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PERSPECTIVE

Organic reactivity in liquid ammonia†

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Liquid ammonia is a useful solvent for many organic reactions including aliphatic and aromatic nucleophilic substitution and metal-ion catalysed reactions. The acidity of acids is modified in liquid ammonia giving rise to differences from conventional solvents. The ionisation constants of phenols and carbon acids are the product of those for ion-pair formation and dissociation to the free ions. There is a linear relationship between the pK_a of phenols and carbon acids in liquid ammonia and those in water of slope 1.68 and 0.7, respectively. Aminium ions exist in their unprotonated free base form in liquid ammonia. The rates of solvolysis and aminolysis by neutral amines of substituted benzyl chlorides in liquid ammonia show little or no dependence upon ring substituents, in stark contrast with the hydrolysis rates of substituted benzyl halides in water which vary 10^7 fold. However, the rates of the reaction of phenoxide ions and amine anions with 4-substituted benzyl chlorides gives a Hammett $\rho = 1.1$ and 0.93, respectively. The second order rate constants for the substitution of benzyl chlorides by neutral and anionic amines show a single Brønsted $\beta_{\text{nuc}} = 0.21$ whereas those for substituted phenoxide ions generate a Brønsted $\beta_{\text{nuc}} = 0.40$. The rates of aromatic nucleophilic substitution reactions in liquid ammonia are much faster than those in protic solvents indicating that liquid ammonia behaves like a typical dipolar aprotic solvent in its solvent effects on organic reactions. Nitrofluorobenzenes (NFB) readily undergo solvolysis in liquid ammonia but oxygen nucleophiles, such as alkoxide and phenoxide ions, displace the fluorine of 4-NFB in liquid ammonia to give the corresponding substitution product with little or no competing solvolysis product. The Brønsted β_{nuc} for the reaction of 4-NFB with para-substituted

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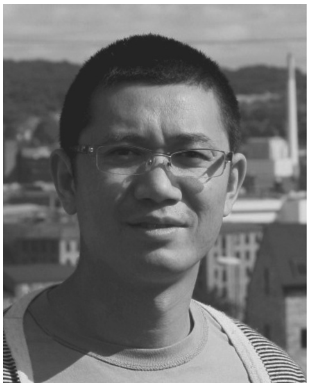


Pengju Ji

Pengju Ji graduated from Northwest University with an MSc in Organic Synthesis before he joined Professors Mike Page and John Atherton's research group at the University of Huddersfield in 2008. His PhD project was to investigate the solvent effects of liquid ammonia on some fundamental organic reactions and thus provide the physical organic chemistry support for future industrial applications of liquid ammonia as a solvent. After he obtained his PhD in 2011, he moved to Tsinghua University as a postdoc to explore the physical organic chemistry in ionic liquids.

John Atherton

John Atherton studied at the University of Manchester Institute of Science and Technology, and worked for 37 years with ICI, Zeneca and Avecia , applying physical organic chemistry to the design and improvement of industrial Fine Chemicals processes. Following his retirement in 2004 he was appointed Visiting and later full Professor in the Department of Chemical and Biological Sciences, Huddersfield University, where he initiated research into the mechanisms of organic reactions in liquid ammonia.

phenoxides is 0.91, indicative that the decomposition of the Meisenheimer σ-intermediate is rate limiting. The aminolysis of 4-NFB occurs without general base catalysis by the amine and the second order rate constants generate a Brønsted β_{nuc} of 0.36, which is also interpreted in terms of rate limiting breakdown of the Meisenheimer σ-intermediate.

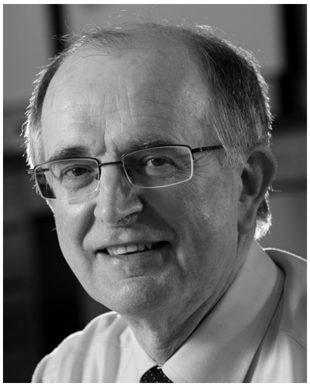
Introduction

The nature of the solvent used for an organic reaction has long been known to influence both the kinetics and mechanisms of the processes.[1] In industry, solvents are used in large quantities and large amounts are used per mass of final product, so solvent choice is a major part of the environmental performance of a process and its impact on cost, safety and hazard issues. Ever increasing health and environmental concerns have resulted in some previously common solvents, such as chloroform, being proscribed, whilst others, although still commonly used in research syntheses, are generally avoided on the manufacturing scale. Dipolar aprotic solvents (*e.g.* DMSO, DMF, DMAc and NMP) are used in around 10% of chemical manufacturing processes but they are expensive, have toxicity concerns, are difficult to recycle due to their water miscibility, and are frequently disposed of by incineration.

Liquid ammonia (LNH$_3$) is a promising candidate to replace dipolar aprotic solvents in a number of applications. Ammonia has only one lone pair for three potential N–H hydrogen bonds, leading to relatively weak association in the liquid state and a boiling point of −33 °C and a vapour pressure of 10 bar at 25 °C.[2] Although it is similar in many ways to conventional dipolar aprotic solvents, it is much easier to recover and can be handled with care in small scale laboratory glassware over a useful temperature range.[3] Despite the low dielectric constant of liquid ammonia (16.9 at 25 °C)[4] many salts and organic compounds have good solubility.[5,6]

It has generally been accepted that liquid ammonia behaves as a typical hydrogen bond donor solvent and this is extensively stated in the literature.[1] However, there is very little evidence to support this assertion. Although liquid ammonia is generally accepted as a protic solvent, like water, with good hydrogen bond donator (HBD) and acceptor (HBA) ability, liquid ammonia actually has a very limited HBD ability not only in the gas phase, but also in the condensed phase. The nitrogen lone pair makes ammonia a good H-bond acceptor and liquid ammonia strongly solvates cations[7] but, unlike water, it is not a good hydrogen bond donor[8] and does not significantly solvate anions.[9] Liquid ammonia thus renders anionic nucleophiles more "naked" than in water which are therefore expected to be more reactive. Similarly as anions are less stable in liquid ammonia, expulsion of the chloride anion from reactants is expected to be more difficult than in water. The normalised donor number (DN^N) of liquid ammonia is 1.52, greater than that of HMPTA (1.0),[10] while its autoprotolysis constant gives a pK_a of 33 (−50 °C), compared with 14 for water (25 °C).[11] Contrary to commonly accepted views,[1] it appears that liquid ammonia acts more like a dipolar aprotic solvent in nucleophilic substitution reactions.

Although there have been many synthetic studies in liquid ammonia,[6] little is known about the kinetics and mechanisms of reactions in this solvent. We are currently investigating the scope of this solvent in synthesis and aim to provide some of the physical organic chemistry required to support the synthesis programme.[12] The physical and chemical properties of liquid ammonia are well documented,[13] as is the reduction of organic compounds using alkali metal–ammonia solution[14] and the use of alkali metal amides in liquid ammonia as strong bases.[15–17]



Mike Page

Mike Page studied Chemistry at Brighton and took his PhD at Glasgow. He was a postdoctoral research fellow with W P Jencks and then R P Bell. He was then appointed Lecturer at the University of Huddersfield where he has been Senior Lecturer, Reader, Professor, Head of the Department, Dean and Deputy Vice-Chancellor. Mike has been a member of many international and UK national bodies and editorial boards. He was Chairman of the Committee of Heads of Polytechnic Chemistry Departments and of the RSC Qualifications and Education Board and a member of Council. He was a member of the RAE panel for Chemistry in 1992. Mike's research interests cover how chemical reactions occur, medicinal chemistry and drug design, the mechanism of action of enzymes and the use of enzymes in synthesis. He has published about 200 research papers, edited three books and co-authored, with Andrew Williams, Organic and BioOrganic Mechanisms. He was awarded the RSC's 150th anniversary Perkin prize in 1991 and the Organic Reaction Mechanisms Prize in 2003.

The ionisation of acids in liquid ammonia

Liquid ammonia is a basic solvent with a very low self-ionisation constant (pK_a = 27.6 at 25 °C)[18] and the ionisation of acids in this solvent generates equivalent amounts of the conjugate base and ammonium ion (eqn (1)). Many ionic species will be strongly associated because of the low

$$HA + NH_3 \overset{K_i}{\rightleftharpoons} [A^-NH_4^+]_{ip} \overset{K_d}{\rightleftharpoons} A^- + NH_4^+ \tag{1}$$

dielectric constant of liquid ammonia, and conductivity data shows that ion-pairing occurs even at low concentrations and larger aggregates may form at higher concentrations.[19] Several methods have been used to determine ionisation and dissociation constants including spectroscopic, conductivity and NMR.[20] Knowledge of how ionisation constants in liquid ammonia vary with substituents is needed to interpret structure–activity relationships of reactions in this solvent.

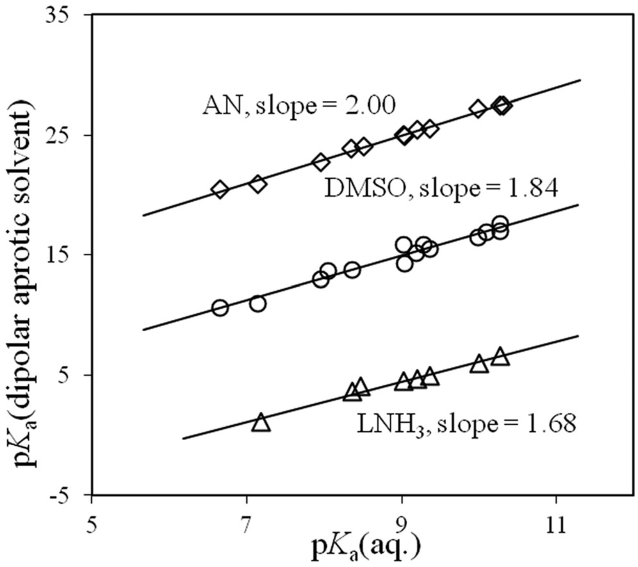


Fig. 1 pK_a of phenol in liquid ammonia (LNH$_3$), DMSO and acetonitrile (AN) against its aqueous pK_a.

Phenols with aqueous pK_a <7.0, but not those with pK_a >8.5, are fully ionised in liquid ammonia at room temperature.[12] Phenols are stronger acids in liquid ammonia than in water and increasing the ionic strength by the addition of salts increases the extent of ionisation. There is a linear relationship between the apparent pK_a values in liquid ammonia[12] and the corresponding aqueous ones with a slope of 1.68, compared with 2.00 and 1.84[21] in acetonitrile and DMSO, respectively (Fig. 1). This greater dependence of the acidity of phenols on substituents in liquid ammonia compared with water presumably results from the poorer solvation of the phenoxide anions in the non-aqueous solvent so their stability is more dependent on negative charge delocalisation through the substituent.

The apparent pK_a's in liquid ammonia are the product of at least two constants, K_i, for ion pair formation, and K_d, for dissociation to the free ions (eqn (1)) and so the degree of dissociation is dependent on the concentration of ammonium ions and the addition of the latter decreases the concentration of phenoxide ion to a constant level when only the ion-pair is present. From these observations, K_i and K_d can be determined.[12] The dissociation constant of the ion-pair to the free ions, K_d, is very dependent on the ionic strength of the medium. For 4-nitrophenol at I = 0.2 M, K_i = 1.9 M^{-1} and K_d = 0.11 M whereas at low ionic strength K_i = 5.6 M^{-1} and K_d = 1.5 × 10^{-2} M. The latter data generates an apparent pK_a for 4-nitrophenol from K_i and K_d of 1.08.

Alkylammonium ions are fully deprotonated in liquid ammonia and so exist as their free bases; the equilibrium (eqn (2)) lies well over to the right, suggesting that ammonia solvent stabilises the ammonium ion (NH$_4^+$) more than the alkylammonium ions (RNH$_3^+$). Although all amines exist effectively solely in their free base form in liquid ammonia, as will be discussed later, their nucleophilic reactivity still varies with their aqueous basicities.

$$\mathrm{RNH_3^+ + NH_3 \overset{K}{\rightleftharpoons} RNH_2 + NH_4^+} \qquad (2)$$

The acidity of carbon acids and their rates of deprotonation and the rates of protonation of their conjugate base carbanions have contributed to our understanding of electronic effects[22] and the 'imbalance' between various motions required in the transition states of their reactions.[23] The solvent plays an important role in these phenomena both in terms of the stability of the carbanion and of the solvent reorganisation that is often required for charged delocalised species.[1] Again due to the relatively low dielectric constant of liquid ammonia, the ionisation of carbon acids in liquid ammonia gives rise to ion-pairs (and higher aggregates)[19] in equilibrium with the dissociated species (eqn (3)), where the product K_iK_d corresponds to the normal ionisation constant K_a.

$$\mathrm{CH + NH_3 \overset{\mathit{K_i}}{\rightleftharpoons} [C^- NH_4^+]_{\mathit{ip}} \overset{\mathit{K}_d}{\rightleftharpoons} C^- + NH_4^+} \qquad (3)$$

Carbonyl activated carbon acids that have an aqueous pK_a of less than 11 are fully ionised in liquid ammonia at 25 °C as shown by ^{1}H and ^{13}C NMR spectra.[24] Diethyl malonate which has an aqueous pK_a of 12.9[25] is not ionised in liquid ammonia but shows a broad single peak of the central methylene protons, probably due to a fast exchange of these protons with the solvent. Mono-cyano-activated carbon acids[26] are not ionised in liquid ammonia, but dicyano derivatives are fully ionised. Malonodinitrile, MDN, with an aqueous pK_a of 11.2[25] shows very unusual behaviour as its ^{1}H NMR spectrum shows no protons attached to the central methylene carbon present in neutral MDN even at −40 °C, where the rate of exchange would be slower.[24] The ^{13}C NMR spectrum of MDN shows a high field carbon signal at −3.12 ppm, consistent with the formation of a negatively charged carbon, and contrasts with that of 11.5 ppm of benzylmalonodinitrile mono-anion in liquid ammonia. However, it would be surprising if both protons of MDN have been removed to form a carbon dianion and it is more likely that it is a monoanion with unusual NMR properties. It has been proposed that the resonance stabilisation of α-cyano carbanions is not significant and the negative charge is localised at the α-carbon, which may explain why there is such a high-field signal for MDN anion in liquid ammonia.[27]

The acidity of carbon acids that do not ionise in liquid ammonia have been estimated from the rates of proton exchange in the deuterated derivatives.[24] The corresponding 'pK_a' values were calculated using the estimated diffusion-controlled rate constant and are uncorrected for any primary kinetic isotope effect on the rate of exchange. There is a reasonable correlation between the apparent ionisation constants of carbon acids in liquid ammonia[24] and those in water with a slope of 0.8, which contrasts with the 1.68 observed for the ionisation of phenols in liquid ammonia against their aqueous pK_a.[12] Evidently, there are different relative roles for solvation and substituents in stabilising the carbanions and phenoxide ions.

Solvolysis in liquid ammonia

The solvolysis of compounds in liquid ammonia may either lead directly to a desired product or it may be a competing process and its rate is a guide to the viability of other reactions in this solvent. The ammonia solvent, in addition to its role as a

Table 1 Solvolysis rate constants of substrates in liquid ammonia at 25 °C[3]

Substrates	$10^6\ k_0(\mathrm{s}^{-1})$	$t_{1/2}$
4-Nitrofluorobenzene[a]	7.86	24.4 h
Benzyl chloride	8.89×10^2	13.0 min
2-Chloropyrimidine	14.2	13.3 h
2,4-Dinitrochlorobenzene	6.18×10^3	1.85 min
4-Nitroazidobenzene[a]	5.11	37.7 h
Styrene oxide[a]	3.06	62.9 h
Styrene oxide–1 M NH_4Cl[a]	6.89	27.9 h
Phenyl benzoate	7.70×10^3	1.50 min
Methyl-4-nitrobenzoate	14.2	13.3 h
4-Nitrophenyl acetate	$>7.0 \times 10^4$	<10 s
Triphenyl phosphate	3.50	54.4 h
Benzene sulfonyl chloride	$>7.0 \times 10^4$	<10 s

[a] At 20 °C.

nucleophile, may possibly act as a general base as in a S_N3 type process.[28] The solvent also can determine the mechanism of substitution by its effects on the stability of the intermediate carbocation and on its solvation of the leaving group. The rate constants for the solvolysis of a variety of substrates (Table 1) show a large range of reactivities.[3] The solvolysis rates of some aromatic halides are relatively slow compared with those for aliphatic halides, and aryl esters react rapidly whereas alkyl ones are more stable. The solvolysis of triphenyl phosphate is slow in liquid ammonia to give only mono-solvolysed product whereas triethyl phosphate does not undergo reaction under the same conditions.

The rates of solvolysis of substituted benzyl chlorides to give the corresponding benzyl amine show little or no dependence on the substituent which is in stark contrast to that in water, where the hydrolysis rates increase by about 4 orders of magnitude on going from 4-nitrobenzyl chloride to 4-methoxybenzyl chloride. The solvolysis rates in liquid ammonia are generally faster than those in water, but the difference decreases with electron-donating substituents so that 4-methoxybenzyl chloride is actually more reactive in water than in liquid ammonia.[3] The rate of solvolysis of *t*-butyl chloride in liquid ammonia is very slow ($t_{1/2} \sim$ 20 weeks)[29] which is about 6 orders of magnitude slower than that in water.[30] Large negative entropies of activation of about $-200\ \mathrm{J\ K^{-1}\ mol^{-1}}$ are observed for the solvolysis of benzyl chlorides in liquid ammonia, indicative of a restricted activated complex relative to the reactant and compatible with a bimolecular concerted S_N2 mechanism.[3]

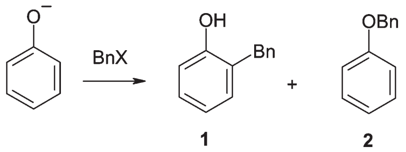
There is little or no dependence of the rate of solvolysis of substituted benzyl chlorides in liquid ammonia upon the substituent, giving a Hammett ρ value of approximately zero, while that in water shows $\rho = -2.0$.[3] In liquid ammonia there is little or no charge developed on the central carbon atom in the transition state whereas there is a large amount of positive charge formed in the hydrolysis reaction in water. The lack of sensitivity of the rate of solvolysis of benzyl chloride in liquid ammonia to the substituent in the aromatic ring is consistent with a concerted S_N2 mechanism with the amount of charge development on the incoming nucleophilic ammonia counterbalanced by that on the departing chloride and with no change in charge on the central benzylic carbon. Despite the low dielectric constant of liquid ammonia it strongly solvates cations[7] which may have indicated stabilisation of an intermediate carbocation and thus support for a S_N1 mechanism; however, liquid ammonia does not significantly solvate anions,[9] which would hinder expulsion of chloride ions. Complete inversion of configuration occurs in the solvolysis of *S*-α-methyl benzyl chloride with almost 100% yield and with no elimination products formed. This is another strong indication that the solvolysis of primary and secondary aliphatic halides in liquid ammonia follows an S_N2 mechanism.[12]

Aliphatic nucleophilic substitution reactions

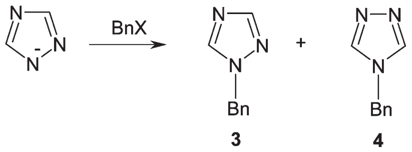
Nucleophilic displacement reactions at saturated carbon centres occur either with simultaneous breaking and forming of the involved bonds (S_N2 or A_ND_N) or by a mechanism where breaking the old bond precedes formation of the new bond (S_N1 or $D_N + A_N$). The nature of the solvent used for these reactions can influence the mechanism adopted and the transition state structure.[31] With liquid ammonia as the solvent, an additional complication is the possible intervention of ion pairs and the degree of solvation of the nucleophile and leaving group which influences the extent of 'push and pull'.

A variety of oxygen nucleophiles react with benzyl chloride in liquid ammonia to give the corresponding substitution products, although solvolysis is sometimes competitive with these reactions and a mixture of products is obtained.[12] There is first order dependence of the pseudo first order constants on the concentration of the nucleophile, indicating that these reactions follow a bimolecular S_N2 type mechanism. There is a large rate enhancement of about 10^4-fold for the reaction of methoxide ion with benzyl chloride in liquid ammonia compared with that in methanol.[32] The second order rate constants for the nucleophilic substitution of benzyl chloride by phenoxide ion are similar in liquid ammonia and DMF, and are about 5000 times greater than that in methanol.[33] These rates increase on going from protic to dipolar aprotic solvents and are attributable to the specific solvation though hydrogen bonding of anionic nucleophiles in protic solvents, which decreases their activity as nucleophiles due to the large desolvation energy required on going from initial state to the transition state.[34] This is also shown by the large positive Gibbs transfer energies of anions from protic solvents to non-polar and dipolar aprotic solvents.[9]

On the other hand, some dipolar aprotic solvents such as ammonia strongly favour the solvation of cations which can lead to the destruction of ion pairs and thus to increased nucleophilicity of the counter-anion. One of the main reasons dipolar aprotic solvents favour bimolecular concerted over a unimolecular mechanism is their poor solvation of the leaving anion. The rates of reaction for substituted phenoxides with benzyl chloride in liquid ammonia are generally several thousand-fold greater than those in methanol and water and the second order rate constants vary significantly with substituents.[12] The rate difference between 4-cyano and 4-methoxy phenoxide ion reactions is about 40-fold in liquid ammonia, whereas in methanol or alcoholic solvent the rate is insensitive to the substituent.[35] The Brønsted plot for the rate constants in liquid ammonia using the aqueous $\mathrm{p}K_\mathrm{a}$ of the phenol or its value in liquid ammonia shows very good linear free energy relationships with $\beta_\mathrm{nuc} = 0.66$ or 0.40, respectively. The latter value indicates the transfer of some negative charge from the attacking phenoxide anion to the



Scheme 1



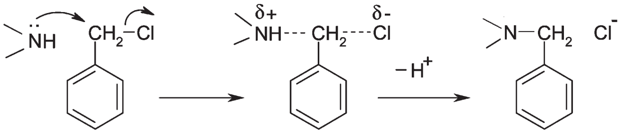
Scheme 2

benzyl group and the leaving chloride ion and partial bond formation between the phenoxide oxygen and the benzylic carbon in the transition state. The solvation ability of a solvent is a function not only of its dielectric constant and dipole moment, but also by its ability to donate protons or electrons. Although the dielectric constant and dipole moment of liquid ammonia are much less than those for common dipolar aprotic and protic solvents, the enhanced rate of reaction between anionic *O*-nucleophiles and alkyl halides in liquid ammonia compared with alcoholic solvents is probably due to the poor solvation of anions in the former compared with the latter and good solvation of the anion's counter-cation by the ammonia lone pair, thus decreasing ion-pair formation.

The second order rate constants for the reaction of phenoxide ion with substituted benzyl chloride in liquid ammonia generate a Hammett ρ = 1.11, apart from the expected deviation for 4-methoxybenzyl chloride.[12] The most likely explanations for the latter are either: (i) a change in the structure of the transition state for a single mechanism but with a differing degree of bond formation and cleavage, so that the 4-methoxy derivative causes a shift to a transition state with more positive charge on the central carbon atom[36] or (ii) a single transition state structure but with the 4-methoxy substituent stabilising the transition state with a different balance of polar and resonance effects.[37] The ρ value of 1.11 suggests that, in the transition state, appreciable charge has been transferred from phenoxide oxygen to benzylic carbon which is more than that lost to the departing chloride ion and contrasts markedly with that of zero for the solvolysis reaction.[3] Overall the transition state structure for phenoxide-ion substitution is negatively charged compared with a neutral one for solvolysis, so it is not surprising that the rate with phenoxide-ion is enhanced by electron-withdrawing groups.

Phenoxide ion is a well known ambident nucleophile and it can undergo both *C*- and *O*-alkylation (Scheme 1) and which reaction dominates depends very much on the medium. In liquid ammonia, there is less than 0.5% solvolysis product and no *C*-alkylated product (**1**) formed, giving a selectivity for *O*-alkylation (**2**) of almost 100%. By contrast in diethyl ether the major product is the *C*-alkylated one.[38] Presumably, the differing solvation of the phenoxide anion, including tight ion-pair formation, affects the relative negative charge density on oxygen and the ring carbons as well as the stability of the two transition states leading to *C*-alkylation in ether and protic solvents.

Benzyl chloride reacts with secondary amines in liquid ammonia to give predominantly the substituted product but, as the differences in solvation of amines in aprotic and dipolar aprotic solvents is not as great as that for anions, the rate differences between protic and dipolar aprotic solvents is not as pronounced as that seen for anionic oxygen nucleophiles. There is a first order dependence of the pseudo first order rate constant for the aminolysis of benzyl chloride[12] on the concentration of the amine, which again confirms that these reactions follow a bimolecular S_N2 type mechanism. The second order rate constants for the aminolysis of benzyl chloride with various neutral and negatively charged amines generate a single Brønsted plot using the aqueous pK_a of the amines to give a β_{nuc} of 0.21. All amines exist in their free base unprotonated form in liquid ammonia but using the aqueous pK_a does indicate that there is some dependence on the basicity of the amine nucleophile, but much less than that for oxygen nucleophiles, suggesting a transition state with little charge developed on the amine nitrogen in the transition state or charge removal in the case of negatively charged amine anions. The second order rate constant for ammonia shows a large negative deviation from the Brønsted plot explaining why aminolysis by weakly basic amines is easily observed in liquid ammonia. 1,2,4-Triazolate and benzotriazolate anions are widely used in the agriculture and pharmaceutical industries[39] and, as they are ambident nucleophiles,[40] the regioselectivity of their nucleophilic reactions is important. In liquid ammonia, in a few hours, the major product of equimolar reaction between benzyl chloride and sodium triazolate is 1-benzyl-1,2,4-triazole (**3**) rather than 4-benzyl-1,2,4-triazole (**4**), in a ratio of 12 : 1 (Scheme 2). In other solvents, the selectivity is much lower and requires longer reaction times.[41]

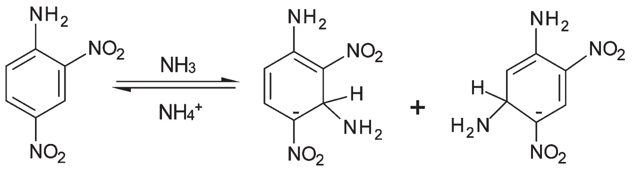


Scheme 3

The reaction with the neutral amines is insensitive to the *para*-substituent in benzyl chloride, similar to that seen for solvolysis, whereas the ρ value for the triazolate anion with 4-substituted benzyl chloride is 0.93, similar to that seen with phenoxide anion. It appears that the increased sensitivity to aromatic ring substituents is due to the requirement to accommodate a negative charge in the transition state.

In summary, liquid ammonia acts like a typical dipolar aprotic solvent in its effect on aliphatic nucleophilic substitution reactions. The activation parameters, substituent and salt effects, and the stereochemistry all indicate that the mechanism of solvolysis and aminolysis with neutral amines of benzyl chlorides in liquid ammonia is forced to be a concerted S_N2 mechanism proceeding through a transition state structure that has little charge development on the incoming nucleophile and the departing nucleofuge and little or no change in charge on the central benzylic carbon compared with that in the reactant state (Scheme 3).

On the other hand, the transition state of nucleophilic substitution between *O*-anions and benzyl chloride has an unsymmetrical transition structure with a relatively appreciable transfer of



Scheme 4

Table 2 Solvolysis rate constants and half-lives at 25 °C of some aromatic compounds in LNH_3

Substrate	$10^6\ k_0(s^{-1})$	$t_{1/2}$
2-Nitrofluorobenzene (2-NFB)	2.15×10^2	54 min
4-Nitrofluorobenzene (4-NFB)[a]	7.86	24.4 h
2,4-Difluoronitrobenzene (2,4-DFNB)	6.72×10^3	1.7 min
2-Nitroazidobenzene (2-NAB)[a]	5.81	33.1 h
4-Nitroazidobenzene (4-NAB)	5.11	37.7 h
2,4-Dinitroazidobenzene	$>1.4 \times 10^5$	<5 s
2-Chloropyrimidine[a]	14.2	13.3 h
2-Chlorobenzthiazole	5.33	36.1 h

[a] at 20 °C

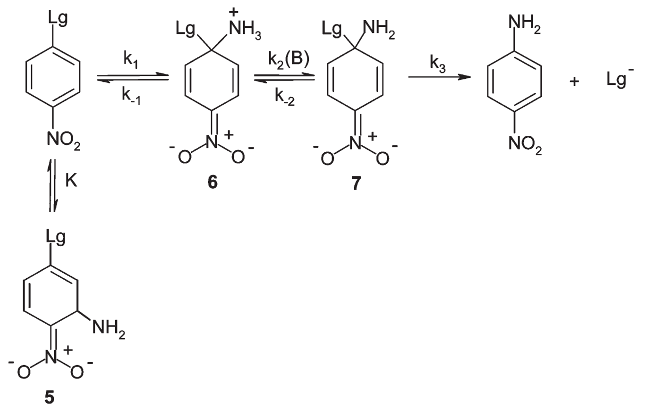
negative charge from the anion to the carbon centre and very little charge on the nucleofuge. The concerted mechanism is probably largely due to the difficulty of expelling a leaving group anion in liquid ammonia and the enhanced nucleophilicity of nucleophiles in this solvent. These facts show that the reactivity of the nucleophile and the nucleofugality of the leaving group can greatly affect the transition structure of the aliphatic nucleophilic substitution reaction in liquid ammonia. Also some reactions show a good selectivity toward ambident nucleophiles, which indicate its potential industrial application in liquid ammonia.

Aromatic nucleophilic substitution

The UV–visible absorption spectrum of 2,4-dinitroaniline in liquid ammonia is consistent with the formation of a stable Meisenheimer complex[42] and can be assigned to one or both of the intermediates shown (Scheme 4), which are written as anions rather than zwitterions, as aminium ions exist as free bases in liquid ammonia.[12] The reactant is recovered unchanged after vapourisation of liquid ammonia from a solution of either 2,4-dinitroaniline or 1,3-dinitrobenzene and it appears that the Meisenheimer complex is formed rapidly but reversibly and removal of the ammonia solvent results in its reversion to starting material.

The first order rate constants for the solvolysis of activated aryl halides and aromatic heterocyclic halides in liquid ammonia to give the corresponding aromatic amines are dependent on the nature of the leaving group and the aromatic substituents and show the expected trends (Tables 1 and 2).

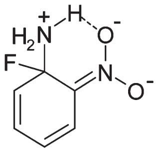
There is no reaction of unsubstituted halobenzenes at ambient temperature but, as expected, the 2- and 4-nitro activated derivatives are much more reactive.[43] The introduction of additional fluoro- or nitro-groups increases the solvolysis rates by more than 4 orders of magnitude.



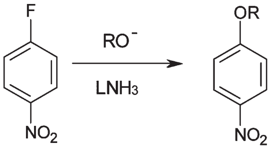
Scheme 5

Given the demonstration that nitro substituted aromatic compounds without a leaving group reversibly form Meisenheimer complexes in liquid ammonia (Scheme 4), it seems reasonable to postulate the complexes as intermediates in solvolysis and nucleophilic substitution reactions of analogous compounds that do contain a leaving group (Scheme 5).[42] However, an unproductive intermediate (**5**) may also be formed by nucleophilic attack on the C-3 unsubstituted position[42,44] and in the case of di-nitro-substituted derivatives these complexes may actually be the effective starting material as they are formed rapidly and are often more stable than the reactants.[42] Attack at the *ipso* C-1-fluoro-substituted position generates the reactive intermediate (**6**) with a charged ammonium ion but product formation probably requires deprotonation to form the anionic intermediate (**7**) before the leaving group can be expelled, especially as liquid ammonia is a poor solvent for anions. As aminium ions in liquid ammonia are invariably deprotonated by the vast excess of basic solvent,[12] it is likely that the zwitterionic intermediate (**6**) is rapidly converted to the thermodynamically more stable anionic intermediate (**7**) by proton transfer to the solvent (k_2 step in Scheme 5 where B = NH_3). In fact the intermediate (**7**) may be formed directly from the reactants by general base catalysis by solvent ammonia. The rate-limiting step for solvolysis is therefore probably the breakdown of the intermediate (**7**), step k_3 (Scheme 5).

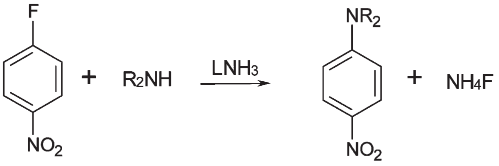
The rate of solvolysis of 4-nitroazidobenzene (4-NAB), in the absence of salts, is similar to that for 4-nitrofluorobenzene (4-NFB), but that for 2-NFB is nearly two orders of magnitude greater than that for 2-NAB (Table 2). Also 2-NFB is nearly 30 times more reactive towards solvolysis than its 4-substituted isomer, whereas the reactivities of 2- and 4-nitroazidobenzenes are similar. This *ortho* effect with 2-NFB, but not with 2-NAB, is also seen in the solvolysis of the more reactive di-substituted 2,4-DFNB which gives almost exclusively the *o*-substituted derivative as product. The enhanced reactivity of 2-NFB over 4-NFB is compatible with the formation of an intramolecular hydrogen bond within the activated complex to stabilise the intermediate (**8**).[45]



8



Scheme 6



Scheme 7

Oxygen nucleophiles, such as alkoxide and phenoxide ions, react readily with 4-NFB in liquid ammonia to give the corresponding substitution product (Scheme 6). There is little solvolysis product formed as the background rate of reaction of 4-NFB with ammonia is too slow to compete with the rates of substitution by anionic *O*-nucleophiles.

The second order rate constants for the reactions of 4-NFB with *O*-nucleophiles are 4–5 orders of magnitude faster in liquid ammonia than in methanol and are similar to those in DMSO. Again this large rate enhancement is probably due to the differences in solvation of the nucleophilic anions in dipolar aprotic and protic solvents, giving rise to enhanced nucleophilicity of anions in liquid ammonia. The second order rate constant for the reaction of phenoxide with 4-nitrochlorobenzene at 25 °C is 5 orders of magnitude smaller than that of 4-nitrofluorobenzene, which probably reflects the less favourable formation of the σ-complex. It is usually assumed that the mechanism of S_NAr reactions involves a charge delocalised Meisenheimer intermediate, the σ-complex (Scheme 5), in which the negative charge of an incoming nucleophile is spread into the aromatic ring and substituents through the resonance, and so the transition state is less dependent on solvation compared with a relatively localised reactant anion. Liquid ammonia, in common with dipolar aprotic solvents and unlike protic ones,[46] increases the rate of aromatic nucleophilic substitution by anions by several orders of magnitude, primarily due to the less solvated but more reactive nucleophile.

The Brønsted plot of the rate constants for reaction of 4-NFB with para-substituted phenoxides in liquid ammonia generates a β_{nuc} of 0.91 using the pK_a of the substituted phenols in liquid ammonia. This value is larger than those for the reactions of 4-NFB with phenoxides or thiophenoxides in protic solvents, which are around 0.5.[47] The β_{nuc} of 0.91 is indicative of almost complete removal of the negative charge on the oxygen anion and complete bond formation in the transition state and therefore suggests that the decomposition of the σ-complex is the rate limiting step or possibly its formation with a very late transition state. This is probably due to the difficulty of expelling and solvating the leaving fluoride anion from the Meisenheimer σ-complex (Scheme 5) in liquid ammonia.

The kinetics and mechanisms of secondary amines reacting with activated aryl halides are often complicated by base catalysis which depends on the reaction medium and reactant structures.[48] General base catalysis is observed, especially in non-polar aprotic solvents, if proton removal is required from the attacking nucleophile before the leaving group is expelled from the Meisenheimer σ-complex. However, in dipolar aprotic solvents general base catalysis is generally not observed.[49] The aminolysis of secondary amines with 4-NFB in liquid ammonia (Scheme 7) is first order in amine concentration indicating the absence of general base catalysis by a second molecule of amine.

The anionic Meisenheimer σ-intermediate (**7**) is thermodynamically more stable than its conjugate acid (**6**) in liquid ammonia (Scheme 5) and other amines are unlikely to be able to compete with solvent ammonia in converting (**6**) to (**7**) and so the absence of general base catalysis by amines is not surprising.

The second order rate constants for the aminolysis of 4-NFB increase with increasing aqueous basicity of the amine and there is a reasonable correlation with the aqueous pK_a values of the amines which generates an apparent Brønsted $\beta_{\text{nuc}} = 0.36$. The small Brønsted β_{nuc} contrasts with the β_{nuc} of 0.91 observed with phenoxide anions, which was obtained using pK_a values for phenols determined in ammonia. Without the knowledge of the relative pK_a values in liquid ammonia it is not possible to interpret the small values of Brønsted β_{nuc} for amines reacting with 4-NFB with any certainty, but it is indicative of only a small amount of positive charge development on the amine nitrogen nucleophile in the transition state. This small value is compatible with rate limiting breakdown of the σ-complex (**7**), following the deprotonation of the aminium ion in the Meisenheimer intermediate (**6**) (Scheme 5). This proton transfer step to the solvent ammonia is probably thermodynamically favourable given the effect of the adjacent fluorine in reducing the pK_a of the aminium ion and the fact that all aminium ions are deprotonated in liquid ammonia. An alternative mechanism could involve proton transfer to solvent being coupled to expulsion of the fluoride ion in a concerted breakdown of the σ-complex.

Summary

Liquid ammonia acts like a typical dipolar aprotic solvent for many reactions and, as an easily recoverable solvent, there is widespread potential for its use in the chemical industry. The ionisation constants of acids in liquid ammonia are the product of those for ion-pair formation and dissociation to the free ions; nonetheless there is often a linear relationship between the pK_a of acids in liquid ammonia and those in water. Aminium ions exist in their unprotonated free base form in liquid ammonia. Aliphatic nucleophilic substitution reactions are forced to occur by a concerted S_N2 mechanism but with variable transition state structures dependent on the nature of the entering and leaving groups. The rates of S_NAr reactions in liquid ammonia are much greater than those in protic solvents and are similar to those in dipolar aprotic solvents. In many cases nucleophilic substitution reactions are sufficiently faster than the background solvolysis reaction that useful synthetic procedures are possible in liquid ammonia. Liquid ammonia can increase the regioselectivity of some reactions compared with more conventional solvents.

On-going work has demonstrated the use of liquid ammonia in metal-ion catalysed reactions including azide–alkyne cycloadditions and the amination of aryl halides. Future work will examine the possibility of some fundamental life processes in liquid ammonia, given its occurrence on some planets.

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