}H NMR spectrum (Table 5.1). 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). Integration shows that we are dealing with a dianion and not with a monoanion, 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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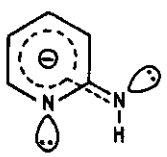

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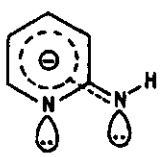

7b

B. Aminopyrazine, 2-aminopyridine, aminopyridazines and aminopyrimidines

The ^{1}H NMR data 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. 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 present in two geometrical isomers at -50°C too (ratio 55:45). The ratio is independent of the concentration of 7 (0.2-2 mmol/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 than in 7 (Table 5.3).
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 present in two geometrical forms as well. The isomer distribution is 50:50, 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 of the anion of 2-amino-4-phenylpyrimidine (10). 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 5.3 show further that for the anion of 4-aminopyrimidine (11) geometrical isomerism also exists; the ratio is 70:30.

Table 5.3 *^1H 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)	-	-	-	6.08[b]	7.75	4.70[b]	50%
	-	-	-	6.12[b]	7.75	4.76[b]	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-dimethyl-aniline (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 this case it cannot be decided which signals belong to each other

[c] Symmetric molecule

[d] Not observed

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 containing potassium amide at +31°C[12].
In our study, however, we find that at -50°C the anions of aniline and 4-methylaniline (12) show the presence of geometrical isomers (Table 5.3).

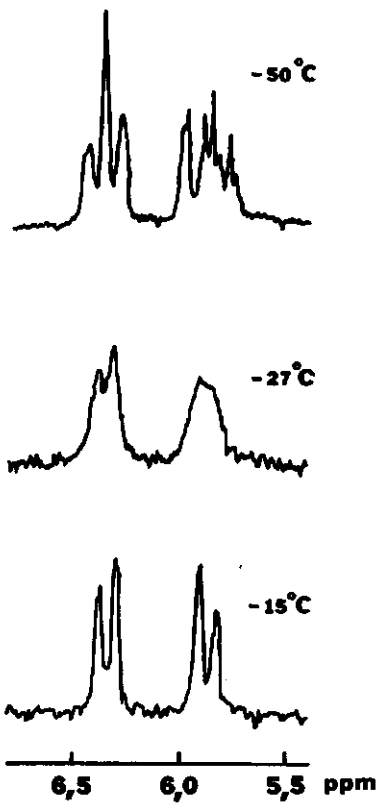

Figure 5.1 Part of the ^1H NMR spectrum of 12 at different temperatures

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. In actual fact coalescence does take place on raising the temperature from -50°C to -27°C. At -15°C the spectrum consists of two doublets, representing both equivalent *ortho* and *meta* hydrogens (Figure 5.1).
The aromatic signals in the spectrum of the anion of aniline at -50°C cannot be interpreted simply, 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) is found to exist in two isomers too, 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 MeSi 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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*Dedicated to Professor Tetsuji Kametani for his pioneering work in natural product chemistry and his contribution to the development of heterocyclic chemistry on the occasion of his retirement from the Chair of Organic Chemistry at the Pharmaceutical Institute of Tohoku University at Sendai.

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6 AN NMR INVESTIGATION OF GEOMETRICAL ISOMERISM IN THE ANIONS OF (METHYLAMINO)-PYRIDINES. ASSIGNMENT OF THE *SYN*- AND *ANTI*-ISOMERS

N.J.Kos, J.Breuker, H.C.van der Plas and A.van Veldhuizen

Introduction

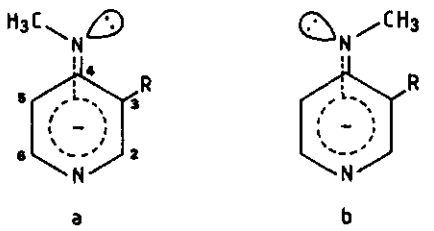
The ^{1}H NMR spectra of the anions of aminopyrazine[1], 2-aminopyridine[1] and several anilines[2] at 25-31°C are reported in the literature. In these studies the existence of geometrical isomers was not mentioned. Geometrical isomerism has been noticed however in the anion of 2,4,6-trinitroaniline[3], and in our own studies evidence for the occurrence of *syn*- and *anti*-isomers of the anions of amino azaaromatics (2-aminopyridine, 2- and 4-aminopyrimidines, aminopyrazine, 3- and 4-aminopyridazine and 2-, 6- and 8-aminopurines) has also been obtained[4,5,6].

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 non-equivalency of H-4 and H-6[5]. In order to investigate the generality of this phenomenon in (methylamino)aza heteroarenes we measured ^{1}H 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 ^{1}H NMR spectrum of the anion of 4-(methylamino)pyridine (1) measured in liquid ammonia containing potassium amide at -50°C shows geometrical isomerism just as the neutral compound[7]. This phenomenon is revealed by the appearence of separate signals for H-3 and H-5 and for H-2 and H-6, showing that these hydrogens are not identical.



1: R = H
2: R = CH_3

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 ^{1}H 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 ^{1}H NMR spectrum of 2 consists only of a singlet (H-2) and two doublets (H-5 and H-6, Table 6.1); 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 *ortho*-methyl substituent[8]; *ii.* the related compound 2-methyl-4-nitro-N-methylaniline is present in only *one* form at temperatures between -150°C and -50°C[7]; *iii.* 4-(methylamino)pyridine (thus not the anion) undergoes coalescence at about -60°C.

Table 6.1 ^{1}H *NMR data of the anions of N-methylaminopyridines in liquid ammonia containing potassium amide at -50°C*[a,b]

Anion of		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-(methyl-amino)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-(methyl-amino)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-(methyl-amino)pyridine[f]	(7a)	-	-	6.50	5.35	7.43	2.71	100

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

[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

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 *ortho*-methyl are directed away from

Table 6.2 ^{13}C NMR data of N-methylaminopyridines in $CDCl_3$ at 35°C and of their anions in liquid ammonia containing potassium amide at -50°C[a]

Compound	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-(methyl-amino)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 ppm relative to Me_4Si (δ = 0 ppm)

[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

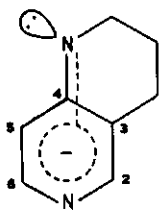
[e] The methyl group at C-4 is found at 19.2 ppm

each other, due to repulsion (structure 2a).

In the ^{1}H NMR spectrum of anion 1 the signals of H-3 and H-5 are well separated (δ = 5.89 and 5.60 ppm relative to Me_4Si), 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 and 7.47 ppm). These close resemblances make it evident to assign the signals in the spectrum of 1 as indicated in Table 6.1. From this result it appears that the *ortho*-hydrogen atom *syn* oriented to the nitrogen lone pair (H-3) resonates further 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 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 en 2a we are able to interpret the ^{13}C NMR spectra of anion 1 by selective decoupling experiments. The results are that the *ortho*-hydrogen resonating at lower field (H-3) is bound to the *ortho*-carbon atom at lower field (C-3), and that the hydrogen at higher field (H-5) is bound to carbon at higher field (C-5). The same relationship is found for the H-2, H-6 hydrogen and C-2 and C-6 carbon atoms. These results lead to the assignment as given in Table 6.2.

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-methyl-4-(methylamino)pyridine in which the *ortho*-hydrogen (H-5) and the lone pair are in the *syn* orientation and the methyl groups are directed towards each other. The *ortho* carbon atom C-5 in anion 3, which is in *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, which is in *syn* position relative to the nitrogen lone pair.



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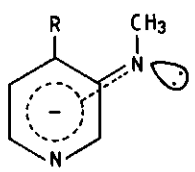
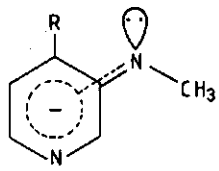
All results indicate that in anion 1 the *ortho*-carbon in the *syn* position relative to the lone pair resonates at a lower field than the *ortho*-carbon in the *anti* position. Thus, this is in analogy to what has been found for the *ortho*-hydrogen atoms.

B. 3-(methylamino)pyridines

In the ^{1}H NMR spectrum of the anion of 3-(methylamino)pyridine (4) H-2 appears as two well-separated signals (7.50 and 7.03 ppm); 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.



a



b

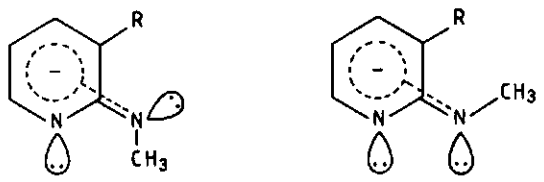
4: R = H
5: R = CH_3

This isomer comprises about 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), which is 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). Hence the less abundant isomer should have structure 4b. This means that *ortho*-hydrogen H-2 in anion 4a, which is in a *syn*-orientation with respect to the nitrogen lone pair, is less shielded than H-2 in 4b (*anti*); H-4 in *syn* orientation is also 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 *ortho*- hydrogens (H-2 in 4a and H-4 in 4b) are bound to the downfield *ortho*-carbons C-2 and C-4 respectively. Thus, the *ortho*-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* posi-

tion. The same relationship is found for C-4. 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) two isomers can again 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°C 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.



a b

6: R = H
7: R = CH_3

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), being expected to exist in conformation 7a only. Thus, the minor isomer has conformation 6a and the more favoured 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 favour 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 increasing concentration of crown-ether the signals of 6b decrease, and even disappear in favour of those for 6a. Furthermore, when caesium amide is used as base instead of potassium amide, a change of the isomeric ratio from 40:60 to 55:45 in favour of conformer 6a has been observed. These results suggest that the complexation of 6b with

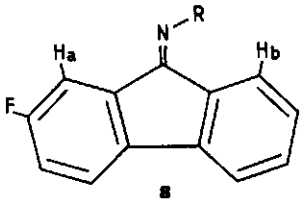
the potassium cation is the dominating factor in determining the isomer distribution. The larger size of the caesium ion makes this complexation less efficient. The preferred formation of 6a under kinetic control is not due to a preference of the neutral compound for a conformation like 6a, because a 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-methylaminopyridine anions the *ortho*-hydrogen *syn* oriented to the amino lone pair is less shielded than that in *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 further downfield[12].

In all three N-methylaminopyridine anions the *ortho*-carbon in *anti* orientation relative to the lone pair resonates at higher field as well. 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 *ortho*-carbon atoms in N-methylaniline[15]. This neutral compound exists in two isomeric forms at -130°C. It was found for the *meta*-carbon atoms that the carbon at the *same* side of the molecule as the N-methyl group was associated with the lower field absorption. This was confirmed by our experiments.



8

R = alkyl

Experimental section

The procedures followed to obtain the ^{1}H and ^{13}C NMR spectra have been described previous[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]).

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7 AN NMR INVESTIGATION OF GEOMETRICAL ISOMERISM IN THE ANIONS OF AROMATIC AMINES. THE EFFECTIVE SIZE OF A LONE ELECTRON PAIR

J.Breuker, N.J.Kos, H.C.van der Plas and A.van Veldhuizen

Introduction

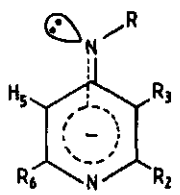
A recent NMR spectroscopic study of the anions of some aromatic amino compounds in liquid ammonia containing potassium amide at -50°C has unequivocally proved the occurrence of geometrical isomerism in these systems[1]. This phenomenon has been ascribed to an enhanced double bond character of the exocyclic carbon-nitrogen bond, leading to restricted rotation. From a ^{1}H and ^{13}C NMR study of the anions of 2-,3- and 4-(methylamino)pyridines, allowing the assignment of the *syn* and *anti*-isomers[2], it appeared that the *ortho*-hydrogen and carbon atoms *syn* oriented to the electron pair of the methylamino group all resonate at a lower field than the hydrogen and carbon atoms in the *anti* position. In continuation of this work we studied the ^{1}H and ^{13}C NMR spectra of the anions of 4-,3- and 2-aminopyridine and some of their C-methyl derivatives, and established the assignment of the signals to either the *syn* or the *anti*-isomer.

Results and discussion

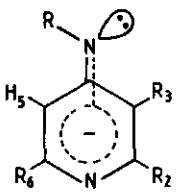
A. 4-Aminopyridines

Different signals appear for all aromatic hydrogen atoms in the ^{1}H NMR spectra of the anions of 4-aminopyridine (1) and 4-amino-2,6-dimethylpyridine (2), measured in liquid ammonia containing potassium amide at -50°C (Table 7.1). The non-equivalency of the H-3 and H-5 and of the H-2 and H-6 is a result of restricted rotation around the exocyclic carbon-nitrogen bond.

Geometrical isomers are also observed for the anion of 4-amino-3-methylpyridine (3) as appears in the ^1H NMR spectra from two signals for each H-2, H-5 and H-6. The isomeric ratio is, of course, 50:50 for anions 1 and 2 due to their symmetry; for anion 3 an isomeric ratio of 75:25 is found (determined by integration of appropriate proton signals), showing that a methyl substituent in *ortho* position to the NH^- group has a considerable influence on the isomer distribution[1]. When the solution containing 3 was allowed to stand for one day at room temperature in a sealed tube, the spectrum did not change. This shows that the *syn* and *anti*-isomers of 3 are in thermodynamic equilibrium.



a



b

	R	R_2	R_3	R_6
1:	H	H	H	H
2:	H	CH_3	H	CH_3
3:	H	H	CH_3	H
4:	CH_3	H	H	H

To decide wich signals belong to the *syn* or *anti* structure of the anions we used both ^1H and ^{13}C NMR spectroscopic data (Tables 7.1 and 7.2) and applied two criteria for discerning these structures. The first one is the well-known dependence of the coupling constant $^3J_{13C-NH}$ on the geometry of the system[3]. When using the $^3J_{13C-NH}$ between the hydrogen of the anionic amino group and the carbon atom in *ortho* position, the coupling constant is larger for the *anti* than for the *syn* structure[3]. The second criterion is the chemical shift of the *ortho* hydrogens. In a previous paper it was unequivocally established that an *ortho*-hydrogen, being in a position *syn* relative to the lone pair of an anionic methylamino group is more deshielded than in the *anti* position and thus appears at lower field[2]. We can use this result in the aminopyridine anions, since the shielding of the *ortho*-hydrogen in these anions will be primarily determined by electric field effects caused by the

lone pair* orientation and to a lesser extent by the N-H or N-CH_3 group. On consideration of the spectra of anion 3, we observed that in the predominant isomer $^3J_{^{13}C-NH}$ for C-5 is larger (15 Hz) than that for the minor isomer (8 Hz); moreover, H-5 in the major isomer resonates at lower field. Based on these two criteria we reached the conclusion that isomer 3a is the predominant one. This result seems to indicate that the 'effective size' of the electron pair on the NH^- group is *larger* than that of the hydrogen atom of NH^-, leading to a preference for 3a in which the proton is near the *ortho*-methyl substituent. This is a somewhat surprising result, since the sp^2 electron pair in pyridine and comparable compounds[4,5,6] as well as the sp^3 electron pair in, for instance, piperidine[7] are found to be 'smaller' than a hydrogen atom. In the anions investigated in this study, however, two distinct differences have to be taken into consideration in comparison with the systems, mentioned in the literature: *i.* in liquid ammonia solvation takes place and probably makes the electron pair effectively larger than a hydrogen[8]; *ii.* we are dealing with an electron pair in an anionic amino group and theoretical calculations have shown that the size of an electron pair increases strongly in the series NH_3-NH_2^--NH^{2-} [9].
It cannot be excluded that isomer 3a is better solvated than isomer 3b, since solvation of the electron pair in 3b may be hindered by the *ortho*-methyl substituent, leading to destabilization. A complication also arises from the possibility that there is an electronic preference for one of the isomers[10]. It is interesting to notice that the coupling constants $^3J_{^{13}C-NH}$ for C-5 of 3a (15 Hz) and 3b (8 Hz) are not smaller than for C-3 and C-5 of 1 and 2. $^3J_{^{13}C-NH}$ strongly depends on the configuration and will be sensitive to rotation of the amino group[3]. Apparently the *ortho*-methyl substituent is not able to push the amino group out of the plane of the aromatic ring[11]. The same two criteria as mentioned above are used for the interpretation of the ^1H and ^{13}C NMR signals of the anions 1 and 2 (Tables 7.1 and 7.2).
The assignments of the signals for C-2 and C-6 in both anions are not completely certain and may ultimately have to be reversed. Comparison with the

* The term 'lone pair' is used for the two electron pairs on the amino nitrogen atom. While the formulas used throughout this paper might suggest an sp^2 lone pair, with a p-orbital in conjugation with the pyridine ring, we realize that this is only an approximation, since the negative charge is not fully delocalized in the aromatic ring.

Table 7.1 ^{1}H *NMR data of anions of aminopyridines and aminopyrimidines in liquid ammonia containing potassium amide at -50°C*[a,b]

Anion of		H-2	H-3	H-4	H-5	H-6	CH_3	NH	isomer distribution %
4-aminopyridine	1a	7.26	5.66	-	5.82	7.18	-	4.00	50:50
4-amino-2,6-dimethylpyridine	2a	-	5.46	-	5.62	-	1.91 1.95	3.86	50:50
4-amino-3-methylpyridine	3a	7.22	-	-	5.89	7.27	1.74	3.84	75
	3b	7.20	-	-	5.64	7.14	1.79	4.12	25
4-(methylamino)pyridine	4a	7.43	5.60	-	5.89	7.22	2.54	-	
3-aminopyridine	5a	7.21	-	6.20	6.39	6.70	-	3.19[c]	60
	5b	7.39	-	6.03	6.47	6.70	-	3.15[c]	40
3-amino-6-methylpyridine[12]	6a	7.15	-	6.16	6.24[c]	-	2.03	2.92	60
	6b	7.32	-	6.00	6.33[c]	-	2.03	2.84	40
3-amino-2-methylpyridine	7a	-	-	6.23	6.47[c]	6.71	2.02	2.90	70
	7b	-	-	5.96	6.39[c]	6.65	2.02	3.33	30
3-amino-4-methylpyridine	8a	7.15	-	-	6.40	6.69	1.87	3.32	35
	8b	7.41	-	-	6.45	6.74	1.82	2.92	65
3-(methylamino)pyridine	9a	7.03	-	d	d	6.84	2.60	-	20
	9b	7.50	-	5.76	d	d	2.50	-	80
2-aminopyridine	10a	-	5.73	6.70	5.49	7.45	-	3.90	55
	10b	-	5.82	6.62	5.42	7.32	-	4.22	45
2-amino-5-methylpyridine	11a	-	5.70	6.55	-	7.25	1.85	3.7	55
	11b	-	5.82	6.52	-	7.12	1.85	4.0	45
2-amino-3-methylpyridine	12a	-	-	6.68	5.51	7.42	1.79	3.74	70
	12b	-	-	6.55	5.40	7.23	1.79	4.39	30

2-(methylamino)pyridine	13a	-	5.58	6.96	5.57	7.57	2.54	-	60
	13b	-	5.81	6.57	5.35	7.50	2.62	-	40
4-aminopyrimidine	14a	7.67	-	-	5.81	7.24	-	4.80	70
	14b	7.82	-	-	5.78	7.24	-	4.74	30
4-amino-6-methylpyrimidine	15a	7.54	-	-	5.58	-	1.83	4.73	70
	15b	7.70	-	-	5.52	-	1.83	4.53	30
4-aminopyrimidine	16a	7.76	-	-	6.34	-	-	5.05	75
	16b	e	-	-	6.26	-	-	4.95	25

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

[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] These assignments may also be interchanged

[d] Present as a complex signal between 6.4 and 6.7 ppm

[e] In same region as the phenyl signals

Table 7.2 ^{13}C *NMR data of aminopyridines and N-methylaminopyridines in* $CDCl_3$ *at 35°C and of their anions in liquid ammonia containing potassium amide at -50°C*[a]

Compound		C-2	C-3	C-4	C-5	C-6	CH_3	$^3J_{^{13}C-NH}$ (Hz)
4-aminopyridine	neutral[19,b]	149.6	109.8	156.3	109.8	149.6	-	
	anion 1a	148.1[c]	112.9	168.6	111.0	148.4[c]	-	5(C-3), 13(C-5)
4-amino-2,6-dimethylpyridine	neutral	158.5	106.5	153.7	106.5	158.5	24.4	
	anion 2a	154.4[c]	108.7	169.1	106.6	154.8[c]	24.0; 24.2	8(C-3). 15(C-5)
4-amino-3-methylpyridine	neutral	150.3	117.0	151.8	109.1	148.3	14.0	
	anion 3a	d	116.4	166.7	110.3	d	15.6	15(C-5)
	anion 3b	d	117.9	166.8	111.3	d	16.5	8(C-5)
4-(methylamino)pyridine	neutral	149.8	107.3	154.9	107.3	149.8	29.2	
	anion 4a	149.5	102.4	163.0	115.0	146.1	36.5	
3-amino-6-methylpyridine[12]	neutral	136.9	140.3	122.8	123.3	148.3	23.3	
	anion 6a	138.3	159.8	118.2	123.2	130.3	22.3	13(C-4)
	anion 6b	137.6	160.0	120.0	123.2	130.3	22.3	8(C-4)
3-(methylamino)pyridine	neutral	135.5	146.0	118.1	124.0	137.7	30.0	
	anion 9a	129.5	159.2	123.0	122.3	125.1	37.3	
	anion 9b	143.6	159.2	107.4	124.8	122.6	37.3	
2-aminopyridine	neutral[20,e]	160.5	108.5	136.8	111.7	147.8	-	
	anion 10a	172.7	112.9	134.9	100.4	149.5	-	6(C-3)
	anion 10b	171.2	111.2	134.7	99.9	149.0	-	13(C-3)
2-amino-5-methylpyridine	neutral[20,e]	158.3	108.4	138.0	121.0	147.4	17.1	
	anion 11a	171.5	112.6	136.3	107.4	148.2	17.2	small (C-3)
	anion 11b	170.2	110.8	136.3	106.8	147.8	17.2	13(C-3)
2-(methylamino)pyridine	neutral	160.0	106.3	137.6	112.7	148.2	29.0	
	anion 13a	166.7	114.5	132.2	99.1	149.1	35.5	
	anion 13b	168.6	102.0	136.2	100.1	149.6	36.6	
4-aminopyrimidine	neutral[21,f]	158.3	-	163.2	105.1	154.6	-	
	anion 14a	159.2	-	169.0	108.6	150.2	-	12(C-5)
	anion 14b	159.8	-	171.1	110.0	150.1	-	7(C-5)

spectra of 3 did not make a definitive assignment of C-2 and C-6 possible either. Comparison of the ^{13}C NMR spectra of the now firmly established structures 1a, 2a and 3a with that of the anion of 4-(methylamino)pyridine (4a) shows the interesting feature that in 4a the signal of the *ortho*-carbon atom *anti* relative to the lone pair (C-3) is found at higher field than C-5[2], while in 1a, 2a and 3a the higher field signal has to be ascribed to the carbon atom in the *syn* position (C-5).

B. 3-Aminopyridines

In the ^{1}H NMR spectrum of the anion of 3-aminopyridine (5) two isomers can be discerned in a ratio 60:40. We applied the same two criteria as mentioned in section A for the signal assignment of the hydrogens in the two isomeric configurations (5a and 5b). Since establishment of the magnitude of the $^{3}J_{13C(4)-NH}$ is disturbed by coupling of C-4 with H-6, we measured $^{3}J_{13C(4)-NH}$ in the anion of 3-amino-6-methylpyridine (6)[12]. Anion 6 gives the same isomeric ratio as 5, *i.e.* 60:40. Application of the two criteria gives the following results for the more abundant isomer of 6: *i.* $^{3}J_{13C-NH}$ for C-4 is 13 Hz and smaller for C-2; *ii.* the *ortho* H-4 is observed at lower field than H-4 in the minor isomer.
These results lead to the conclusion that isomer 6a is predominant over 6b. This is confirmed by the chemical shift of H-2, which lies further upfield in 6a than H-2 in 6b, and the magnitude of $^{3}J_{13C-NH}$ of the less abundant isomer, which is 8 Hz for C-4. The same result is obtained for 5.
The chemical shifts of H-4 in the anion of 3-amino-2-methylpyridine (7) show that the preferred isomer has configuration a. The isomer ratio has slightly changed in favour of structure a (70:30). Thus, it is evident that the presence of a methyl group at position 2 promotes the formation of 4-methylpyri-

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Notes to Table 7.2

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

[b] Measured in ethanol

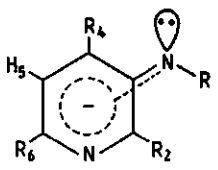
[c] These assignments may be interchanged

[d] A complex spectrum is found at 146.6-147.1 ppm

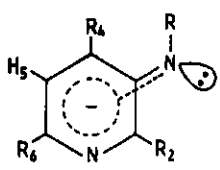
[e] Measured in hexamethylphosphoramide

[f] Measured in dimethylsulphoxide

dine (8), which is at lower field in the more abundant isomer, 8b is the favoured isomer. From these results it is evident that a methyl substituent *ortho* to the anionic amino group causes a preference for the isomer in which the amino hydrogen is directed to the methyl group. This indicates that the steric requirement of the electron cloud on the anionic amino group can be considered as 'effectively larger' than the amino hydrogen. This conclusion is in agreement with the one reached in section A.
On consideration of the ^{13}C NMR spectra of anion 6 it appears that the carbon atom *syn* to the lone pair (C-4, $^{3}J_{^{13}C\text{-}NH}$ = 13 Hz) resonates at higher field than C-4 in the *anti* position ($^{3}J_{^{13}C\text{-}NH}$ = 8 Hz). An analogous difference is observed for C-2. When we compare this result with that of our previous study concerning the anion of 3-(methylamino)pyridine (9) we see that this relationship is reversed: both in 9a and 9b the *ortho* carbon atoms *syn* to the lone pair are found further downfield than in the *anti* position[2].
In section A an analogous difference between 4-aminopyridine and 4-(methylamino)pyridine was found. A second interesting difference between 5 and 9 concerns the isomer ratio. Anion 9 exists mainly (80%) in configuration b, whereas for 5 structure a is predominant.



a



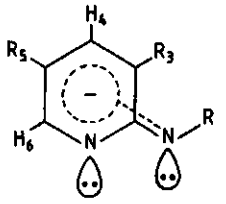
b

	R	R_2	R_4	R_6
5:	H	H	H	H
6:	H	H	H	CH_3
7:	H	CH_3	H	H
8:	H	H	CH_3	H
9:	CH_3	H	H	H

C. 2-Aminopyridines

We have already reported that the anion of 2-aminopyridine (10) exists in two isomeric forms (ratio 55:45)[1]. This ratio was shown to be independent of the concentration of both 10 and potassium amide[1]. To facilitate the deter-

mination of $^{3}J_{13C-NH}$ we measured the ^{13}C NMR spectrum of the anion of 2-amino-5-methylpyridine (11). The isomeric forms of 11 are present in the same ratio as in 10. For the *syn- anti* assignment we again used the two criteria as discussed already, *i.e.* $^{3}J_{13C-NH}$ for C-3 and the chemical shift difference of H-3.



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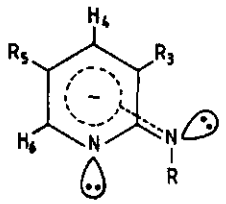


b

	R	R_3	R_5
10:	H	H	H
11:	H	H	CH_3
12:	H	CH_3	H
13:	CH_3	H	H

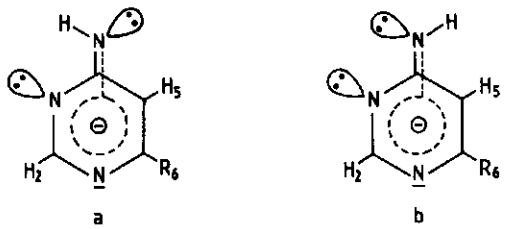
The results shown in Tables 7.1 and 7.2 lead to the conclusion that conformer 10a, in which the two electron pairs are in the *syn* orientation is slightly preferred, although by repulsion of the electron pairs on the two nitrogen atoms and intramolecular hydrogen bonding[13] 10b would be expected to be favoured. The observed predominancy of 10a may be ascribed to stabilization as a result of complexation of the potassium cations with both lone pairs. Some evidence for this hypothesis was obtained from the observation that the amount of 10a decreases and even disappears in favour of 10b on addition of 18-crown-6-ether, a compound known to form complexes with potassium cations. Using caesium amide instead of potassium amide also slightly favours 10b (ratio 35:65). These results are analogous to the behaviour of the anion of 2-(methylamino)pyridine (13).

The *syn-anti* assignment in the anion of 2-amino-3-methylpyridine (12) cannot be based on the position of a hydrogen atom *ortho* to the amino group, but comparison of the chemical shifts of H-4, H-5 and H-6 in the anions 10, 11 and 12 indicates that the predominant structure is 12a. This is confirmed by the change in isomeric ratio in favour of 12b, when using 18-crown-6-ether or adding caesium amide instead of potassium amide. The preference for 12a is stronger (70:30) than for 10a and 11a (55:45), and does not alter when

the temperature is allowed to rise to 20°C. This result can again be explained in terms of the electron pair being 'larger' than a hydrogen atom. Considering the position of the C-3 signal in the ^{13}C NMR spectrum of anions 10 and 11, it is evident that this *ortho*-carbon atom in the *syn* position relative to the lone pair ($^{3}J_{13C-NH}$ = 13 Hz) is observed at higher field than in the *anti* position ($^{3}J_{13C-NH}$ = 6 Hz). In anion 13 this relationship is reversed. This is in agreement with the results in sections A and B.

D. 4-Aminopyrimidines

We have already reported that the anion of 4-aminopyrimidine (14) gives two isomeric conformations in the ratio of 70:30[1]. This ratio does not change on standing at room temperature for an hour, so we are dealing with a thermodynamic equilibrium. We can use the signals of H-5 and C-5 and $^{3}J_{13C-NH}$ for the *syn-anti* assignment. In the more abundant isomer H-5 appears at lower field and C-5 at higher field, while $^{3}J_{13C-NH}$ is 12 Hz compared with 7 Hz for the other isomer, showing that 14a is the predominant isomer.



14: $R_6 = H$
15: $R_6 = CH_3$
16: $R_6 = C_6H_5$

This conclusion is further substantiated by the observation that on addition of 18-crown-6-ether the signals of the minor isomer 14b, which is probably stabilized by complexation with the potassium cation, disappear. When caesium amide is used instead of potassium amide we also find less of 14b.
It is evident from the ^{1}H NMR spectra of the anions of 4-amino-6-methylpyrimidine (15) and 4-amino-6-phenylpyrimidine (16) that these anions are preferably present in configuration a as well. Apparently a methyl of phenyl group in position 6 does not significantly influence the isomer ratio.

The interesting fact that the anions 14,15 and 16 prefer the isomeric form in which the two electron pairs are in the *anti* orientation, while the anion of 2-aminopyridine (10) slightly prefers the *syn* structure, is possibly caused by a different delocalization pattern of the negative charge. This may be due to the fact that in 4-aminopyrimidine (14b) a part of the negative charge is present on the *para* ring nitrogen atom. This decreased electron density on N-3 and on the NH^- group may cause a less efficient complexation of the potassium cation[14]. As a result hydrogen bonding[13] and mutual repulsion of the electron pairs will favour 14a.

Conclusion

It is evident from this study that an electron pair is 'larger' than a proton on an NH^- group, but this result cannot be completely ascribed to steric factors. It is possible that the preferred isomer is also favoured by better solvation than the other isomer and a difference in electronic stabilization may also exist. The results are complicated further by the fact that there are two lone pairs present on the NH^- group which will both have some conjugation with the aromatic ring.
This study clearly shows that, in contrast to what has been observed with the anions of the methylaminopyridines, the carbon atom in the *syn* orientation to the lone pair appears at higher field than the corresponding carbon in the *anti* position. As the chemical shifts of the *syn* carbon atoms in the methylaminopyridines are predominantly determined by steric compression[2], it is evident that other factors working in an opposite direction are involved here.

Experimental section

The procedures followed to obtain the ^1H and ^{13}C NMR spectra have been described previously[1].
All compounds were commercially available or synthesized according to known procedures (4-amino-2,6-dimethylpyridine[15], 4-amino-3-methylpyridine[16], 5-amino-2-methylpyridine[17], 3-amino-2-methylpyridine[17], 3-amino-4-methylpyridine[17], 4-amino-6-methylpyrimidine[18] and 4-amino-6-phenylpyrimidine[18]).

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10. It seems possible that hyperconjugation with the methyl group can lead to more stabilization in 3a (trans conformation) than in 3b.
11. Only little steric hindrance is supposed to be present in 3-methyl-4-(dimethylamino)pyridine (Z.Proba and K.L.Wierzchowski, J.Chem.Soc.Perkin II, 1119 (1978)).
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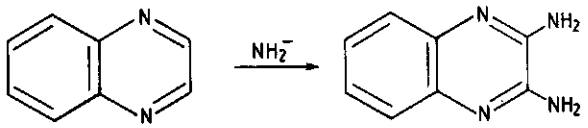
8 GENERAL DISCUSSION

A. Diamination

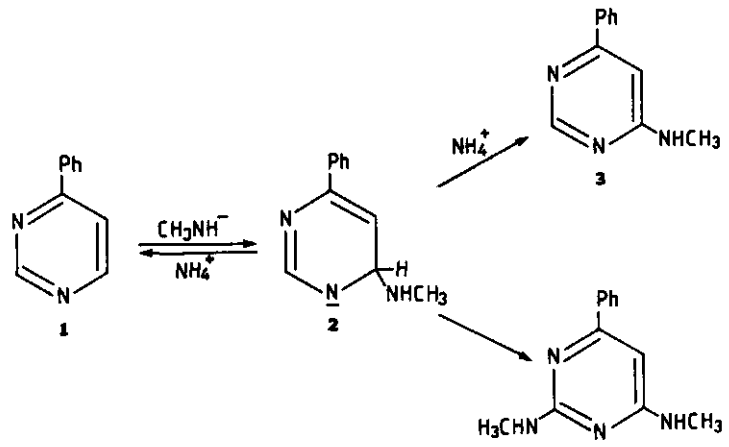
One aspect that has not been discussed in the previous chapters is the formation of diamino products during the Chichibabin amination. The occurrence of diamination depends largely on the solvent. In inert solvents the primarily formed monoamino compounds can undergo a subsequent amination[1]. If the reaction is carried out with potassium amide in liquid ammonia, however, and quenched with ammonium chloride, no disubstitution has been found. This result can be rationalized since the product is formed *after* quenching (chapter 3) and the introduction of another amino group is then no longer possible. There is not even a trace of a diamino product when 2-amino- or 6-amino-4-phenylpyrimidine is treated with KNH_2/NH_3. This is due to the fact that the amino compounds are deprotonated, deactivating the ring for nucleophilic attack (chapters 5, 7). Nevertheless disubstitution can be achieved in some aminations in KNH_2/NH_3 if the reaction is not quenched with ammonium salt. Pyrazine is an example. Although pyrazine forms a 1:1 σ-adduct[2], diaminopyrazine is obtained on evaporation of the ammonia. Quinoxaline is converted into 2,3-aminoquinoxaline under these conditions as well (Scheme 8.1).



Scheme 8.1

These diamination reactions may be ascribed to the increasing amide concentration during the evaporation of the solvent. It seems quite reasonable to assume that the 2,3-diamino adduct is an intermediate in the last-mentioned

reaction. That pteridine forms a diadduct on the pyrazine part of the molecule in KNH_2/NH_3 is known[3].
Reaction of 4-phenylpyrimidine (1) with methylamine containing potassium methylamide also leads to disubstitution. Evidence is presented for the formation of an adduct on C-6 (chapter 3). Addition of ammonium chloride yields a small amount of 6-methylamino-4-phenylpyrimidine (3). If quenching is omitted a high yield (75-80%) of 2,6-di(methylamino)-4-phenylpyrimidine is obtained (Scheme 8.2).



Scheme 8.2

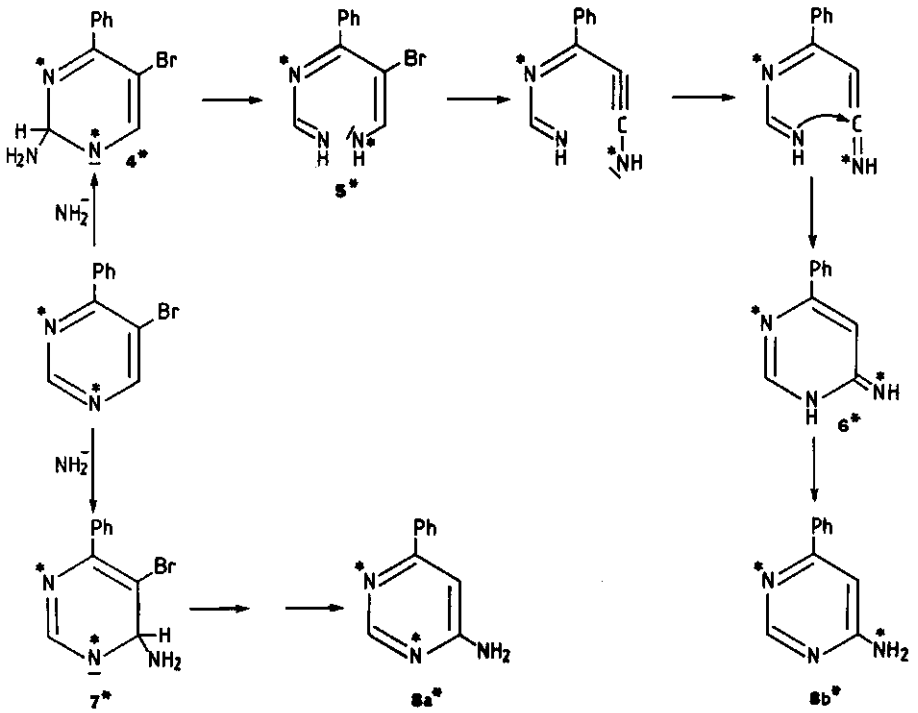
Besides the high amide concentration on evaporation of the solvent, the higher reaction temperature (-6°C) may also be an important factor for directing a second nucleophilic attack on C-2 in either the C-6 adduct 2 or the monosubstituted product 3.

B. Chichibabin amination versus amino-dehalogenation

The main difference between the substrates used in this study and those in previous investigations is the absence of a leaving group. This has important consequences for the occurrence of the S_N(ANRORC) mechanism. During the amination of a heterocycle in which a good leaving group like a chloro- or bromosubstituent is present, the anionic σ-adduct[4,5] can eliminate the halo-

gen ion, leading to an uncharged open-chain intermediate which in KNH_2/NH_3 may undergo recyclization into a heteroaromatic product[6,7]. On the other hand, the σ-adduct is quite stable in the Chichibabin amination with KNH_2/NH_3 and the amination does not proceed until the reaction mixture is quenched. The subsequent intermediates then formed are present in liquid ammonia without amide ions because of the quenching (chapter 3). It is not surprising that pyrazine and quinazoline do not undergo an S_N(ANRORC) mechanism under these milder conditions in contrast to chloropyrazine[8] and 4-chloroquinazoline[9], which show ring opening reactions in KNH_2/NH_3.

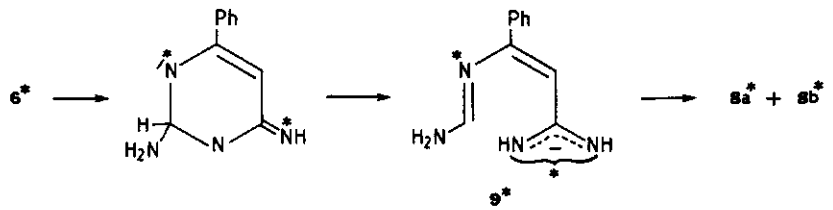
Our results induced us to reconsider the S_N(ANRORC) mechanism proposed in some amino-dehalogenations studied earlier. In the *cine*-amination of 5-bromo-4-phenylpyrimidine into 6-amino-4-phenylpyrimidine (8) for instance, it has been found that adduct formation initially takes place at C-6 and that one of the pyrimidine nitrogen atoms of the starting material is found in



Scheme 8.3

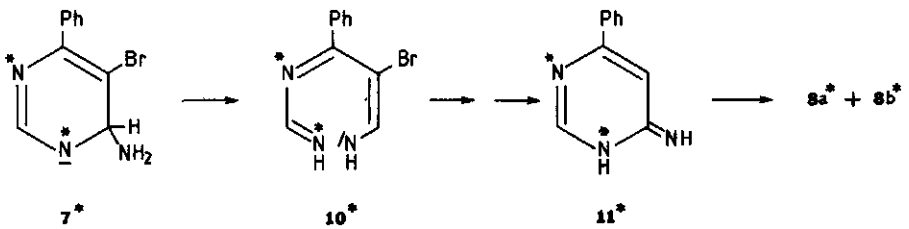
the exocyclic amino group of the final product for 52%, as proven with ^{15}N labeling[10]. To explain these results it was assumed that the 6-amino product 8b* is formed *via* the C-2 adduct 4* and that addition on C-6 gives product 8a* (Scheme 8.3).

It may be suggested that 8a* and 8b* are not formed from two different σ-adducts but that they both result from the imino compound 6* which undergoes a Dimroth-like rearrangement into 8a* and 8b* (Scheme 8.4). The intermediacy of 9* causes scrambling of the ^{15}N label over N-1 and the amino group in 8*.



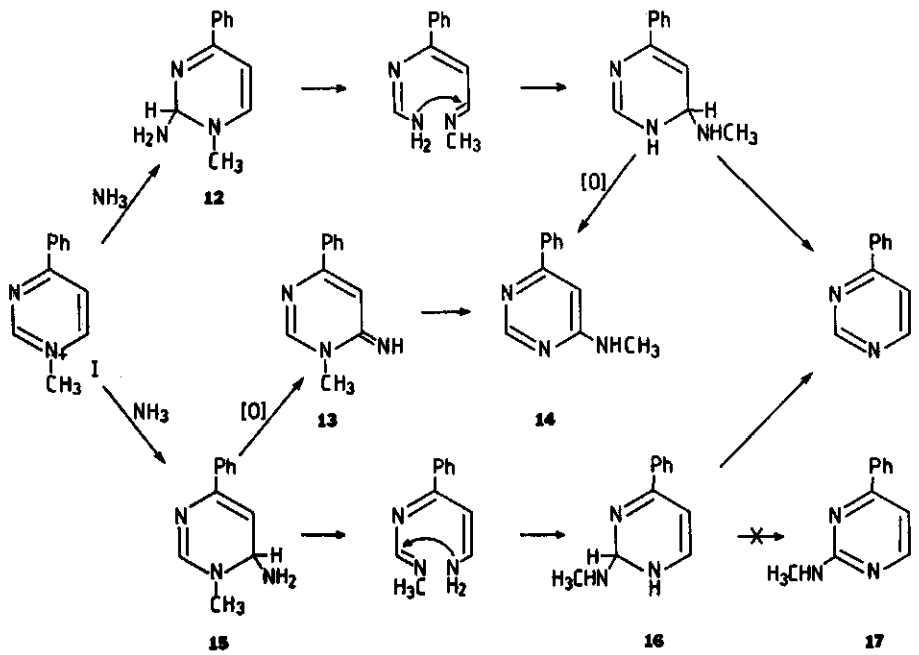
Scheme 8.4

If this rearrangement contributes to a considerable degree, the C-2 adduct 4* does not necessarily have to be involved. It is possible to account for the experimental data starting from the observed C-6 adduct 7* (Scheme 8.5). Ring opening of 7* leads to 10*, differing from 5* in the position of the label. Following the same series of steps as depicted in scheme 8.3 the 1,6-dihydro-6-imino-4-phenylpyrimidine (11*) is obtained, which differs from 6* only in the location of ^{15}N. Rearrangement according to scheme 8.4 leads to the amino product 8* with the label scrambled over the ring nitrogen and the exocyclic amino group, as actually found. A similar sequence has been proposed for the amination of 4-chloroquinazoline[9].



Scheme 8.5

This mechanism as alternative for the pathway outlined in scheme 8.3 cannot occur in the Chichibabin amination because the position of the first nucleophilic attack is not the same as that of the amino function in the product, as would be necessary in the Dimroth rearrangement. In spite of this, we observed an example of a reaction in which the possibility of a rapid rearrangement cannot be excluded. Reaction of 1-methyl-4-phenylpyrimidinium iodide in concentrated aqueous ammonia gives demethylation into 1. An attack at C-6 assumed, but the reaction rate is so high that the intermediacy of this adduct 15 cannot be observed. Potassium permanganate was added to the reaction mixture in an attempt to prove the existence of the dihydro compound 16. The oxidation did not yield the expected 2-(methylamino)-4-phenylpyrimidine (17), but the isomeric 6-(methylamino)-4-phenylpyrimidine (14). This result can be explained either by ring opening of the C-2 adduct 12, or by a Dimroth rearrangement of 1,6-dihydro-1-methyl-6-imino-4-phenylpyrimidine (13), formed by oxidation of 15 (Scheme 8.6). The pathway *via* 12 seems less attractive because the formation of a C-6 adduct in pyrimidinium salts is favoured and our studies of the Chichibabin amination of 1 showed that the C-2 adduct is not inclined to undergo a ring opening (chapter 3).



Scheme 8.6

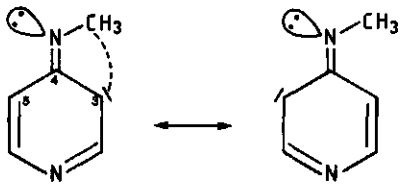
C. Geometrical isomerism

In spite of the fact that geometrical isomerism in imines has been known for some time, most of the literature in this field reports the presence of the isomers without assigning the spectral data to the individual E- or Z-structures. It is not quite clear from the NMR data given which criteria have general validity, since especially the relative positions of ^{1}H and ^{13}C NMR signals in the two isomers appear to depend on the type of compound[1-4]. Sound evidence was needed for the assignment of the NMR spectra of the arylamino anions in our investigations.

The dependency of the coupling constant $^{3}J_{C-H}$ on the orientation is a well-established criterion[15a]. This, together with selective decoupling, enabled unequivocal determination of the signals of the anions of the aminopyridines (chapter 7). Of the two *ortho*-hydrogens the one resonating at higher field is attached to the carbon atom, which is the less shielded of the two *ortho*-carbons, and *vice-versa*. Apparently the dipole moment of the lone electron pair on the exocyclic nitrogen induces polarization in the *ortho* C-H bond in parallel position. A similar field effect is reported for aromatic compounds bearing other asymmetric substituents with restricted rotation, *e.g.* nitrosobenzene[16], 2-, 3- and 4-formylpyridine[17].

This reasoning does not account for all results found with the anions of (methylamino)pyridines (chapter 6). The *ortho*-hydrogens *syn* to the lone pair are more deshielded because their chemical shifts are primarily determined by field effects, as discussed above. On the contrary, the *ortho*-carbon atoms show quite different behaviour: *i*. The variations in chemical shifts for the two isomers are very large (12-16 ppm, compared to 1-2 ppm in the aminopyridine anions). Considerable differences between the two *ortho*-carbons are also reported for other compounds[18,19]. *ii*. The more shielded *ortho*-carbon is in an *anti* position to the exocyclic nitrogen lone pair, whereas in the anions of aminopyridines the higher field signal is assigned to the *syn* oriented *ortho*-carbon. This shielding has been ascribed to steric compression[18], although such effects in general lead to much smaller upfield shifts[15b].

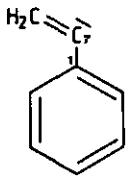
These facts may be rationalized by applying the ideas of Forsyth *et al.*[20], developed to explain the ^{13}C NMR spectra of aromatic cations. We illustrate this principle with the anion of 4-(methylamino)pyridine (18).



18a 18b

18a and 18b are important mesomeric structures of anion 18. The basic idea is to consider the four-membered ring consisting of C-3, C-4, the exocyclic nitrogen and the carbon of the methyl group in 18a. The methyl group is regarded as supplying two electrons (hyperconjugation) which form an aromatic ring current with the C=N π-electrons and the negative charge on C-3 (rule of Hückel). In 18b no aromatic (or anti-aromatic) character can be ascribed to this ring. Structure 18a is therefore more favourable than 18b and C-3 will have a higher electron density than C-5, leading to a C-3 signal at higher field.

A similar ring is not possible in the aminopyridine anions. The lack of this extra stabilizing effect and of steric compression causes the weaker field effects to be the determining factor.



19

We also wish to mention the possible influence of the counterion. In solutions of styrene anions (19) the position of the metal cation relative to the anion depends on its nature, and in consequence different charge distributions and chemical shifts of the carbon atoms are found when different cations are used. It appears that the bond order between C-1 and C-7 is higher with Li^+ as cation than on use of K^+, and the rotation around this bond is less hindered[21].

Nevertheless we feel that the explanation given for the effect of caesium amide as base instead of potassium amide on the spectra of the 2-amino- and 2-(methylamino)pyridine anions (chapters 6 and 7) can be maintained. The negative charge of the anion is less delocalized in the solvating liquid ammonia, and this fact causes a relatively strong association with the metal cations.

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SUMMARY

The first part of this thesis describes investigations into the mechanistic aspects of the Chichibabin amination of some diazines in liquid ammonia containing potassium amide.
The nucleophilic attack of the amide ion on 4-phenylpyrimidine readily takes place at C-2, due to its low electron density, and at C-6 because of the thermodynamic stability of the resulting σ-adduct. The former kinetically determined C-2 adduct isomerizes into the latter as shown by NMR spectroscopy. Both adducts, but no analogous isomerization are observed in 4-*t*-butylpyrimidine. In 5-phenylpyrimidine an adduct on C-2 is not formed.
Phenylpyrazine initially undergoes nucleophilic addition in KNH_2/NH_3 at all three unsubstituted pyrazine carbon atoms. The C-5 adduct is thermodynamically the most stable one.
Amination of 4-phenylpyrimidine in ^{15}N-labeled KNH_2/NH_3 clearly shows that a ring opening-ring closure sequence (the S_N(ANRORC) mechanism) must be involved in the formation of the main product 2-amino-4-phenylpyrimidine. Quenching of the reaction with ammonium salt is an essential requirement for this mechanism. The conclusion is that the intermediate 6-amino-1,6-dihydro-4-phenylpyrimidine undergoes the ring opening. In the amination of 5-phenylpyrimidine the product 2-amino-5-phenylpyrimidine is also formed *via* an acyclic intermediate. In contrast, 4-*t*-butylpyrimidine, pyrazine and phenylpyrazine do not follow this S_N(ANRORC) mechanism.

The second part of this thesis deals with the occurrence of geometrical isomerism in the anions of aromatic amino compounds. NMR spectroscopy reveals the presence of two isomers of azaaromatic amines in liquid ammonia containing potassium amide, and even of anilines, in which the rotational barrier is lower. Coalescence is observed on increasing the temperature. The ^1H and ^{13}C NMR spectra are assigned to the *syn*- and *anti*-isomers. In all anions the *ortho*-hydrogen atom in the *syn* position relative to the lone pair

of the exocyclic nitrogen atom resonates at lower field than in the *anti* position.

In contrast, the *ortho* ^{13}C atoms do not show such a straightforward relationship in the anions of amino- as well as (methylamino)pyridines. In the former ions the signal of the *ortho*-carbon in the *syn* position relative to the nitrogen lone pair is found at *higher* field than in the *anti* position, whereas in the (methylamino)pyridine anions this signal is observed at *lower* field.

With these data it is shown that the presence of a methyl substituent *ortho* to the amino group in aminopyridine anions causes a preference for the isomer in which the amino hydrogen and the methyl group are directed towards each other. The conclusion is that the effective size of the lone pair is larger than that of an amino hydrogen, probably due to solvation. Stabilization of the preferred isomer by other effects, however, cannot be excluded.

SAMENVATTING

In het eerste gedeelte van dit proefschrift wordt een onderzoek beschreven aan de mechanistische aspecten van de Chichibabin aminering van enige diazines met kalium amide in vloeibare ammoniak.
De nucleofiele aanval van het amide ion op 4-fenylpyrimidine vindt gemakkelijk plaats op C-2 door de lage elektronendichtheid op dat atoom, en op C-6 vanwege de thermodynamische stabiliteit van het σ-adduct dat ontstaat. Met behulp van kernspinresonantie wordt aangetoond dat het kinetisch bepaalde C-2 adduct isomeriseert naar het C-6 adduct.
Van 4-*t*-butylpyrimidine worden wel twee adducten waargenomen, maar van isomerisatie is geen sprake. 5-Fenylpyrimidine vormt geen adduct op C-2.
Fenylpyrazine ondergaat in KNH_2/NH_3 aanvankelijk nucleofiele additie aan alle drie ongesubstitueerde koolstof atomen van de pyrazine ring. Het adduct op C-5 is thermodynamisch het meest stabiel.
De resultaten van de aminering van 4-fenylpyrimidine in ^{15}N gemerkt KNH_2/NH_3 tonen duidelijk aan dat ring opening en ring sluiting (het S_N(ANRORS) mechanisme) moet optreden bij de vorming van het hoofdprodukt 2-amino-4-fenylpyrimidine. Blussen van de reaktie met een ammonium zout is voor dit mechanisme vereist. De konklusie luidt dat het intermediair 6-amino-4-fenyl-1,6-dihydropyrimidine de ring opening ondergaat.
Bij de aminering van 5-fenylpyrimidine wordt het produkt 2-amino-5-fenylpyrimidine eveneens gevormd via een open-keten intermediair. De aminerings-reakties van 4-*t*-butylpyrimidine, pyrazine en fenylpyrazine verlopen daarentegen niet volgens dit S_N(ANRORS) mechanisme.

Het tweede gedeelte van dit proefschrift gaat over het vòòrkomen van geometrische isomerie in de anionen van aromatische amino verbindingen. Door middel van kernspinresonantie wordt in KNH_2/NH_3 de aanwezigheid aangetoond van twee isomeren van azaaromatische amines en zelfs van anilines, waarin de rotatiebarrière lager is. Bij toenemende temperatuur treedt coalescentie op.

De ^{1}H en ^{13}C NMR spectra worden aan de *syn*- en *anti*-isomeren toegekend. In alle anionen resoneert het *ortho*-proton in de *syn* positie ten opzichte van het vrije elektronenpaar van het exocyclische stikstof atoom bij lagere veldsterkte dan in de *anti* positie.
Een dergelijk eenduidig verband voor de *ortho*-koolstof atomen in de anionen van zowel amino- als (methylamino)pyridines bestaat echter niet. Voor eerstgenoemde groep anionen ligt het signaal van het *ortho*-^{13}C atoom in de *syn* positie ten opzichte van het vrije elektronenpaar van het stikstof atoom bij *hoger* veld dan in de *anti* positie, terwijl voor de (methylamino)pyridine anionen dit signaal bij *lager* veld wordt waargenomen.
Aan de hand van deze gegevens blijkt dat in aanwezigheid van een *ortho* methyl substituent in aminopyridine anionen een voorkeur bestaat voor de isomeer waarin het amino proton en deze methyl groep naar elkaar toe gericht zijn. Hieruit wordt de konklusie getrokken dat het vrije elektronenpaar effectief groter is dan een waterstof atoom in een amino groep, waarschijnlijk als gevolg van solvatatie. Stabilisatie van de voorkeursisomeer door andere effecten kan echter niet worden uitgesloten.

CURRICULUM VITAE

Op 1 december 1950 ben ik in Leiden geboren. Het diploma gymnasium-β heb ik op het Rembrandt Lyceum aldaar behaald in 1968. Aansluitend begon ik met de studie scheikunde aan de Rijksuniversiteit te Leiden. Het kandidaatsexamen S2 werd afgelegd in juni 1971. De doctoraalstudie omvatte als hoofdvak organische chemie bij prof.dr.E.Havinga en prof.dr.J.H.van Boom (synthese van oligonucleotiden), als bijvak fysische biochemie bij prof.dr.H.L.Booy en dr.J.Riemersma (aktief ionentransport door celmembranen) en als derde richting heterogene katalyse bij prof.dr.V.Ponec. Daarnaast werd de onderwijsbevoegdheid behaald. In juni 1975 werd het doctoraalexamen cum laude afgelegd. Van oktober 1975 tot januari 1982 ben ik werkzaam geweest op het Laboratorium voor Organische Chemie van de Landbouwhogeschool in Wageningen. Mijn onderwijstaak bestond uit het begeleiden van studenten op praktika in de KA en KB fase en van twee HBO stagiaires. Onder leiding van prof.dr.H.C.van der Plas werd aldaar het in dit proefschrift beschreven onderzoek verricht.