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The Acid Properties of the Amino-group

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The acid properties of primary *C*-amino-groups in amines, amides, and amidines have been examined. The methods of preparation and the physical and chemical properties of the metal salts of amines are discussed.
The bibliography includes 219 references.

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I. INTRODUCTION

Amino-compounds are usually regarded as bases capable of combining with a proton to form an ammonium ion (I). A less well known property of the NH_2 group is its capacity for acid dissociation. Indeed primary amines can be regarded as dibasic acids, which, following the ionisation of N–H bonds, can give rise to two series of conjugate bases—the monoanion (II) and the dianion (III):

$$\underset{(I)}{\overset{+}{R}NH_3} \overset{H^+}{\rightleftarrows} \underset{}{RNH_2} \rightleftarrows \underset{(II)}{RNH^-} + H^+ \rightleftarrows \underset{(III)}{RN^{2-}} + 2H^+ .$$

Many investigations of methods for the preparation of *N*-anions of type (II) and (III) and their chemistry have been made, but there are almost no reviews on the acid properties of the amino-group. In the literature there exists only a brief compilation of data of metal salts of amines in a handbook[1], a review of magnesylamines[2], and a monograph[3] in which the ionisation of N–H bonds in liquid ammonia is considered. Strange as it may seem, the question of the acid properties of the amino-group is not discussed either in the extensive monograph[4] published in 1968 and specially devoted to the chemistry of the amino-group.

The main aim of the present paper is to review the accumulated literature data concerning the acid properties of the primary amino-group linked to a carbon atom. The review is thus devoted to aliphatic, aromatic, and heterocyclic amines and also to acid amides and amidines. Compounds in which the amino-group is linked to non-carbon atoms (hydrazines, halogenoamines, etc.) are not considered. Selected data on the acid properties of secondary amines are discussed.

The first section of the review is concerned with the acidity of the N–H bonds in various amino-compounds and with methods for the preparation of *N*-anions. The second section deals with the chemical properties of *N*-anions and their employment in organic synthesis. By analogy with carbanions[5], *N*-anions can be defined as conjugate bases of the corresponding N–H acids. The term "*N*-anions" thus refers to all salts of primary amines with alkali metals. It is then immaterial whether the M^+ ion is linked to the *N* anion with formation of a closely linked ion pair or whether the N–M bond is fully ionised. Only in those cases where the N–M bond is clearly covalent (>N–HgR, magnesylamines) is the employment of the term "*N*-anion" unjustified.

II. METHODS OF PREPARATION OF *N*-ANIONS

1. IONISATION OF N–H BONDS

a. General Information about the Acidity of the Amino-group. Solvents and Bases Inducing the Ionisation of N–H Bonds

The acidity of N–H bonds is usually much lower than that of O–H bonds. For example, ammonia, the simplest N–H acid, is weaker by 20 powers of 10 than water [pK_a = 34 (Smith[3])† and 14 respectively]. Therefore N–H bonds in amines are as a rule ionised in non-aqueous solvents by treatment with strong bases. The solvents employed are aromatic hydrocarbons and ethers: tetrahydrofuran (THF), dimethoxyethane, dioxan, etc., dimethyl sulphoxide (DMSO), and hexamethylphosphoramide (hexametapol or HMPA). Liquid ammonia is particularly valuable as a solvent, because it exhibits a high solvent and ionising power.

The bases most often used to ionise N–H bonds are alkali metal amides and organometallic compounds. Sodium hydride and alkali metals are frequently employed for this purpose. Alkali metal and ammonium hydroxides can also be used to ionise relatively strong N–H acids. However, when the pK_a of the amine is appreciably above 14–16, it is necessary to use a solvent or system of solvents in which hydroxide ions have an enhanced reactivity. The DMSO–water system has been used to ionise amines with pK_a values not exceeding 25–26.[8] Thus in an aqueous mixture containing 99.6 mole % DMSO, it was possible to ionise 3-chloroaniline (pK_a = 25.6) by treatment with tetramethylammonium hydroxide[9]. Overall, the bases enumerated can be arranged in the following series in terms of their ionising activity: carbanions (alkyl- and aryl-metals), sodium hydrides, alkali metal amides, alkali metals, and alkali metal hydroxides.

In order to follow the acid–base reaction and to determine the number of ionising N–H bonds when amines in aprotic solvents are treated with lithium alkyls, metal amides, and metal hydrides (or the metals themselves), the gases evolved (hydrocarbon, ammonia, and hydrogen respectively) are measured quantitatively. When alkali

† Other values for the ammonia pK_a are also quoted in the literature: 35 (Bell[6]) and 36 (Audrieth and Kleinberg[7]). They all refer to 33°C.

metal amides are employed in liquid ammonia, it is difficult to determine which type of species (the monoanion or the dianion) is formed as a result of the reaction. In this case one relies on chemical evidence, physical methods, or the elemental analysis of the salt isolated. It is very convenient to follow the ionisation of N–H acids in liquid ammonia when the acids are treated with alkali metals [10]. The process is carried out by the gradual addition of sodium (or potassium) to a solution (or suspension) of the amine in liquid ammonia. Apart from the evolution of hydrogen, the occurrence of the reaction is demonstrated by rapid (1–2 min) disappearance of the initial blue colour characteristic of solutions of alkali metals in liquid ammonia. The number of ionised N–H bonds is inferred from the amount of metal required to form a stable blue colour.

It is noteworthy that certain amines (for example 1-alkyl-5-aminobenzimidazoles and aniline) do not react with sodium in liquid ammonia. Nevertheless their anions, obtained by another procedure, are capable of existing in this solvent without appreciable ammonolysis‡. There is a fairly small number of quantitative data on the acidity of primary amines. On McEwen's thermodynamic scale [11] (in ether), the same $pK_a = 27$ is quoted for three aromatic amines: aniline, *p*-toluidine, and *p*-anisidine. Although the acidity of aniline specified by the pK_a is probably close to the true value, it is unlikely that the *p*-methyl and *p*-methoxy-groups have no appreciable influence on the acidity of the NH_2 group (by analogy with the influence of these groups on the acidity of the amino-nitrogen).

Systematic determinations of the acid dissociation constants of series of anilines and diphenylamines containing electron-accepting substituents have been made by Stewart and coworkers [8,9,12,13]. They employed a technique in which H_- functions§ were derived for various indicators and solvent systems. Using the pyridine–water, sulpholane–water, and DMSO–water solvent systems and tetramethyl- and trimethylbenzylammonium hydroxides as bases, they determined spectrophotometrically the acid dissociation constants of amines up to $pK_a = 25.6$.

For the determination of the acidity of relatively strong N–H acids ($pK_a < 19$), other solvent systems were also proposed: ethylenediamine–water [14], ethanolamine–water [15,16], hydrazine–water [18,19], t-pentyl alcohol–water [20], and ethanol–water [21]. It is remarkable that the pK_a of the same N–H acids, determined in different solvents of the above series, differ little from one another with rare exceptions.

The use of liquid ammonia as a solvent made it possible to extend the measurements to the region of even lower acidities of amines. Three groups of investigators have worked on the development of an acidity scale for arylamines in liquid ammonia [22–24]. With the aid of ^{1}H NMR, Birchall and Jolly investigated the position of acid–base equilibrium in a mixture of two acids HA and HB in liquid ammonia in the presence of sodamide [22]. On the basis of the results, the difference between the strengths of the two acids was determined from the following formula:

$$\Delta pK_a = \lg\left[\frac{(HB)}{(B^-)}\right] - \lg\left[\frac{(HA)}{(A^-)}\right] .$$

The authors then found the difference $\Delta pK'_a$ between the acidities of the next acid pair (HB and HC). Having accumulated a large number of such measurements, they constructed a relative acidity scale for aromatic amines in liquid ammonia, in which 2,5-dichloroaniline, the most acidic of the amines investigated, was adopted as a standard ($pK_a = 0$). This scale covers a range of 6.58 pK_a units towards lower acidities. A disadvantage of liquid ammonia proved to be the impossibility of measuring the acidities of stronger N–H acids, in particular nitroanilines, since the latter formed Meisenheimer type complexes with ammonia or the amide ion.

Takemoto and Lagowski, who employed ^{1}H NMR combined with spectrophotometric analysis¶ of the position of equilibrium, related the acidities of many weak N–H and C–H acids and thereby established an absolute acidity scale in liquid ammonia [23]. *NN*-Dimethyl-*p*-phenylenediamine (the weakest of the N–H acids, whose pK_a has been determined) and di-(*p*-tolyl)methane were selected as the linking pair of N–H and C–H acids. The acidity scale of Takemoto and Lagowski [23] covers the range of 13 pK_a units, the limit of the series corresponding to 2,5-dichloroaniline.

Herlem and Thiebault calculated the acid dissociation constants of substituted anilines from the results of their potentiometric titration in liquid ammonia with a potassamide solution using a hydrogen electrode [24]. It is noteworthy that the pK_a (Table 2) determined by the ^{1}H NMR and potentiometric methods differ from one another by 7–12 powers of 10 in absolute magnitude. It is at present difficult to say whether this is a consequence solely of differences in the temperatures at which the measurements were made (+25 °C for the ^{1}H NMR method and −60 °C for the potentiometric method) or whether some other factors also play a role. At any rate the acidities of liquid ammonia at +25° and −60 °C [$pK_a = 27.7$ (Coutler et al. [25]) and 32.5 (Herlem [26]) respectively] do not differ from one another very markedly.

b. Alkylamines and Cycloalkylamines

Alkylamines are even less acid compared with ammonia (there are no quantitative data). Therefore they cannot be converted into salts in liquid ammonia either with the aid of alkali metal amides [27] or the metals themselves [7]. However, in aprotic inert solvents (toluene, octane, etc.) or altogether in the absence of a solvent, alkylamines and

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‡ The term "ammonolysis" implies an acid–base reaction between ammonia and the conjugate states of an acid BH weaker than ammonia:

$$B^- + NH_3 \rightleftarrows BH + NH_2^- .$$

The weaker the BH acid the greater the shift of the above equilibrium to the right.

§ The function H_- defines the capacity of the solvent to abstract a proton from a neutral acid HA and is calculated from the formula [12]

$$H_- = -\lg\frac{a_{H^+}f_{A^-}}{f_{HA}} = pK_a + \lg\frac{[A^-]}{[HA]} .$$

In dilute aqueous solutions H_- is identical with pH.

¶ One of the disadvantages of the spectrophotometric method for solutions of liquid ammonia is the impossibility of measuring the acidity of amines weaker than aniline. This is due to the insignificant degree of ionisation of such acids and the consequent masking effect of the amide present in large excess, which absorbs at 350 nm. [22]

cycloalkylamines can be converted into metal salts by prolonged heating with alkali metal amides in nitrogen [28-30]. A necessary condition for the success of this reaction is the removal of the ammonia formed from the reaction zone. If ammonia is not removed, an equilibrium is established between the initial and final products [31]:

$$CH_3NH_2 + LiNH_2 \rightleftarrows CH_3NHLi + NH_3 .$$

Therefore it is technically simplest to obtain with the aid of this method metal salts of high-boiling amines (butylamines, cyclohexylamine, etc.).

Alkali metals dissolve in the lowest alkylamines to form blue solutions, the properties and structures of which are close to those of solutions of alkali metals in liquid ammonia [32]. However, on heating, a slow reaction takes place between alkylamines and cycloalkylamines on the one hand and the alkali metals on the other, and is accompanied by the evolution of hydrogen and the formation of the corresponding salt. This reaction is frequently employed for preparative purposes and is usually carried out without a solvent:

$$RNH_2 + M \rightarrow RNH^-M^+ + {}^1/_2H_2 .$$

In the preparation of metal salts of methylamine by this method, one should guard against a side reaction involving the formation of cyanides [33,34]. The conversion of methylamine into potassium methylamide can be achieved smoothly with the aid of potassium hydride [34].

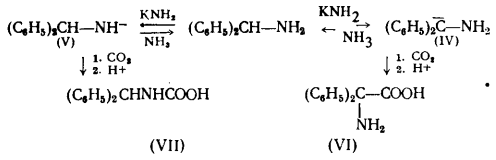
The best method for the preparation of lithium salts of alkylamines and cycloalkylamines is apparently the reaction of amines with organolithium compounds. Usually lithium alkyls in benzene, hexane, or ethers are employed for this purpose. Table 1 gives a compilation of certain data for the preparation of metal salts of alkylamines and cycloalkylamines.

Table 1. Metal salts of certain alkyl- and cycloalkylamines.

Salt	Ionising agent	Conditions	Ссылки на литературу
CH_3NHLi	Li	60°, in sealed tube	33
CH_3NHK	KH	20-25°, 4-6 h	34
C_6H_5NHNa	—	—	29, 30
C_6H_5NHK	K	Ethylamine passed slowly over heated potassium	35
iso-C_3H_7NHNa	$NaNH_2$	Toluene, 121 h	29, 30
n-C_4H_9NHNa	$NaNH_2$	Toluene, 97-109°, 63 h	29, 30
t-C_4H_9NHLi	CH_3Li	Ether, 0°	36
n-$C_8H_{17}NHNa$	$NaNH_2$	—	29, 30
$C_6H_{11}NHLi$	n-C_4H_9Li	In excess of cyclohexylamine	37
$C_6H_{11}NHNa$	$NaNH_2$	Heating in iso-octane	—
$C_6H_{11}NHCs$	Cs	In excess of cyclohexylamine	37

c. Arylalkylamines

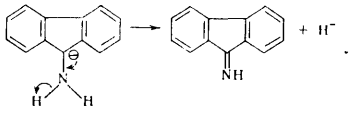
On going from methylamine to benzylamine, diphenylmethylamine, and finally to triphenylmethylamine, the acidity of N–H bonds should increase somewhat owing to the electron-accepting influence of the aryl group. Simultaneously there should be an even greater increase in the acidity of the C–H bonds adjoining the amino-group. As a result, when strong bases act on benzylamine and particularly on diphenylmethylamine, the N–H and C–H bond ionisation processes compete. Hauser et al. established that, when diphenylmethylamine is treated with potassamide in liquid ammonia, a mixture of the carbanion (IV) and the *N*-anion (V) is formed[39]:



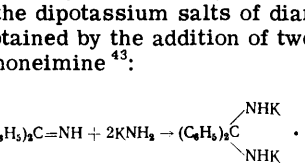
The formation of the carbanion (IV) is proved by the appearance of the red colour characteristic of arylalkyl carbanions and also its conversion into the aminoacid (VI) when the reaction mixture is carboxylated after the evaporation of ammonia. The presence in the mixture of the *N*-anion (V) has been less definitely established. The presence of the carbamic acid (VII) in the carboxylation products cannot serve in this case as unambiguous proof that the *N*-anion is present, since the initial diphenylmethylamine also gives rise to the acid (VII) on interaction with CO_2.

The formation of the carbanion is promoted by its resonance stabilisation, while the *N*-anion is stabilised in arylalkylamines only by the *-I* effect of the arylalkyl group.

Benzylamine itself is probably still a very weak acid. Thus Picon failed to obtain sodium benzylamide by the reaction of benzylamine with sodium or with $NaNH_2$ in liquid ammonia even after a long time in an autoclave [38]. However, the appearance of a red colour when benzylamine is treated with various bases [39-41] indicates the formation of a certain amount of carbanions. This is also suggested by certain indirect data. For example, 9-aminofluorene, diphenylmethylamine, and benzylamine are converted into the corresponding imines on standing in liquid ammonia in the presence of potassamide [42]. It appears likely that the reason for this phenomenon consists in the β-elimination of a hydride ion from the corresponding carbanion:

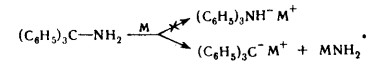


The fact that the amino-group in arylalkylamines is more acid in ammonia than in alkylamines can be inferred from the existence in liquid ammonia, without appreciable ammonolysis, of the dipotassium salts of diaminodiphenylmethane (VIII), obtained by the addition of two KNH_2 molecules to benzophenoneimine [43]:



(VIII)

In this connection, it is difficult to understand why triphenylmethylamine fails to give an *N*-anion when acted upon both by potassamide in liquid ammonia [44] and by alkali metals in liquid ammonia or in ether [45]. Sodium and potassium in liquid ammonia cleave the C–N bond in triphenylmethylamine with formation of a carbanion and an amide ion [44]:



Steric factors can hardly be responsible for the difficulty of the ionisation of the N–H bonds in triphenylmethylamine, since triphenylmethane, where the steric effect

should be even more pronounced, readily ionises in liquid ammonia in the presence of metal amides and alkali metals. Such behaviour of triphenylmethylamine suggests that the ionisation of diphenylmethylamine and benzylamine (weaker N–H acids than triphenylmethylamine) involves preferentially the C–H bonds, i.e. the formation of a carbanion. Metallation of CH–NH systems is fairly common in organic chemistry. For example, acetamido-[46-48] and benzamido-malonic esters[49] give rise to carbanions and not *N*-anions when acted upon by bases, a fact which is used in the synthesis of aminoacids.

d. Arylamines

Although aromatic amines are very weak N–H acids, their acidity is nevertheless much greater than that of aliphatic amines and ammonia. This can be accounted for by the possibility of the resonance stabilisation of the arylamine *N*-anions:

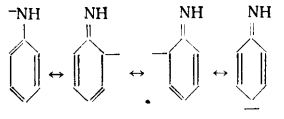
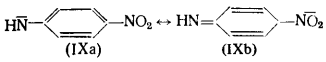


Table 2. Acid dissociation constants (pK_a) of a series of anilines.[a]

Substituent in benzene ring of aniline	Solvent, temp., °C			Substituent in benzene ring of aniline	Solvent, temp., °C		
	+25[9,12,13][b]	NH_3, +25[23]	NH_3, −60[24]		+25[9,12,13][b]	NH_3, +25[23]	NH_3, −60[24]
H	27.3[c]	21.2	28.8	4-Cl	—	19.9	27.4
2-NO_2	17.88	—	—	4-CN	22.68	15.9	28.5
3-Cl	25.63	—	—	4-NO_2	18.37	—	—
3-CF_3	25.40	18.7	—	2,4-$(NO_2)_2$	15.00	—	—
4-CH_3	—	22.1	—	2,4,6-$(NO_2)_3$	12.20	—	—
4-$N(CH_3)_2$	—	25.6	—				

[a] The acidity constants of many other anilines are quoted in the literature[9,12,13,23,24].
[b] The average pK_a values for various solvent systems: DMSO–water (99.9 mole % DMSO), sulpholane–water (95.5 mole % sulpholane), and others.
[c] pK_a = 27.3 was obtained for aniline by extrapolation.

Table 2 shows that aniline is a stronger acid by 6–7 powers of ten than ammonia. Introduction of electron-accepting substituents into the benzene ring of aniline cause an even greater increase of the acidity of the NH_2 group and the 2,4,6-trinitroaniline anion can exist even in water. The inductive effect of the nitro-group in the series of anilines is greater than in the series of phenols. It is believed that in the *N*-anions of *o*- and *p*-nitroarylamines most of the negative charge is localised at the NO_2 group, i.e. structure (IXb) makes a large contribution to the resonance state[50]:



In certain cases (3-nitroaniline), on treatment with hydroxyl-containing bases the ionisation of the N–H bond is accompanied by a competing process involving the nucleophilic addition of the OH^- ion to the aromatic ring. The two reactions can be distinguished spectrophotometrically: in contrast to the addition process, ionisation takes place instantaneously[9].

It has been found[22] that there is a satisfactory correlation between the σ constants of substituents (σ^- constants must be employed for the *p*-NO_2, *p*-CN, and *p*-F substituents) and the pK_a values of substituted anilines with a constant $\rho = -5.3$. Such a high value of ρ shows that the acidity of aniline depends significantly on the effect of substituents and, as shown by experiment, to a greater extent than the acidity of anilinium ions. The ρ constant for the acid dissociation of substituted diphenylamines is also very high (−4.07).[9]

Stewart and Dolman[50] (see also Birchall and Jolly[22]) established that there is a fairly satisfactory linear relation between the basicities pK_{BH^+} (acidities of anilinium ions) and the acidities of pK_{HA} of substituted anilines and diphenylamines (with the exception, for reasons stated above, of compounds with nitro-groups):

$$pK_{HA} = 21.4 + 1.30\ pK_{BH^+} . \quad (1)$$

This equation can be used for an approximate estimation of the acidities of amines whose pK_{HA} have not been determined for one reason or another, but the basicity pK_{BH^+}, which can be determined more readily and accurately, is known. For example the basicities of aniline, *p*-toluidine, and *p*-anisidine are 4.60, 5.10, and 5.34,[51] from which we have the acidities 27.52, 28.03, and 28.34 respectively. The value 27.5 for aniline agrees satisfactorily with other data[11,24].

For preparative purposes, when it is necessary to employ aprotic solvents, the *N*-anions of aromatic amines are obtained by treating the amines with sodium hydride[52], lithium alkyls[53], lithium aryls[54], or organomagnesium compounds[2,55-57]. In the cold, the metal usually substitutes one hydrogen atom in the NH_2 group, while on brief heating the second hydrogen atom is also readily replaced at a temperature as low as 35–40°C:

$$ArNH_2 + RMgX \xrightarrow[-RH]{20-25^\circ} ArNHMgX \xrightarrow[\Delta]{RMgX} ArN\begin{matrix}MgX\\MgX\end{matrix} + RH .$$

This reaction serves as a basis for the quantitative determination of active hydrogen in arylamines[58].

At room temperature, neither sodium nor sodamide reacts with aniline at an appreciable rate, but, when aniline is refluxed with these bases in xylene[59] or in the absence of a solvent[35,60], the sodium salt of aniline is formed fairly readily. The use of HMPA, the high ionising power of which makes it possible to carry out the process under mild conditions[61,62], is extremely convenient in the preparation of sodium arylamides. It is believed[61] that, when two equivalents of sodamide are employed in HMPA, the disodium salts of aromatic amines are also formed. However, this conclusion is based on alkylation data which, as will be shown below, do not constitute convincing proof.

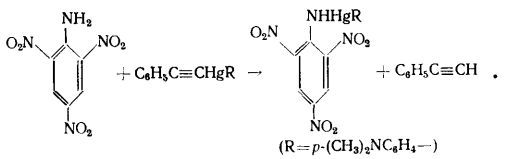
The preparation of the anions of more acid amines (for example *p*-nitroaniline) can be achieved in DMSO by treatment with alkali metal hydroxides[9].

The generation of the *N*-anions of aromatic amines in liquid ammonia requires special consideration. The ionisation of the N–H bonds in aniline and its derivatives with electron-donating substituents on treatment with alkali metals or $NaNH_2$ takes place in this solvent only at room

temperature and under pressure [38]. Under the usual conditions for experiments in liquid ammonia (temperature between −33° and −60°C), the N−H bonds in aniline cannot be ionised by treatment with alkali metals or $NaNH_2$. This is very surprising bearing in mind that the sodium and potassium salts of diphenyl- and triphenylmethane, which are weaker C−H acids than aniline, are readily formed in liquid ammonia under analogous conditions. Probably the solvating power of liquid ammonia in relation to carbanions is greater than in relation to *N*-anions.

According to the data of Bunnett and Moyer [63], when aniline is treated with potassamide in liquid ammonia at a temperature as low as at −33°C, potassium anilide is readily formed. The ease of this reaction can probably be explained by the higher solubility of potassamide in liquid ammonia (450 g litre^{-1} at −33°C) compared with sodamide (1.5 g litre^{-1} 25°C). [64] However, one should note that rigorous proof of the complete conversion of aniline into its *N*-anion was not obtained, since the salt was not isolated in a pure form.

In a series of investigations, Nesmeyanov and Kravtsov showed that aromatic amines containing also acidifying substituents such as NO, NO_2, and −N=N− readily form arylmercury derivatives on reaction with arylmercury hydroxides [65-68]. For fairly acid amines (picramide), arylmercury derivatives of acetic acid, phenylacetylene, or *p*-nitroaniline can also be employed as bases [65]:



Aniline itself and its *p*-chloro- and *p*-bromo-derivatives do not form arylmercury derivatives under these conditions [65].

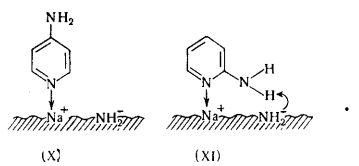
e. Heterocyclic Amines

In the amino-derivatives of aromatic aza-systems, the amino-group is much more acidic than aniline owing to activating effect of aza-nitrogen. It appears that there are no quantitative literature data for the acidities of *N*-heteroaromatic amines. However, one can suppose that the pK_a for 2- and 4-aminopyridines should be intermediate between the acidities of 2-nitroaniline (pK_a = 17.9) and 2,4-dinitroaniline (pK_a = 15.0). This estimate is based on a comparison of the values of σ_p for the pyridine nitrogen atom and the NO_2 group, which are +0.93 and +0.778 respectively [69] (the literature values of σ_o for the pyridine N atom are +0.81, +1.02, etc.). [69]

It is therefore not surprising that α-amino-derivatives of pyridine [59,70-79], quinoline [88], isoquinoline [71], thiazole [80], benzimidazole [71], and pyrimidine [70,78,81] readily form salts when acted upon by alkali metal amides and hydrides, alkali metals themselves, and even their hydroxides under certain conditions [79]. Aromatic hydrocarbons, liquid ammonia, HMPA, and sometimes ether or dioxan are usually employed as solvents. It is noteworthy that in only a few cases these salts were isolated in a crystalline state and investigated [59,70,74]. Usually, after preparation in solution (liquid ammonia, HMPA) or in a suspension (ether, dioxan, hydrocarbons), the salts were immediately introduced into further reactions without preliminary isolation.

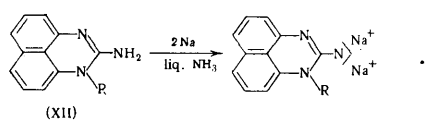
In β- and γ-aminoheterocycles containing a pyridine *N*-heteroatom, the amino-group is also appreciably activated and readily ionises when treated with alkali metals or their amides in liquid ammonia or in HMPA. [71,82,83] However, the formation of metal salts of such amines in weakly polar aprotic solvents proceeds with greater difficulty. For example, 4-aminopyridine hardly reacts (in contrast to 2-aminopyridine) with sodamide in ether [84], while in benzene and xylene the reaction proceeds very slowly even at 140−150°C and can hardly be used for preparative purposes [59,84].

This observation is in sharp contrast to the known sequence of acidities of the CH_3 group in isomeric picolines: 4-CH_3 > 2-CH_3 > 3-CH_3. [85] One of the possible reasons for the difficulty of the ionisation of the NH_2 group in non-polar aprotic solvents is that the reaction takes place in a heterogeneous medium. Therefore the amino-derivative may be sorbed on the surface of sodamide crystals via the coordination of the pyridine N-atom (the most basic centre in the molecules of α- and γ-aminoheterocycles) to the Na^+ ion as in (X). It is quite clear that, for geometrical reasons, such sorption should greatly increase the ionisation of the NH_2 group in 4-amino-derivatives. On the other hand, in the case of α-amino-compounds it should serve as an additional factor promoting the ionisation of the N−H bond, as in (XI):

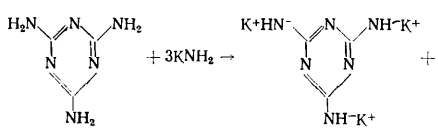


In solvents where alkali metal amides are soluble (liquid ammonia, HMP), the ionisation of N−H bonds takes place equally readily for both α- and γ-amino-derivatives owing to the homogeneity of the system.

In *N*-heteroaromatic amines, one may expect a greater ease of formation of dianions compared with aromatic amines. Nevertheless, the vast majority of amines, including all three pyridylamines, form monoanions in liquid ammonia when acted upon by alkali metals and apparently metal amides [71]. Among all the amines investigated in this respect, only the 2-amino-derivatives of perimidine (XII) and aceperimidine form dianions under these conditions [71]:



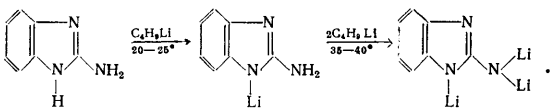
Triamino-1,3,5-triazine (melamine) exhibits very acidic properties. In liquid ammonia it can give rise to mono-, di-, and even tri-anions when acted upon by potassamide [86]:



The amino-group in a benzene ring condensed with a heterocyclic nucleus can be both actived and passivated, depending on the nature of the latter. For example, aminoquinolines in liquid ammonia readily form anions on treatment with potassamide [87]. On the other hand, 1-R-5-aminobenzimidazoles cannot be converted into

N-anions in liquid ammonia by treatment with alkali metals or their amides [71]. Reductive cleavage of azides, discussed in section II, 2, gives very satisfactory results in the synthesis of such *N*-anions.

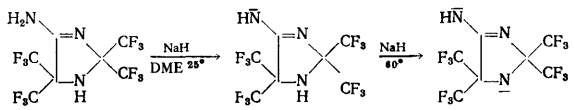
In *N*-heteroaromatic amines containing an endocyclic N–H pyrrole bond in addition to the NH_2 group, the former is as a rule more acidic and ionises first. This applies also to compounds containing an amino-group in the side chain (histidine [88], tryptophan [89]) and to true heteroaromatic amines. Thus, when 2-aminobenzimidazole (XIII) is treated with butyl-lithium or with butylmagnesium bromide, initially the H atom of the endocyclic N–H bond is substituted and only then, on heating to 40°C, is the trilithium salt or trimagnesylamine formed [90]:



(XIII)

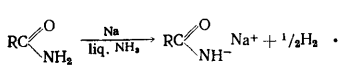
When the amine (XIII) is treated with an excess of an alkali metal amide in liquid ammonia, an equilibrium mixture of di- and tri-anions is formed, with the former predominating [91]. When sodium or potassium is employed as the base, the reaction stops at the monoanion stage [91].

In amino-derivatives of certain partly hydrogenated *N*-heterocycles, the amino-group may be ionised first provided that it is conjugated with an endocyclic C=N bond [92]:



f. Carboxylic Acid Amides

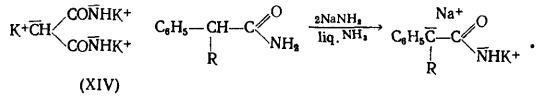
The amides of carboxylic and particularly thiocarboxylic acids exhibit a much greater acidity than other amino-compounds (Table 3). Thus the pK_a's for acetamide and benzamide are in the range 14–15. [93,94] The acidity of thioacetamide in liquid ammonia at −60°C is estimated as 4.6 pK_a units [24]. When treated with alkali metals or their amides, acid amides in liquid ammonia readily form monoanions [95–98]:



The report that dianions are formed under these conditions [96] was subsequently disproved by the same author [64]. Nevertheless, bearing in mind the very high acidity (among N–H acids) of acid amides, the possibility of the existence in liquid ammonia of their dianions, generated by another procedure, appears to be extremely probable.

Franklin obtained in liquid ammonia and isolated in a crystalline form a large series of carboxylic acid amide salts with alkali and alkaline earth metals [64]. When acid amides are treated with phenylmercury hydroxide, one H-atom of the NH_2 group also ionises and a phenylmercury derivative is formed [65].

The amides of dibasic acids can form in liquid ammonia also polyanions, in which, however, each amino-group carries only one negative charge. For example, malonamide forms a trianion (XIV) when treated with potassamide in liquid ammonia [64]. Phenyl- and diphenyl-acetamides give rise to *CN*-dianions under analogous conditions, the N–H bond being the first to ionise [99,100]:



(XIV)

The use of organometallic reagents gives rise to a wide scope for the ionisation of N–H bonds in acid amides. Hauser and coworkers showed that, when aliphatic and aromatic acid amides are treated with an excess of butyl-lithium in THF or ether, dilithium salts are formed, to which the structure of *ON*-dianions was ascribed [101,102]:

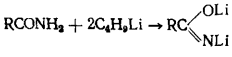
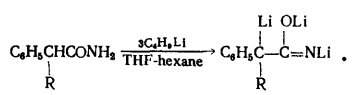


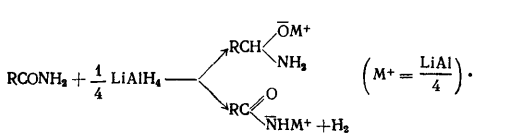
Table 3. Acid dissociation constants (pK'_a) of certain N–H acids.

Compound	pK'_a	Conditions	Refs.	Compound	pK'_a	Conditions	Refs.
Acetamide	14	NH_3	3	Thiourea	8.5	NH_3,—60°	24
"	15	25°	93, 94	*N*-Phenylthiourea	3.8	NH_3,—60°	24
Benzamide	14—15	—	93, 94	Semicarbazide	25—33	NH_3,—33°	112
Thioacetamide	4.6	NH_3,—60°	24	Carbohydrazide	21—25	NH_3,—33°	112
Urea	12.9	NH_3,—60°	24	*NN'*-Diphenylguanidine	10.7	NH_3,—60°	24
"	25—33	NH_3,—33°	112	Cyanamide	7	NH_3	3
NN'-Diphenyl urea	7.0	NH_3,—60°	24	Hydrazine	13.5	NH_3,—60°	24

The reaction with organomagnesium compounds takes place similarly, and is used in the quantitative determination of active hydrogen in acid amides by the Tserevitinov method [103]. The amides of aliphatic-aromatic acids, containing a C–H bond in the α-position relative to the $CONH_2$ group, form trianions when acted upon by an excess of butyl-lithium [100,101]:



When acid amides are treated with lithium aluminium hydride, two competing reactions take place: the addition of $LiAlH_4$ to the C=O group and the ionisation of the N–H bond [104]:



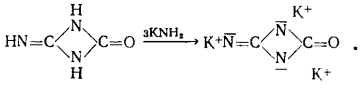
Usually the addition reaction takes place preferentially, but when R is a fairly bulky group, mono- or di-metallated derivatives are mainly produced.

g. Urea, Thiourea, and Guanidine

It was established that, when acted upon by alkali metal alkoxides in an alcoholic medium, urea behaves as a monobasic acid [105]. However, when sodium [106,107] or potassamide [96,108] are employed as bases in liquid ammonia, it

is possible to obtain both mono- and di-anions. In contrast to the monopotassium salt of urea, its dipotassium salt is sparingly soluble in liquid ammonia and is usually precipitated when a second equivalent of the base is added[109]. The monosodium salt is also sparingly soluble in liquid ammonia[106]. Therefore it is clear that, when urea is treated with two equivalents of sodium or sodamide, a mixture of mono- and di-sodium salts is formed, i.e. the second ionisation takes place with somewhat greater difficulty. The monosodium salt of urea has been isolated in a crystalline form and investigated in detail[106].

Among urea derivatives, cyanourea, the cyclic form of which gives rise to a trianion when treated with potassamide in liquid ammonia, is of interest[110]:



In water cyanourea behaves as a monobasic acid.

Thiourea and guanidine can also behave as mono- or di-basic acids depending on the conditions. The monosilver and dipotassium salts of guanidine[86] and the monopotassium[111] and dipotassium[109] salts of thiourea have been obtained. The formation of dipotassium salts of urea, thiourea, and guanidine in liquid ammonia has been demonstrated unambiguously[109] by the potentiometric titration of liquid ammonia solutions of these acids with a potassamide solution. On this basis, the following sequence of relative acidities has been established:

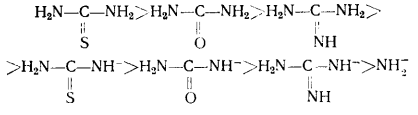
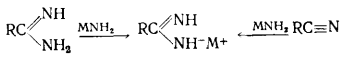


Table 3 presents quantitative data for the acidities of urea, thiourea, and certain related compounds. According to French workers, the first acid dissociation constants (pK'_a) of urea and thiourea in liquid ammonia are respectively 12.9 and 8.5.[24] The second dissociation constants (pK''_a) have not so far been determined, but, judging from the ease of formation of dianions by urea and thiourea in liquid ammonia, they should be in the range 25–30.

An attempt has been made to estimate the acidity of urea by titrating its ammonia solution with a solution of triphenylmethylsodium in the presence of indicators such as indene and fluorene[112]. It was found that the addition of even one drop of the triphenylmethylsodium solution to a mixture of urea and fluorene in liquid ammonia results in the appearance of the yellow colour characteristic of the fluorene anion. Assuming that pK_a for fluorene is 25, Corwin and Reinheimer[112] concluded that the acid dissociation constant of urea (judging from the experimental conditions, the constant is pK_a') is in the range 25–33. However, this value contradicts all previously known facts concerning the acidity of urea and can probably be accounted for by the unsuitability of fluorene as an indicator in this case (possibly because of the greater kinetic acidity of fluorene, which is not always the same as the thermodynamic acidity).

h. Amidines

In water amidines behave as very powerful bases but in liquid ammonia they exhibit the properties of monobasic acids, readily forming monoanions when treated with alkali metals or metal amides[64,113]. A more usual method for the preparation of sodium and potassium salts of amidines involves the addition of an alkali metal amide to the corresponding nitrile[114,115]:

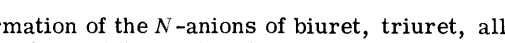


A large number of sodium, potassium, and calcium salts of aliphatic and aromatic amidines have been obtained in this way. The silver and copper salts of amidines, which are insoluble in liquid ammonia, can be obtained by the double decomposition between the potassium or sodium salt of the corresponding amidine and the metal nitrate[113].

i. Other Compounds

One of the simplest compounds containing the *C*-amino-group is cyanamide. It exhibits a very high acidity ($pK_a = 7$) and readily forms salts with alkali and alkaline earth metals in liquid ammonia. Numerous examples of such salts are quoted in a handbook[116] and in other publications[86,96].

Carbamic acid can exist in liquid ammonia in the form of the mono- and di-potassium salts, which are obtained by treating ammonium carbamate with potassamide[108]. When acted upon by potassamide in liquid ammonia, ethyl carbamate forms an unstable potassium salt which decomposes according to the following equation:[108]

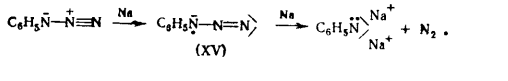


The formation of the *N*-anions of biuret, triuret, allophanic acid, biguanidine and certain other compounds with a *C*-amino-group in liquid ammonia has been discussed in a monograph[3].

2. REDUCTIVE CLEAVAGE OF N–X BONDS

a. Azides

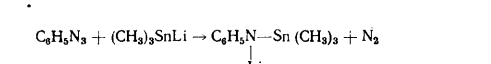
Phenyl azide is reduced by metallic sodium in boiling ether with formation of the disodium salt of aniline and evolution of nitrogen[117]. The reduction proceeds via the stage in which a radical-anion (XV) is formed; it was detected by its characteristic red colour and the ESR spectrum:



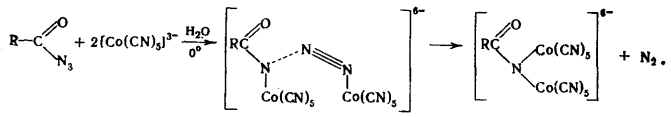
Later it was found for aromatic and heterocyclic azides that liquid ammonia is a very convenient solvent for this reaction[118,119]. The synthesis of *N*-anions via azides is the only one possible in those cases where the ionisation of the N–H bonds in the amino-group proceeds with difficulty or not at all[71].

Initially it was postulated that the dianions of aromatic amines obtained from azides are stable in liquid ammonia[118,119], although recently certain data have been obtained indicating their ammonolysis to the monoanions[71,120].

It was possible to reduce aromatic azides by organometallic compounds, which also leads to dimetal salts of the amines[121]:

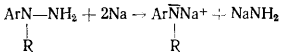


Only one example of reactions of this type is known for acyl azides [122]:

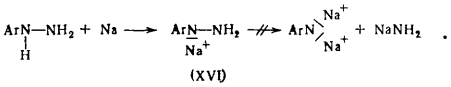


b. Hydrazines

In an unpublished study, referred to by Smith [3] and Watt [10], Fernelius and coworkers investigated the action of sodium in liquid ammonia on a large number of various substituted hydrazines. They established that, when the nitrogen atom linked to the benzene ring in aromatic hydrazines is not joined to a free hydrogen atom, the N–N bond undergoes reductive cleavage on treatment with sodium, which results in the formation of the sodium salt of a secondary amine:

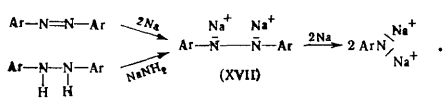


In hydrazines with a free N–H group in the α-position relative to the aromatic ring, the N–H α-bond is the first to ionise on treatment with sodium with formation of the resonance-stabilised N-anion (XVI), which is resistant to further reduction:



(XVI)

There are contradictory views in the literature concerning the possibility of the cleavage of the N–N bonds in the dianion of hydrazobenzene (XVII), formed when hydrazobenzene or azobenzene are treated with metal amides and alkali metals respectively:

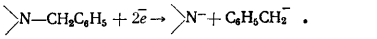


(XVII)

Data [123] supporting such cleavage, which leads to disodium anilide, were not subsequently confirmed [124]. According to the observations of the authors of the review, the N–N bond in the dianions of heterocyclic hydrazocompounds is not cleaved either, for example in 1,1′-dialkyl-2,2′-hydrazobenzimidazoles.

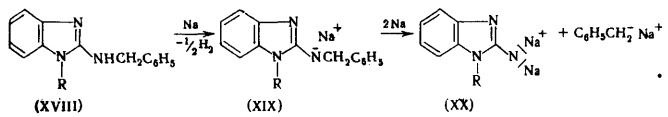
c. Cleavage of the N–C Bond in Benzylamines

The removal of the N-benzyl protecting group by solutions of alkali metals in liquid ammonia is a well known synthetic procedure. It is usually employed in the N-heteroaromatic series for compounds with a pyrrole nitrogen atom. The process takes place as a two-electron reduction of the C–N bond and leads to the formation of the N-anion of the secondary amine and the benzyl anion†, which subsequently undergoes ammonolysis and gives rise to toluene:



† The theory of reductive debenzylation with the aid of liquid ammonia solutions of alkali metals is described by Birch [125].

N-Benzyl derivatives of primary aromatic (for example benzylaniline [10]) and heteroaromatic amines enter into an analogous reaction. It has been shown for 2-benzylaminobenzimidazoles (XVIII) [90,120] that the action of sodium in liquid ammonia on such compounds begins with rapid ionisation of the N–H bond, which is followed by slow debenzylation of the N-anion (XIX). Ultimately, the amine dianion (XX) and the benzyl anion are formed and gradually undergo ammonolysis:



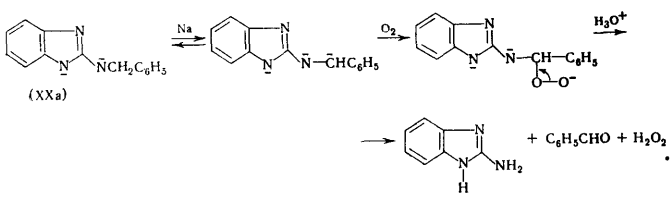
(XVIII) (XIX) (XX)

Reductive debenzylation proceeds more readily the greater the effective positive charge on the nitrogen atom to which the benzyl group is linked. Therefore the benzyl group joined to the pyrrole nitrogen atom is eliminated on treatment with sodium in liquid ammonia more readily than the benzyl substituent linked to an exocyclic amino-group [126,127].

If the benzyl group is joined to a negatively charged nitrogen atom, two outcomes are possible from the standpoint of the mechanism of the debenzylation process.

1. The negative charge on the nitrogen atom is effectively delocalised owing to conjugation with the aromatic π-electron system. In this case [a typical example is provided by the monoanion (XIX)] debenzylation still proceeds as a two-electron reductive process, albeit extremely slowly, and the reaction is accompanied by the formation of toluene.

2. The negative charge is located preferentially on the nitrogen atom. This case obtains when sodium acts upon 2-benzylaminobenzimidazole (XVIII, R = H) and on 1-benzyl-2-benzylaminobenzimidazole (XVIII, R = $C_6H_5CH_2$). [126] The dianion (XXa) is then formed initially. The addition of two-electrons to the C–N bond in this dianion should be extremely unfavourable on energy grounds. Indeed debenzylation should take place with difficulty and involve the formation of a considerable amount of benzaldehyde. Although the mechanism of this reaction is not in fact completely clear, it evidently includes an autoxidation stage and can be tentatively described by the following scheme:



(XXa)

Thus in principle one should distinguish two mechanisms of the debenzylation of benzylamines with the aid of solutions of metals in liquid ammonia—reductive and oxidative. The oxidative debenzylation mechanism requires further study.

Apart from the benzyl group, N-methoxymethyl [128] and other arylalkyl groups (ring-substituted benzyl groups, the diphenylmethyl group, the α-phenylethyl group [90], etc.) can undergo reductive elimination with formation of N-anions. When attempt was made to cleave the N–allyl bond by sodium in liquid ammonia, a difficulty was encountered owing to the reduction of the double bond of the allyl substituent, after which the N–C bond was no longer cleaved [129].

III. THE NATURE OF THE NITROGEN–METAL BOND AND THE STRUCTURE AND PHYSICAL PROPERTIES OF METAL SALTS OF AMINES

There have been few studies specially undertaken to investigate the nature of the nitrogen–metal bond in metal salts of amines. Two parameters of this bond, its polarity and the type of hybridisation of the N atom, can exert a major influence on the physical properties and reactivity of such salts. The use of Pauling's formula [130] $i = 100\ (1 - e^{-0.25(\chi_a - \chi_b)^2})$ to calculate the percentage ionic character of certain N–M bonds yields the results presented in Table 4 (here $\chi_N - \chi_M$ represents the difference between the relative electronegativites of nitrogen and metal atoms between which the bond is formed).

It follows from Table 4 that the bonds between nitrogen and alkali metals must be regarded as largely ionic, the amount of ionic character increasing in the sequence Li < Na < K. This agrees with the experimental measurements of the conductance of lithium [131] and caesium [132] cyclohexylamides in cyclohexylamine.

Table 4. Percentage of ionic character of certain nitrogen–metal bonds.

Bond	$\chi_N - \chi_M$	Amount of ionic character, %	Bond	$\chi_N - \chi_M$	Amount of ionic character, %
N—K	2.2	70	N—Mg	1.8	55
N—Na	2.1	67	N—Ag	1.2	30
N—Li	2.0	63	$N—Hg^{II}$	1.1	26

In magnesylamines, the N–Mg bond is equally covalent and ionic. The bond between nitrogen and metals such as copper, silver, and mercury is mainly covalent. Naturally, the degree of polarity of the N–M bond is also influenced by the type of hybridisation of the nitrogen atom and the nature of the hydrocarbon groups to which the nitrogen and metal atoms are linked (provided that the valence of the metal is greater than unity). These additional factors are not taken into account in the calculation of the percentage ionic character of the N–M bond.

Qualitative data on the amount of ionic character of the N–M bond agree fully with the properties of metal salts of amines. Thus silver and mercury salts of amines are as a rule resistant to the action of water and alcohol. They dissolve in certain organic solvents and can be actually recrystallised from them [68]. Although magnesylamines are usually readily decomposed by water, they are frequently soluble in ethereal solvents. In this respect they resemble the lithium salts of amines.

The sodium and potassium salts of alkylamines are highly hygroscopic and pyrophoric[34], like alkali metal amides. They are liable to explode in air and react vigorously with water and alcohols. Therefore they must be handled and stored in a completely inert atmosphere. Similar precautions must be observed in work with sodium, potassium, and lithium salts of arylamines and heterocyclic amines. However some of the latter (for example, the sodium salt of 2-aminopyrimidine [70,81]) are completely stable in air and are non-hygroscopic.

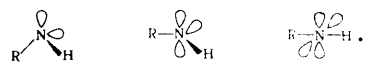
Many salts of amino-compounds with alkali metals are readily soluble in liquid ammonia, where they are apparently appreciably dissociated. This hypothesis is based on ultraviolet spectroscopic data for liquid ammonia solutions of potassamide [33], from which it follows that, depending on the concentration of the solution, the degree of dissociation of potassamide is 30–75%. DMSO [9,12,13] and HMPA [62] also exhibit a high solvent power in relation to metal salts of amines.

In solvents with a low dielectric constant, amides are dissociated into free ions only to an insignificant extent ($K_d \simeq 10^{-10}$–10^{-12} M) and are present largely in the form of ion pairs. The relevant data have been obtained by Streitwieser et al. for solutions of lithium and caesium cyclohexylamides in cyclohexylamine [131]. There is an important difference between the two salts. While caesium cyclohexylamide exists in cyclohexylamines in the form of monomeric ion pairs regardless of concentration [132], lithium cyclohexylamide also forms dimers, trimers, and other aggregates in equilibrium with the monomeric form [134,135].

The majority of metal salts of amino-compounds are extremely high-melting crystalline substances. It is somewhat surprising that the sodium salts of aniline and a number of other aromatic amines, obtained in liquid ammonia and then isolated in a pure form (judging from the results of elemental analysis), proved to be liquids [38].

There are apparently no literature data concerning the crystal structures of metal salts of amines. However, there are data on the structures of the crystal lattices of lithium [136] and sodium [137] amides. It is interesting that there are no hydrogen bonds in sodamide crystals. This is consistent also with the infrared spectrum of a crystalline specimen of sodamide, which contains sharp peaks at 3264 and 3218 cm^{-1}, associated respectively with antisymmetric and symmetric stretching vibrations of the N–H bonds, while bands which might be assigned to associated N–H groups are absent [59]. The infrared spectra of the potassium salt of methylamine [34] and the sodium salts of 5-aminoacridine and 2-amino-1-methylperimidine [59] are distinguished by similar characteristics, which indicates the absence of hydrogen bonds from their crystal lattices too. On the other hand, the spectra of the sodium salts of 2-aminopyridine and 1-alkyl-2-aminobenzimidazoles contain a number of diffuse bands in the region of N–H stretching vibrations, which is evidence of an appreciable association of the salts in the crystalline state.

Theoretically the nitrogen atom in the *N*-anions may be in the sp^3-, sp^2-, or *sp*-hybridised state:



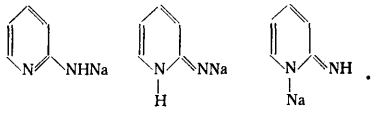
sp^3-hybridisation sp^2-hybridisation *sp*-hybridisation

Infrared spectroscopic data indicate a change in the state of hybridisation of the nitrogen atom in the *N*-anions compared with the parent amines. Thus the N–H stretching vibration band in the spectrum of potassium methylamide occurs at higher frequencies than in the spectrum of dimethylamine [34,138]. A similar phenomenon was observed for sodium salts of 5-aminoacridine and 1-alkyl-2-aminobenzimidazoles [59]. This probably indicates an increase of the *s*-character of the nitrogen hybrid orbitals and consequently of the force constant of the N–H bond on conversion of the amine into the corresponding metal salt. However, there are also exceptions to this rule [59].

In the infrared spectra of crystalline specimens of metal salts of methylamine and heterocyclic amines, almost all the bands characteristic of the initial amine are

retained with only a slight displacement. This must correspond to tight binding of the counterions in the crystal lattices of the salts, so that the negative charge remains largely localised on the nitrogen atom.

The similarity of the infrared spectra of the sodium salts of heterocyclic amines to those of the amines themselves led to the conclusion that in the crystalline state they exist in the amino-form (XXI) and not in the imino-forms (XXIa) or (XXIb):



(XXI) (XXIa) (XXIb)

Infrared spectra have been used successfully to elucidate the structures of arylmercury derivatives of nitro-, nitroso-, and azoaryl-amines [66,68].

Certain information concerning the characteristics of the structure of *N*-anions can be obtained also from ultraviolet spectroscopic data. Measurements have been made [9,12,13] of the ultraviolet spectra of a large series of sodium salts of anilines containing electron-accepting substituents and it was concluded, in particular, that the sodium salt of *p*-nitroaniline exists mainly in form (Xb). The ultraviolet spectrum of lithium cyclohexylamide has also been measured [36]. This salt (in cyclohexylamine) absorbs appreciably at 375 nm, which is at the boundary with the visible region.

The aromatic proton signals in the ^1H NMR spectra of the *N*-anions of aromatic amines, measured in liquid ammonia, are appreciably displaced towards higher fields compared with the unionised molecules, on average by 1 p.p.m. [22,23] The shift for different protons decreases in the sequence *para* > *ortho* > *meta*, which suggests an appreciable mesomeric interaction between the negatively charged nitrogen atom and the aromatic π-electron sextet.

There are also data for the electronegativities of the *N*-anions of aromatic amines in liquid ammonia solution [124,139].

II REACTIONS OF METAL SALTS OF AMINES

1. N-ANIONS AS STRONG BASES

Shatenshtein was the first to employ the KNH_2-NH_3 system to determine the kinetic acidity of C–H acids, including weak acids such as alkanes [140,141]. These studies stimulated the search for other *N*-anionic systems which might be used as suitable bases for the ionisation of weakly acid X–H bonds. The lithium (or caesium) cyclohexylamide–cyclohexylamine system, proposed and investigated in detail by Streitwieser [36,142] (see Ref. 143 for a review of Streitwieser's studies), has been recognised as one of the most successful. It was found that the ionising capacity of the cyclohexylamide anion depends on the type of metal cation [142]. For example, caesium cyclohexylamide in cyclohexylamine completely converts diphenylmethane and triphenylmethane into the carbanions, while the reaction with lithium cyclohexylamide does not go to completion and the following equilibrium is established:

$$\rangle C-H + C_6H_{11}NH^-Li^+ \rightleftarrows \rangle C^-Li^+ + C_6H_{11}NH_2 .$$

The higher reactivity (by a factor of 3300) of caesium cyclohexylamide in the ionisation of weak C–H acids can be accounted for in the first place by the monomeric nature of this salt in solution and in the second phase by the higher ionic radius of Cs^+ compared with Li^+. As a result, the Cs^+ ion is more remote from the $C_6H_{11}NH^-$ counterion, which enhances the reactivity of the latter.

Lithium di-isopropylamide (a Hünig salt) has found a wide-scale application as a deprotonating agent. Its advantages are due to the steric blocking of the *N*-anionic centre, which reduces to a minimum the probability of nucleophilic side reactions [144].

The 1,2,4-trihalogenobenzene → 1,2,5-trihalogenobenzene isomerisation in liquid ammonia, which involves a stage in which a C–H bond of the aromatic ring is deprotonated, proceeds most effectively in the presence of potassium anilide [63].

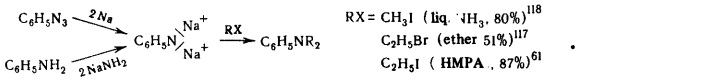
2. DEUTERIATION OF THE AMINO-GROUP VIA N-ANIONS

The amino-group is usually deuteriated by repeated refluxing of the amine in heavy water or in deuterio-alcohol [145]. For weakly acidic amines, deuterium exchange under these conditions is very slow. According to the results of the authors of this review, obtained for a series of *N*-heteroaromatic amines, and other data [101] for acid amides, a convenient method for the deuteriation of the NH_2 group consists in the decomposition of the metal salts of amines with heavy water (for a modification of this method, see Bassindale et al. [146]):

$$RN\bar{H}M^+ + D_2O \rightarrow RNHD + MOD,$$
$$RN^{2-}M_2^+ + 2D_2O \rightarrow RND_2 + 2\,MOD.$$

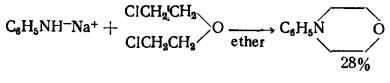
3. ALKYLATION

Many cases of alkylation of aromatic amines via *N*-anions have been described. For example, the aniline *N*-anions obtained from phenyl azide or aniline (by treatment with two moles of $NaNH_2$) give high yields of the corresponding *NN*-dialkylanilines with an admixture of the monoalkyl derivatives on alkylation with alkyl halides:



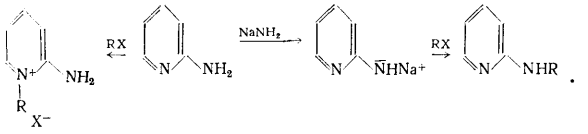
The preferential formation of the tertiary amine has been regarded as evidence for the involvement in the reaction of the disodium and not the monosodium salt of aniline.

Monosodium anilide is ethylated in ether at −40°C to monoethylaniline [38]. An unusual example of the employment of monosodium anilide is the following synthesis of *N*-phenylmorpholine [147]:



However, the alkylation of amines with a fairly active lone electron pair (these include aniline itself, aromatic amines with electron-donating substituents, and alkyl- and cycloalkyl-amines) can be carried out also without the preliminary ionisation of the N–H bond [148]. The alkylation of the amino-group via metal salts is important for amines with a reduced basicity, such as *p*-nitroaniline or 1-amino-1-phenylazonaphthalene.

Similarly the alkylation of the *N*-anions of tautomeric heterocyclic amines of the 2-aminopyridine type, is hardly the only practical method for the direct introduction of substituents into the NH_2 group. On the other hand, it is known that, when alkyl halides act directly on *N*-heteroaromatic amines, the reaction involves the endocyclic *N* atom:



When the NH_2 group is alkylated, it is important to be able to control the degree of reaction with formation of mono- or di-alkyl derivatives. The type of solvent employed is significant in this respect. In the alkylation of monosodium salts of aromatic or heteroaromatic amines in aprotic solvents of low polarity (aromatic hydrocarbons, ethers, dioxan), the reaction as a rule proceeds smoothly up to the formation of the corresponding monoalkyl derivative. In particular, derivatives of 2-aminopyridines with the following substituents in the NH_2 groups were obtained in this way: methyl [76], ethyl [140], propyl [150], isopropyl [149,151], butyl [150], isopentyl [149,152], cetyl [151], benzyl [153], diphenylmethyl [154], allyl [77,151], and dialkylaminoalkyl [78,155]. The interaction of the sodium salt of 2-aminopyridine with $\alpha\omega$-dihalogenoalkanes leads to $\alpha\omega$-dipyridylaminoalkanes [156]. Examples of such monoalkylation of the amino-group have been described for the 2-amino-derivatives of pyrimidine [78,81,147], quinoxaline [157], thiazole [80,158], lepidine [78,159], 1-alkylbenzimidazoles [71], and adenosine [160].

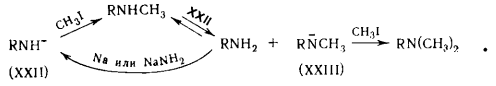
In order to rule out completely the possible formation of the dialkyl derivatives, in some cases the NH_2 group is first protected by formylation [161] or benzylation [59].

An attempt to obtain the dialkylamino-derivative by treating the monosodium salt of the amine with an excess of alkyl halide in a non-polar solvent usually leads to a complex mixture of substances containing not less than 50% of the tertiary amine [75]. Excellent results in the synthesis of dialkylamino-derivatives are obtained when liquid ammonia [71,82,83] or HMPA [82] are used as solvents.

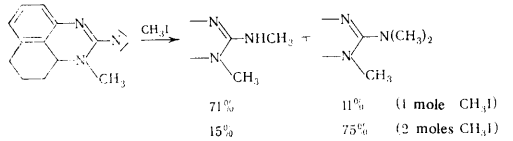
A remarkable characteristic of the reactions of the monoanions of aromatic and heteroaromatic amines with C_1-C_3 alkyl halides in liquid ammonia is that, regardless of the amine : alkyl halide ratio, the process does not stop at the monoalkylation stage [71,82]. Even in the presence of a deficiency of the alkyl halide, the corresponding dialkylamino-derivative is formed almost exclusively. The reaction is very fast with a high yield of the tertiary amine and undoubtedly constitutes the most convenient method of dialkylation of the amino-group. Similar results were obtained for the reaction of the *N*-anions of 4-aminoquinolines with halides of the allyl and benzyl type in HMPA [82].

The reaction of branched and more bulky (C_4 and above) alkyl halides with *N*-anions proceeds slowly snd gives mainly a low yield of the monoalkylation product [162]. It has been shown for aminoquinolines that γ-diethylaminopropyl chloride reacts with monoanions to form the monoalkyl-substituted derivative in nearly quantitative yield [87].

The preferential formation of the dialkylamino-substituted derivative on alkylation of monoanions with reactive alkyl halides in liquid ammonia and HMPA can probably be accounted for, as for the phenylacetonitrile carbanion [163], by the stepwise nature of the reaction. Of the two types of monoanions, (XXII) and (XXIII), present in solution, (XXIII) is probably alkylated at a rate which greatly exceeds that of (XXII). Therefore, despite the low equilibrium concentration of (XXIII), the dialkylamino-derivative and not the monoalkyl-amino-derivative accumulates continuously in the reaction mixture:



In contrast to the monoanions, the alkylation of the dianions in liquid ammonia is susceptible to definite control and, depending on the amount of the initial alkyl halide, the reaction can be directed towards the preferential formation of the mono- or di-alkyl derivative [71]:



This behaviour of the dianions is quite reasonable, since their reactivity should be higher than that of the monoanion of a secondary amine. As a result, the secondary amine, the alkylation of which becomes significant only after the disappearance of the dianion or a sharp decrease of their concentration, accumulates in the reaction mixture. The existence in solution of a particular anionic species has been frequently inferred in the literature from the results of alkylation experiments.

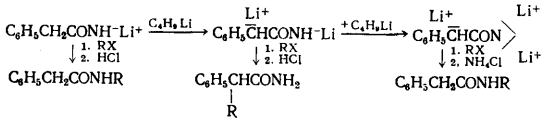
It follows from the foregoing data that the formation of the dialkyl derivative when an excess of alkyl halide acts on the *N*-anions of aniline and other amines in liquid ammonia [118] (and also in HMPA) cannot be regarded as unambiguous proof of the presence of dianions in solution. The same results might be obtained by the alkylation of the corresponding monoanions in the same solvents. It is more correct to employ as a basis the results of the alkylation of the *N*-anions by one equivalent of methyl iodide [71]. In this case the preferential formation of the dimethylamino-derivative should be regarded as evidence of the formation of the monoanion in solution and the formation of a secondary amine should indicate the presence of the dianion. The use of this test for the *N*-anions of 2- and 5-aminobenzimidazoles obtained from the corresponding azides [71] showed that the dianions, formed initially in liquid ammonia, are appreciably ammonolysed to the monoanions. Bearing in mind the low acidity of aniline, it is unlikely that its dianion, obtained from phenyl azide, is stable in liquid ammonia and does not undergo ammonolysis.

Incidentally, this test is not universal. It has been found that the monoanions of acidic amines capable of forming dianions simply on treatment with sodium, are not susceptible to stepwise alkylation in liquid ammonia and, on treatment with one mole of methyl iodide, form preferentially the monoalkylation product [71]. However, the identification of the *N*-anions of such amines presents no difficulties even without alkylation, since the very fact of their conversion into dianions on treatment with sodium is evidence of the stability of both their monoanions and dianions in liquid ammonia.

An interesting feature of the alkylation of the *N*-anions of heteroaromatic and aromatic amines consists in the fact that, despite their formal ambident nature [see, for example, structures (XXI) and (XXIb)], the reaction involves exclusively the amino-nitrogen, i.e. takes place

without transfer of the reaction centre. This indicates an appreciable localisation of the negative charge on the exocyclic *N*-atom not only in the isolated but also in the reacting molecule.

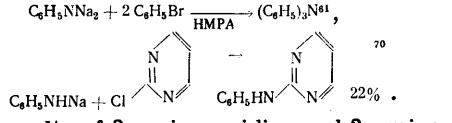
If the molecule contains several anionic centres, the centre formed last, i.e. the one to which corresponds the less acidic X–H bond, is the first to be alkylated [99,101]:



Less nucleophilic and hence less reactive *N*-anions correspond to acid amides as well as N–H acids stronger than amines. The alkylation and benzylation of the sodium salts of carboxylic acid amides in liquid ammonia [164], HMPA, [61] or non-polar aprotic solvents [165,166] takes place slowly and leads to the formation of *N*-monosubstituted derivatives in low yields. The sodium salt of urea does not react in liquid ammonia with butyl and dodecyl bromides, but monobenzylurea is formed by the reaction with benzyl chloride [106].

4. ARYLATION

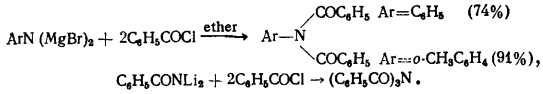
The arylation of the amino-group and the introduction of heterocyclic substituents into it via the *N*-anions usually take place slowly and require heating of the reactants for many hours in a high-boiling solvent or even without a solvent. The yields of reaction products are as a rule low. Characteristic examples are provided by the following reactions:



The sodium salts of 2-aminopyridine and 2-aminopyrimidine interact with 2-chlorothiazole to form 2-(α-thiazolylamino)-derivatives in yields of 40 and 9.5% respectively [70]. The reaction of the sodium salt of 2-aminopyrimidine takes place only in the absence of solvent, which can be accounted for by its lower nucleophilicity compared with the *N*-anion of 2-aminopyrimidine.

5. ACYLATION

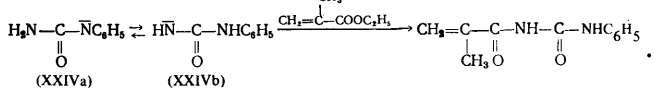
The acylation of the amino-group via metal salts is usually achieved with the aid of carboxylic acid chlorides or esters. The use of the latter leads to monoacyl derivatives regardless of whether the mono- or di-anion is introduced into the reaction. When acid chlorides act upon monometal salts, monoacylation products are also formed, but with dimetal salts high yields of *NN*-diacyl derivatives can also be obtained. Examples of reactions of this kind are known for both a series of amines [55,167–169] and a series of acid amides [101]:



It is noteworthy that mainly the diacylation of the NH_2 groups via *N*-anions is of preparative importance, since almost all amines can be readily monoacylated as such with the aid of acid anhydrides or chlorides. On the other hand, the acylation of a second N–H bond in the monoacyl derivative formed is much more difficult without its conversion into the *N*-anion.

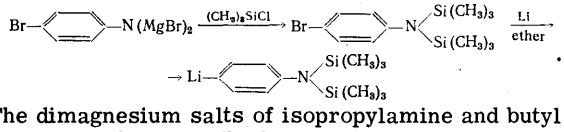
In only a few cases, when the acid chloride or anhydride is difficult to obtain or cannot be employed for one reason or another, the use of esters for the monoacylation of the amino-group also assumes synthetic importance. A characteristic example is provided by the acylation of aromatic amines via magnesylamines with the aid of ethyl β-hydroxy-ββ-diphenylpropionate [168]. As might have been expected, dimagnesylamines are more reactive in this process [55].

The monosodium salts of urea and *N*-phenylurea are acylated in liquid ammonia or acetone with the aid of acid chlorides or esters [106], including ethyl methacrylate [169], to give the corresponding monoacyl derivatives. It is interesting that the reaction with *N*-phenylurea involves the primary amino-group, although the *N*-anion (XXIVa) and not (XXIVb) should be more stable in this case. Probably the anion (XXIVb), although present at a low concentration, reacts with the acylating agent much faster than does (XXIVa):



6. REACTION OF N-ANIONS WITH CHLOROTRIMETHYLSILANE

Magnesium [56,57] and lithium salts [146] of aromatic amines react under mild conditions with chlorotrimethylsilane, giving a high yield of the corresponding trimethylsilyl derivatives. The reaction has been used to protect the amino-group in organometallic syntheses [57,170]:



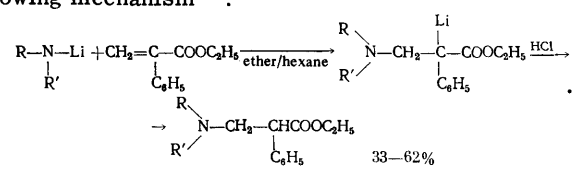
The dimagnesium salts of isopropylamine and butylamines do not form *N*-alkylhexamethyldisilazanes on treatment with chlorotrimethylsilane. However, the lithium salts of alkylamines, for example of t-butylamine [36] and *N*-phenylethylenediamine [171], react readily under these conditions.

7. NUCLEOPHILIC ADDITION OF N-ANIONS TO MULTIPLE BONDS

Compared with amines, *N*-anions are much more nucleophilic and add more readily to polarised multiple bonds. This factor is very widely used in organic synthesis.

a. Addition to Carbon–Carbon Multiple Bonds

Reactions of this type have been little investigated. It has been found that lithium salts of secondary amines add to the C=C bond of ethyl α-phenylacrylate according to the following mechanism [172]:



The mode of this reaction is the opposite of that of primary amine *N*-anions with ethyl methacrylate in which there is addition to the C=O bond followed by acylation of the amino-group.

Sodium anilide adds to the triple bond of dehydrobenzene, yielding *N*- and *C*-arylation products: diphenylamine, 2-aminobiphenyl, and 4-aminobiphenyl[173]. The formation of biphenyl derivatives in this reaction clearly demonstrates the ambident nature of the aniline *N*-anion.

b. Addition to the C=O bond

One of the examples of such reactions may be the carboxylation of the diphenylmethylamine *N*-anion by carbon dioxide leading to the formation of diphenylmethylcarbamic acid, as already mentioned above. The acylation of the amino-group via the *N*-anion by carboxylic acid esters also includes a stage involving addition to the C=O bond and constitutes another example of this kind.

It has been shown recently that the *N*-anions of primary amines add to the triple bond of carbon monoxide[174]. The lithium salt of t-butylamine gives rise to orange t-butylcarbamoyl-lithium (XXV):

$$(CH_3)_3CNH^-Li^+ + \bar{C}\equiv\overset{+}{O} \rightarrow (CH_3)_3CNH-\underset{\underset{O}{\|}}{C}-Li$$

(XXV)

Many condensation reactions involve as an intermediate stage the formation of an *N*-anion, which behaves as an active species and adds directly to the carbonyl group. Such reactions include, in particular, the hydroxymethylation of carboxylic acid amides by formaldehyde in an alkaline medium[175].

Although the Schiff reaction is known to be usually catalysed by acids, cases of base catalysis have also been noted for amines with an inactive electron pair at the nitrogen atom. For example, 2-aminobenzimidazoles react with aldehydes of the furan series in the presence of alkali much more readily than in its absence[176]. Bearing in mind the enhanced acidity of the N–H bonds in such amines, there can be hardly any doubt that the species involved in such reactions is not the amine itself but the *N*-anion in equilibrium with it:

$$RNH_2 + OH^- \rightleftharpoons RNH^- + H_2O \xrightarrow{R'CHO} R-\underset{\underset{H}{|}}{N}-\underset{\underset{O^-}{|}}{CH}-R' \longrightarrow R-N=CH-R' + OH^-$$

It has been suggested that *N*-anions participate also in the complex Marschalk reaction in which the sodium salts of the leuco-derivatives of aminoanthraquinones are acted upon by aldehydes[177] with formation of *C*-alkylated aminoanthraquinones.

c. Addition to the C≡N Group

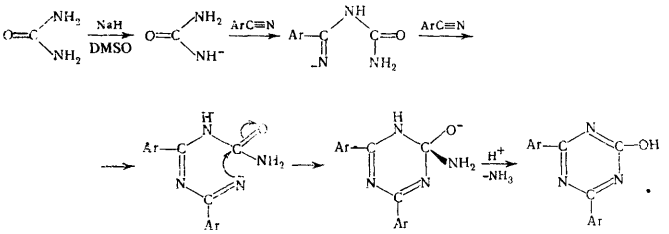
The addition of metal salts of amines to the C≡N bonds of nitriles constitutes the basis of one of the simplest methods for the synthesis of substituted amidines:

$$RNH^-M^+ + R'C\equiv N \rightarrow R'-C\begin{matrix}\diagup NM\\ \diagdown NHR\end{matrix} \xrightarrow{HCl} R'-C\begin{matrix}\diagup NH\\ \diagdown NHR\end{matrix}$$

Although this reaction has been known for a long time[2,178,179], it was not investigated in detail and for a large number of examples until 1970.[180] It was shown that the most suitable solvent for the process is liquid ammonia. The reaction then proceeds much faster and with a higher yield of amidine than in non-polar aprotic solvents. Good results are apparently obtained also in DMSO.[181]

However, only aromatic and heteroaromatic amines and nitriles enter into this reaction. The reaction with alkylamines (n-$C_4H_9NH_2$) takes place with a low yield or not at all (iso-$C_3H_7NH_2$). Somewhat better results were obtained for benzylamine and diphenylmethylamine. When these are acted upon by potassamide in liquid ammonia with subsequent introduction of benzonitrile, the yields of the substituted amidine are 29 and 73% respectively[180]. All these results apparently reflect the relative acidity of the N–H bonds in amines and the ease of formation by them of *N*-anions in liquid ammonia.

The interaction of the *N*-anion of urea and aromatic nitriles in DMSO is unusual. The product of the two-stage process is a 2-hydroxy-4,6-diphenyl-*s*-triazine[181]:



d. Addition to the N=O Bond

Aromatic amines, in particular aniline, are readily condensed with nitrobenzene and its derivatives in the presence of strong bases (for example t-BuOK in DMSO), yielding the corresponding azo-compounds[182–184]. The role of the base consists in the conversion of the amine into the *N*-anion, which is more reactive in relation to the nitroso-group:

$$ArNH_2 + B^- \rightleftharpoons ArNH^- + BH \xrightarrow{Ar'N=O} Ar-\underset{\underset{H}{|}}{N}-\underset{\underset{O^-}{|}}{N}-Ar' \longrightarrow Ar-N=N-Ar' + OH^-$$

This reaction is very important in the series of *N*-heteroaromatic amines which are otherwise difficult to convert into azo-compounds, since the amino-group is diazotised with difficulty and the corresponding diazonium salts are extremely unstable. Such amines include, for example, α- and γ-amino-derivatives of pyridine[72,73,79,185], quinoline[72], and benzimidazole[186].

A similar type of reaction constitutes the basis of the method proposed by Bamberger and Rust for the diazotisation of aromatic amines[187]. In this procedure, the aromatic amine is treated with pentyl nitrite in the presence of an alkali metal alkoxide, which results in the formation of the corresponding diazotate:

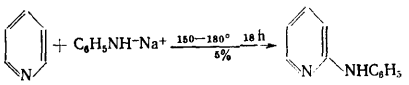
$$ArNH_2 + C_2H_5O^- \rightleftharpoons C_2H_5OH + ArNH^- \xrightarrow{C_5H_{11}ONO} Ar-\underset{\underset{H}{|}}{N}-\underset{\underset{O^-}{|}}{N}-OC_5H_{11} \longrightarrow$$

$$\longrightarrow Ar-N=N-O^-Na^+ + C_5H_{11}OH$$

Chichibabin showed for 2-aminopyridine that the sodium salt of the amine beforehand can also be introduced into the Bamberger reaction[188].

8. ALKYL- AND ARYL-AMINATION OF ORGANIC COMPOUNDS WITH THE AID OF N-ANIONS (REACTIONS WITH ELIMINATION OF THE HYDRIDE ION)

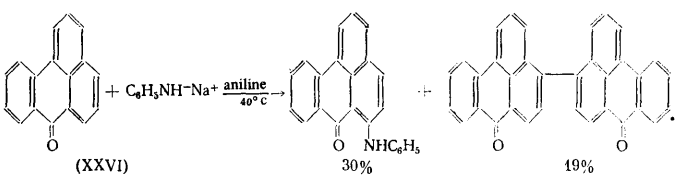
By analogy with the amination of nitrogenous heterocycles with sodamide (Chichibabin reaction)[189], it is very tempting to employ for the same purpose organic derivatives of sodamide. Chichibabin[190] already found that sodium anilide reacts with pyridine under severe conditions to form an insignificant amount of 2-phenylaminopyridine:



The formation of 2,2′-dipyridylamine as a side product in the reaction of pyridine with sodamide was also accounted for by the reaction of pyridine with the sodium salt of 2-aminopyridine formed as a result of amination[190,191].

However, on the whole the salts of aromatic amines are not sufficiently nucleophilic in relation to *N*-heterocyclic compounds and the yields of amination products are extremely low. Even more frequently, the reaction does not proceed at all, for example with quinoline[192] and isoquinoline[193] or when pyridine is acted upon by sodium *N*-methylanilide[194].

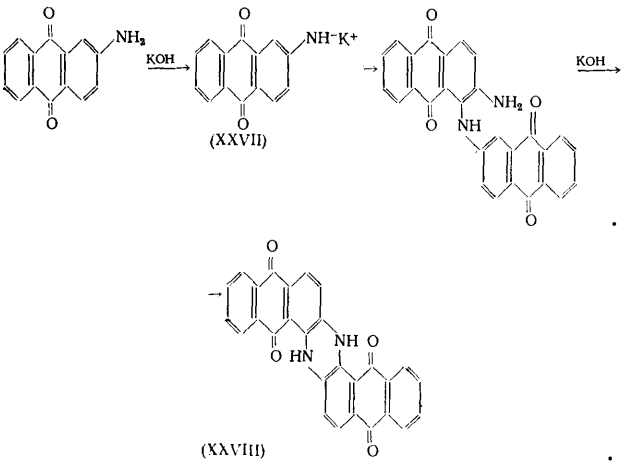
Phenylamination with the aid of sodium anilide takes place somewhat more readily in the series of certain polynuclear systems: mesobenzanthrone (XXVI),[195,196] 1,8,9-naphthanthr-10-one,[197] 1,9-pyrazolanthrone[60], and 1,8-naphthalimide[198]. Bradley, who made a detailed study of these reactions[196-199], showed that in all cases two competing processes take place—direct phenylamination and dimerisation of the initial compound:



(XXVI) 30% 19%

Bradley assumed that the dimerisation reaction is due to the ionisation of the C–H bond in the molecule of the initial compound under the influence of $C_6H_5NH^-Na^+$ with subsequent addition of the carbanion formed to another molecule of the initial compound[196]. However, bearing in mind that dimers are formed also when the above polynuclear compounds are acted upon by metal alkoxides in alcohol or by alkalis, which can hardly cause the ionisation of aromatic C–H bonds under the reaction conditions, a reductive dimerisation mechanism is more likely: electron transfer from the base to the aromatic substrate, cross-linking of the two radical-anions formed, and subsequent oxidation of the dihydro-derivative of the dimer to the aromatised dimer. The amination and dimerisation processes compete with one another also in the Chichibabin reaction (the reaction of sodamide with *N*-heteroaromatic compounds). It was shown recently that dimerisation in the Chichibabin reaction proceeds most probably via a stage involving the formation of a carbanion[90].

When β-aminoanthraquinone is heated with potassium hydroxide in pyridine or in the absence of solvent, the resulting *N*-anion (XXVII) can enter into a nucleophilic interaction with a molecule of the initial compound[199]. Ultimately this reaction leads to the formation of the dye indanthrone (XXVIII):[200]

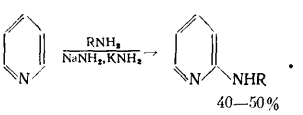


(XXVII) (XXVIII)

The *N*-anion (XXVII) also adds to nitrobenzene[199]. The more readily formed but less nucleophilic *N*-anions of 2-amino-1-chloro- and 2-amino-1-nitro-anthraquinones do not react with nitrobenzene[199].

One may suppose that the reactivity of metal salts of alkylamines as nucleophilic agents should be greater. However, there are very few data concerning this problem. Thus, when quinoline is acted upon by sodium methylamide in ether, it forms 2-methylaminoquinoline (yield not stated)[201,202]. Alkali metal dialkylamides do not react at all (even when the conditions are altered) with nitrogenous bases or cause charring[193,201,203].

Bergstrom et al. succeeded in alkylaminating pyridine and quinoline in the 2-position by treating them with a eutectic mixture of sodamide and potassamide in the presence of primary aliphatic or alicyclic amines and potassium nitrate[204]:



40–50%

Kovacs and Vajda modified this method, having replaced the eutectic mixture of the two amides by metallic sodium[205-208]. Both groups of investigators failed to obtain evidence for the involvement in this reaction of the alkylamine *N*-anion as a nucleophilic agent (on the basis of the absence of visible signs of interaction between the amine and the base) and therefore the problem of its mechanism remains open. However, it is difficult to imagine a mechanism for this reaction other than one involving the alkylamide anion. It is likely that the formation of even a small equilibrium amount of the metal salt of the amine (it is quite possible under the reaction conditions) followed by its interaction with heterocyclic compounds gradually displaces the amine $\rightleftharpoons$ *N*-anion equilibrium to the right.

The majority of alkyl- and aryl-amination reactions involving *N*-anions are not accompanied by the evolution of hydrogen, in contrast to the Chichibabin reaction. To eliminate the hydride ion from the intermediate σ-complex, oxidising agents must be employed: potassium nitrate, air, or pure oxygen.

9. OXIDATION REACTIONS OF N-ANIONS

In general *N*-anions are oxidised much more readily than the neutral amines. Most data have been obtained for the autoxidation reaction. The reactivity of metal salts of amines in relation to molecular oxygen may be extremely varied: ranging from nitroarylamine and 2-amino-pyrimidine salts, which are completely stable in air, to metal salts of alkylamines which react vigorously with oxygen. Thus less reactive amines give rise to more readily oxidised *N*-anions and conversely.

Sodium anilide and metal salts of arylamines with electron-donating substituents rapidly blacken in air and are converted into a mixture of high-molecular-weight autoxidation products. A controlled and mild autoxidation of the *N*-anions of aromatic amines to azo-compounds has been achieved in the NaH–THF,[52] t-C_4H_9OK–toluene[209], and t-C_4H_9OK–DMSO[183,184,210] systems. Two views have been expressed concerning the mechanism of this reaction. According to the first, on being acted upon by oxygen, the *N*-anion is converted into a radical (**XXIX**), which dimerises to the corresponding hydrazobenzene. The latter is then transformed (also via the *N*-anion) into azobenzene[209]:

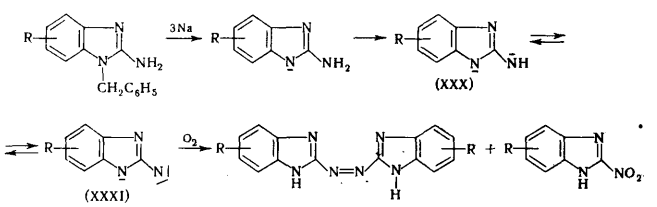
$$ArNH_2 + t\text{-}C_4H_9OK \rightleftarrows ArNH^-K^+ + t\text{-}C_4H_9OH,$$
$$2\,ArNH^-K^+ + O_2 \rightarrow 2\,ArNH + O_2^-,$$
(XXIX)
$$2\,\mathbf{XXIX} \rightarrow ArNH{-}NHAr \rightarrow ArN(K^+){-}N(K^+){-}Ar \xrightarrow{O_2} Ar{-}N{=}N{-}Ar + K_2O_2.$$

This mechanism probably obtains in many cases (see, for example, Filipskikh et al.[120]), but, as shown recently[182,210], the reaction involving aniline itself and its substituted derivatives proceeds via a different pathway involving the condensation of an intermediate nitroso-compound with the amine *N*-anion.

The *N*-anions of α- and β-aminoanilines form dibenzo[*a*,*h*]phenazine on oxidation with oxygen[209].

The monoanions of 2-amino-derivatives of pyridine, benzimidazole, thiazole, and other nitrogenous heterocycles react very slowly with oxygen. Usually the corresponding azo-compound is formed in low yields under these conditions[91]. An exception is the monoanion of the less acid 2-amino-4,5-diphenylimidazole, which readily oxidises in air to 2,2′-azoimidazole[91].

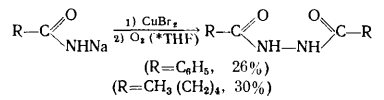
The polyanions of 2-aminobenzimidazole and certain other 2-aminoimidazoles exhibit an unusually high reactivity in the autoxidation reaction for reasons which are not obvious[91]. It was found that the polyanions (**XXX**) and (**XXXI**), formed on debenzylation of 2-amino-1-benzylbenzimidazoles with sodium or potassium in liquid ammonia, react rapidly with atmospheric oxygen at temperatures as low as −70°C, being converted quantitatively into a mixture of 2,2′-azo- and (unexpectedly) 2-nitrobenzimidazoles[91,211,212]:



This reaction is the only known example of such ready autoxidation of the amino-group to the nitro-group.

The polyanions (**XXX**) and (**XXXI**) can also be obtained from 2-azido-,[119] 2-benzylamino-,[126] 2-amino-1-arylalkyl-,[90] and 2-amino-benzimidazoles.[91] The attempts to drive the autoxidation process towards the preferential formation of the more valuable 2-nitrobenzimidazole (analogue of the antibiotic azomycin) have so far remained unsuccessful: the maximum yield of the nitro-derivative achieved does not exceed 45%. The mechanism of the formation of 2-nitrobenzimidazole is still obscure; however, it has been established that the reaction is influenced by a series of factors: the type of the imidazole system, the nature of the solvent, the metal, the substituent at $N_{(1)}$, the method of generation of the *N*-anion, and others. For example, the trilithium salt of 2-aminobenzimidazole is oxidised by oxygen in ether only as far as 2,2′-azobenzimidazole (yield 90%).

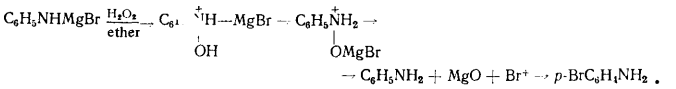
It has also proved possible to achieve the oxidative dimerisation of metal salts of acid amides and amidines. It was found that copper salts of N–H acids are oxidised by oxygen much more readily than the sodium or lithium salts[213]:



It is remarkable that copper(I) chloride catalyses (also, it is believed, via the formation of a copper salt) the autoxidation of aniline to azobenzene in pyridine solution[214,215].

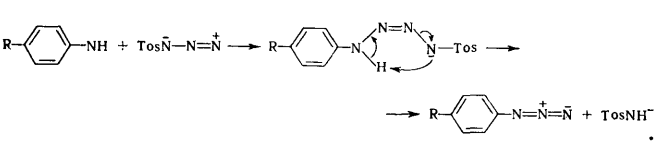
The oxidation of *N*-anions by other oxidising agents has been little studied. The anions of certain *N*-heteroaromatic amines (triazoles[216,217], benzothiazoles[218], and benzimidazoles[120,219]) are oxidised by $KMnO_4$, $K_2S_2O_8$, and NaOCl to the corresponding azo-compounds, the reaction being of preparative value in some cases.

When hydrogen peroxide in ether is allowed to react with the bromomagnesium salt of aniline, *p*-bromoaniline[220] (and not phenylhydroxylamine as reported earlier[221]) is formed. The mechanism proposed for this reaction involves the intermediate formation of positively charged bromine[220]:



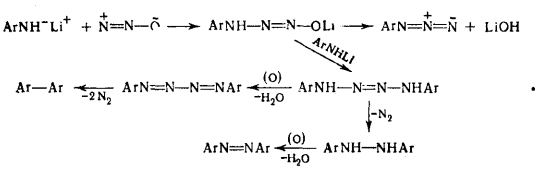
10. OTHER REACTIONS OF N-ANIONS

An unusual conversion of amine *N*-anions into azides with the aid of *p*-toluenesulphonyl azide (TSA), which plays the role of a diazo-transferring agent, was discovered by American workers[222]. The reaction is believed to proceed via a triazene intermediate and reduces in the initial stage to the addition of the *N*-anion to the azido-group of TSA in one of its resonance forms with the positive charge at the terminal nitrogen atom:

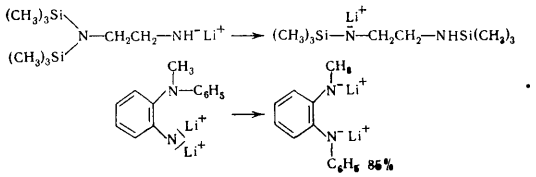


The *N*-anion of benzylamine has been converted into benzyl azide in a yield of 26%. The less nucleophilic *N*-anions of acid amides and *p*-nitroanilines could not be converted into azides in this way.

The interaction of the *N*-anions of amines with nitrous oxide [53,54] is closely related to the above reaction. However, in this case the yield of the azide does not exceed 10–35%. The corresponding biphenyl and azobenzene, which is the main reaction product, are also formed [54]. In general, the processes can be represented as follows:

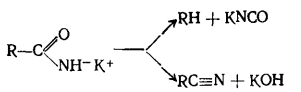


In a study of *N*-anionic rearrangements in the series of asymmetric hydrazines, West observed that to some extent they are characteristic also of the *N*-anions of aromatic and aliphatic diamines. The following two examples illustrate the 1,4-anionic rearrangements of this type [170,223]:

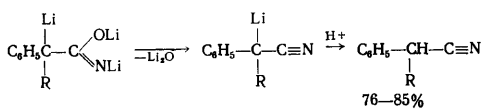


It is remarkable that in the case of *o*-aminobiphenylyl-*N*-methylamine, only the dianion undergoes a rearrangement [223].

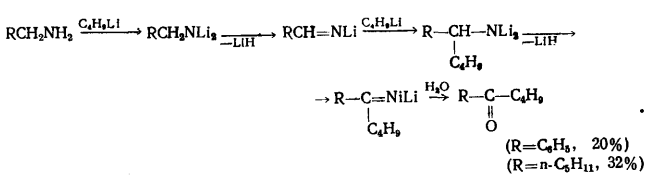
Elimination reactions with conversion into nitrile and certain other compounds are characteristic of the *N*-anions of many acid amides. For example, the potassium salts of formamide and urea decompose extremely readily with formation of potassium cyanate and the evolution of hydrogen and ammonia respectively [224]. The *N*-anions of other amides of aliphatic [224] and aliphatic-aromatic [100] acids decompose on heating via two pathways—with formation of a hydrocarbon and a nitrile:



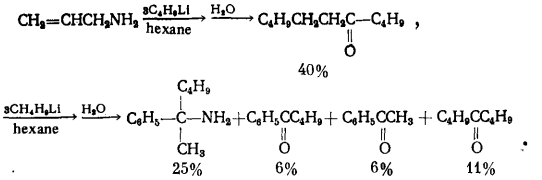
Hauser and coworkers used this property of the *N*-anions of acid amides for preparative purposes. They established that the trianions of aryl- and diaryl-acetamides are converted under mild conditions into the corresponding nitriles in high yields [98,99]:



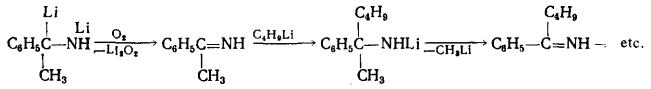
Interesting reactions of the dilithium salts of primary alkyl- and arylalkylamines were discovered recently [225]. On refluxing in hexane in the presence of an excess of butyl-lithium and subsequent hydrolysis, the dilithium salts of alkylamines yield ketones with a butyl group. The authors suggested that the reaction proceeds according to the following elimination–addition mechanism



The reaction involving allylamine and α-phenylethylamine proceeds in a more complex manner:



Unfortunately the question of the possible ionisation of the C–H bond in the methine group of α-phenylethylamine was not investigated in the study quoted above. In the light of what has been said earlier concerning the metallation of CH–NH systems (p.39), this is a very likely possibility and the formation of all the products enumerated could be predicted theoretically also on the basis of the conversion of the *CN*-dianion:



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Interesting studies on the gas-phase acidity of alkyl- and dialkyl-amines [226] and on the synthesis of substituted acid amides from esters and sodium salts of aryl- and cycloalkyl-amines [227] were published recently.

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