KINETICS AND MECHANISMS OF ORGANIC REACTIONS IN LIQUID AMMONIA

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Abstract

The rate constants for the reactions of a variety of nucleophiles reacting with substituted benzyl chlorides in liquid ammonia (LNH_3) have been determined. To fully interpret the associated linear free-energy relationships, the ionisation constants of phenols ions in liquid ammonia were obtained using UV spectra. These equilibrium constants are the product of those for ion-pair formation and dissociation to the free ions, which can be separated by evaluating the effect of added ammonium ions. There is a linear relationship between the pK_a of phenols in liquid ammonia and those in water of slope 1.68. Aminium ions exist in their unprotonated free base form in liquid ammonia and their ionisation constants could not be determined by NMR. The rates of solvolysis of substituted benzyl chlorides in liquid ammonia at 25 ^oC show a Hammett ρ of zero, having little or no dependence upon ring substituents, which is in stark contrast with the hydrolysis rates of substituted benzyl halides in water, which vary 10^7 fold. The rate of substitution of benzyl chloride by substituted phenoxide ions is first order in the concentration of the nucleophile indicative of a S_N2 process, and the dependence of the rate constants on the pK_a of the phenol in liquid ammonia generates a Brønsted $\beta_{nuc} = 0.40$. Contrary to the solvolysis reaction, the reaction of phenoxide ion with 4-substituted benzyl chlorides gives a Hammett $\rho = 1.1$, excluding the 4-methoxy derivative, which shows the normal positive deviation. The second order rate constants for the substitution of benzyl chlorides by neutral and anionic amines show a single Brønsted $\beta_{nuc} = 0.21$ (based on the aqueous pK_a of amine), but their dependence on the substituent in substituted benzyl chlorides varies with a Hammett ρ of 0 for neutral amines, similar to that seen for solvolysis, whereas that for amine anions is 0.93, similar to that seen for phenoxide ion.

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 (NFBs) readily undergo solvolysis in liquid ammonia and 2-NFB is about 30 times more reactive than the 4-substituted isomer. Oxygen nucleophiles, such as alkoxide and phenoxide ions, readily displace fluorine of 4-NFB in liquid ammonia to give the corresponding substitution product with little or no competing solvolysis product. Using the pK_a of the substituted phenols in

liquid ammonia, the Brønsted β_{nuc} for the reaction of 4-NFB with para-substituted phenoxides is 0.91, indicative of the removal of most of the negative charge on the oxygen anion and complete bond formation in the transition state and therefore suggests 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 using either the pK_a of aminium ion in acetonitrile or in water, which is also interpreted in terms of rate limiting breakdown of Meisenheimer σ-intermediate. Nitrobenzene and diazene are formed as unusual products from the reaction between sodium azide and 4-NFB which may be due to the initially formed 4-nitroazidobenzene decomposing to give a nitrene intermediate, which may dimerise and be trapped by ammonia to give the unstable hydrazine which then yields nitrobenzene.

We have developed a method for the amination of aryl halides in liquid ammonia using copper (I) catalysis which enables direct synthesis of a number of primary amines with excellent yields. This method does not require strong base and ligands as additives and the amination in liquid ammonia has exclusive selectivity for the formation of primary amines, even under relative higher temperature. The amount of catalyst required for the reaction is relatively lower than that generally used, and the convenience of products separation with liquid ammonia as reaction medium indicate its potential industrial application. The preliminary mechanistic investigation indicates that the rate of the amination is first order dependence on the concentration of copper (I) catalyst, and the formation of triamminecopper (I)-aryl ring intermediate is probably the rate limiting step in liquid ammonia. Due to strong coordination of solvent molecules to the copper (I) ion, the kinetics of the reaction are generally insensitive to the addition of other conventional ligands in liquid ammonia.

The copper (I) catalysed 1,3-Huisgen cycloaddition reaction of azide and alkynes ($Cu^{I}AAC$) in liquid ammonia requires less catalyst than those in conventionally used solvents. The excellent yield, exclusive selectivity, and most importantly, the ease of separation of the product indicate the potential advantages of using liquid ammonia as the solvent for this reaction. The preliminary mechanistic investigation suggests that $Cu^{I}AAC$ reaction in liquid ammonia is a stepwise process with the initial formation of copper (I)-acetylide ion complex, followed by its combination with copper (I) coordinated azide.

A list of commonly used symbols and abbreviations in this thesis

LNH_3	liquid ammonia
HBD	hydrogen bond donor
HBA	hydrogen bond acceptor
ε_r	dielectric constant
λ_{max}	maximum absorbance wavelength (nm)
ε_{max}	molar extinction coefficient at λ_{max}
DMSO	dimethyl sulphoxide
DCM	dichloromethane
THF	tetrahydrofuran
DMF	N,N-dimethyl formaldehyde
HMPT	hexamethylphosphoramide
AN	acetonitrile
DMAc	N,N-dimethylacetamide
NMP	N-methyl-2-pyrrolidone
k_{obs}	observed pseudo-first-order rate constant
k_{sol}	solvolysis rate constant (s^{-1})
k_2	second order rate constant ($M^{-1}s^{-1}$)
$t_{1/2}$	half-life of reaction(s^{-1} or hr^{-1})
GC	gas chromatography
HPLC	high performance liquid chromatography
DSC	differential scanning calorimetry
DN	donor number, qualitative measure of Lewis basicity (kcal mol^{-1})
I	ionic strength (M)
K_i	equilibrium constant for ion-pair formation
K_d	equilibrium constant for ion-pair dissociation
K	equilibrium constant
DEPT	distortionless enhancement by polarisation transfer
MDN	malonodinitrile

NFBs	nitrofluorobenzenes
4-NFB	4-nitrofluorobenzene
2-NFB	2-nitrofluorobenzene
2,4-DFNB	2,4-difluoronitrobenzene
4-NAB	4-nitroazidobenzene
2-NAB	2-nitroazidobenzene
ρ	Hammett reaction constant
σ	Hammett substituent constant
β_{nuc}	Brønsted constant for nucleophilic substitution reaction
S_NAr	nucleophilic aromatic substitution with addition-elimination mechanism

Contents Page

Introduction Page

1. Solvent effects on organic reactions

Solvents are ubiquitous, and in most circumstances, are indispensable in chemistry and, in a sense, the extent of understanding of solutions reflects the development in chemistry. The history of utilising and developing solvents can be traced back to the times of when Greek Alchemists were searching for a universal solvent so-called "Alkahest".[1] Solvents are widely used in nowadays, not only in academic research, but most importantly, in industry, in fact the global solvents market is estimated to reach 19.9 million tons by 2015, according to a report by Global Industry Analysts, Inc.[2] Therefore, knowledge of solution properties and investigations of solvents effects on organic reactions benefit academic chemical research as well as industry, and the choice of the solvents has significant impact on the efficiency and even nature of organic reactions. Although there have been many achievements on understanding solvent properties and their influences on the organic reaction in recent years,[1,3] due to the complex nature of solution and solvent effects on the reactions, our understanding of solutions are still imperfect and the progress of research has been relatively slow compared with the breakthrough in other chemical research areas, such as catalysis, synthesis and materials. In addition, most modern research in this area remains academic and, therefore can only benefit industry in a limited way. In recent years, as environmental issues become more and more crucial, some conventionally used solvents in industry are listed as 'unclean', and potentially may harm the ecosystem. Thus it is imperative to discover 'greener' solvents which could replace some of the currently used ones but not at the expense of losing their beneficial solvent effects.[4]

1.1 The classification of solvents

The nature of solvents can be quite different. Solvents can be classified in terms of chemical constitution, physical properties, and acid-base behaviours.[1] Despite the many criteria for the classification of solvents, the solvents are often broadly divided into two different categories, nonpolar and polar. The dielectric constants (ε_r) of solvents can provide a rough indication of a solvent's polarity. Generally speaking, solvents with a dielectric constant of less than 15 are considered to be nonpolar. Theoretically, the dielectric constant measures the solvent's ability to decrease the field strength of the electric field surrounding a charged species immersed in it. This reduction is then compared to the field strength of the charged species in vacuum.[5]

Although the dielectric constant gives a general indicator to group the solvents, considering the enormous number of solvents, such a single parameter based classification is far from satisfactory. For example, methanol ($\varepsilon_r = 33$) has roughly the same dielectric constant as DMF ($\varepsilon_r = 36.7$) at 25 ^oC, but their other solvent properties including the solubility of solutes are quite different, these differences become more pronounced when considering solvent effects on the rates of nucleophilic substitution reactions in these two solvents. Obviously, the classification of solvents needs to consider more parameters to fully explain and understand solvent effects. Current classifications of solvents combine dielectric constant, dipole moment (D), hydrogen bond donor (HBD) and acceptor (HBA) abilities of the solvent. Generally speaking, solvents fall into one of three main categories:[6]

1. **Protic**: refer to solvents that possess a proton donating function, normally the solvent molecule contains an -OH or -NH- group. Typical examples are alcohols, amines, carboxylic acids and water. These have a large dipole moment and a capacity for hydrogen bonding.
2. **Dipolar aprotic**: solvents of this category have no acidic proton, but possess a large dipole moment. Representative examples are DMSO, DMF, acetonitrile, nitromethane and ketones.
3. **Non-polar aprotic**: these solvents, which have only a small dipole moment, no acidic protons, and also have a very weak or no ability to donate or accept electrons. The intermolecular forces between solvent molecules are very weak. Hydrocarbons, halocarbons and ethers are among the typical examples.

It is worth noting that due to the physical and chemical differences between solvents, it is sometimes difficult to classify them neatly into one of the above classes and some are within borderline. Some solvents that belong to protic category can be considered as amphiprotic and act both as HBD and HBA. **Table 1** shows the physical properties and classification of some conventionally used solvents.

Table 1 Physical properties of some commonly used solvents at 25 °C[7]

solvent	boiling point (°C)	dielectric constant	dipole moment (D)	classification
n-hexane	69	1.88	0	non-polar
benzene	80	2.3	0	non-polar
1,4-dioxane	101	2.3	0.45	non-polar
toluene	81	2.4	0.36	non-polar
diethyl ether	35	4.3	1.15	non-polar
chloroform	61	4.8	1.04	non-polar
ethyl acetate	77	6.0	1.78	polar aprotic
acetic acid	118	6.2	1.74	protic, amphiprotic
THF	66	7.5	1.75	polar aprotic
DCM	40	9.1	1.60	polar aprotic
Ammonia[a]	-33	16.7	1.42	dipolar aprotic
isopropanol	82	18	1.63	protic, amphiprotic
acetone	56	21	2.88	polar aprotic
ethanol	79	30	1.69	protic, amphiprotic
methanol	65	33	1.70	protic, amphiprotic
acetonitrile	82	37.5	3.92	dipolar aprotic
DMF	153	38	3.82	dipolar aprotic
DMSO	189	46.7	3.96	dipolar aprotic
water	100	80	1.85	protic, amphiprotic

[a] Reference 8.

1.2 Solvent effects on solubility

The solubility of chemicals in solvents is one of the fundamental and direct factors that affect the efficiency of organic reactions. The state of reactants dispersed in the solvent dictates whether the reaction is under homogeneous and heterogeneous conditions, which is of great importance for the kinetics and mechanisms of the reactions involved, more often than not, this is also true for the selectivity and product yields of reactions. The classical view of solvation process includes the following steps:[9]

1. A cavity must be created within the solvent to hold the solute molecule, this requires the solvent molecules to overcome the intermolecular forces, such as hydrogen bonding and dipole-dipole interaction between solvent molecules, so it is an enthalpically unfavourable process. The creation of cavity also causes the order of the solvent to increase, thus it is also an entropically unfavourable and so the total contribution of this process to the overall free energy of solvation process is positive.
2. The solute must be separated from the bulk solute (solid or liquid) and requires the conquest of solute-solute interactions to enable solute molecules to become free from, for example, the restriction of crystal lattice energies in solid solutes. This process is enthalpically unfavourable but generally entropically favourable. The net contribution to the overall free energy of solvation is usually also positive.
3. The solute molecule inserts into the solvent cavity, and interacts and mixes with the bulk solvent molecules. This usually results in enthalpically favourable solute-solvent interactions, and due to the mixing, the mixture may become more disordered. Therefore, this step is the key step for the dissolution of a solute, it contributes negatively to the overall free energy of solvation.

The total free energy of solvation (ΔG_{sol}) is the sum of the free energy changes from each individual step. If dissolution of solute is to occur spontaneously, it must be accompanied by a reduction in free energy. Empirically, dissolution occurs when solvent-solvent interactions are similar to the interactions between solvent and solute, which is the principle behind the well-known term "*similia similibus solvuntur* (like dissolves like)." There are several key interactions that can affect the free energy of solvation, such as ion-dipole, dipole-dipole, dipole-induced dipole, hydrogen bonding, electron-pair donor/electron-pair acceptor interactions and last but not least, hydrophobic forces.

$$[B\text{-}A]_{solv} \underset{\text{Ionisation}}{\overset{K_{ion\text{-}pair}}{\rightleftharpoons}} [B^{\oplus}\ A^{\ominus}]_{solv} \underset{\text{Dissociation}}{\overset{K_{dissoc.}}{\rightleftharpoons}} [B^{\oplus}]_{solv} + [A^{\ominus}]_{solv}$$

Scheme 1

Solutions of compounds that can undergo ionisation and dissociation in solvents to produce ion-pairs and free-ions involve further free energy changes (**Scheme 1**). The associated equilibrium constants are: $K_{ion\text{-}pair} = [B^{\ominus}A^{\oplus}] / [B\text{-}A]$; $K_{dissoc.} = [B^{\ominus}] \bullet [A^{\oplus}] / [B^{\ominus}A^{\oplus}]$.

A clear distinction must be made for the ionisation and dissociation steps, the former produces solvent caged ion pairs by heterolysis of a covalent bond, or reduces the electrostatic forces of the ionic bond by forming the solvent intervened contact ion-pairs (but still in a single solvent cage), while the dissociation produces free-ions which are solvated and separated completely by solvent molecules. The solvent can influence these two steps very differently, according to the theoretical model (**Equation 1**), the potential energy of an ion-ion interaction of the solvent separated ion pair is influenced by dielectric constant (ε_r), charge on the ion ($Z \bullet e$) and the distance between two charges (r).

$$U_{\text{ion-ion}} = -\frac{1}{4\pi\varepsilon_0} \bullet \frac{z^{\oplus} \bullet z^{\ominus} \bullet e^2}{\varepsilon_r \bullet r}$$

Equation 1

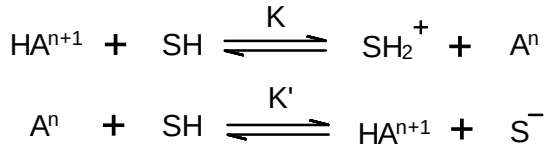
Therefore, those solvents which have a sufficiently high dielectric constant are more likely to cause the ion-pairs to become fully dissociated and solvated ions.

1.3 Solvent effects on chemical equilibria

Since the dissolution of chemicals in solvent to make a homogeneous solution involves the interactions between solute and solvent molecules, and these interactions are key to the solvation energy, it is not difficult to imagine that different solvents may exert a specific solvation preference towards different solutes, which generates a differential stabilisation of the reactant or product which is the origin of solvents effects on the chemical equilibrium. In general, the equilibrium will be shifted by a change in solvent so as to favour the side most stabilised by solvation.

1.3.1 Acid/Base equilibria

Of all the equilibria that can be affected by solvent effects, acid/base equilibria are probably the most important and have been widely investigated.[10] The ionisation equilibrium of an acid or a base (**Scheme 2**), is often strongly influenced by a solvent change. Obviously, the basicity or acidity of the solvent plays an important role in the ionisation of acids or protonation of bases, respectively. For example, the ionisation of acids is essentially a proton transfer reaction from the acid to the solvent. However, the dielectric constant and the ability of the solvent to preferentially solvate the various species are also of crucial importance. The dielectric constant of a solvent can, in some cases, significantly affect the acidity or basicity of



Scheme 2

compounds. For example, acetic acid has a pK_a of 4.76 in water (ε_r = 78.4, 25°C) at 25°C, while that in methanol[11] (ε_r = 32.7, 25°C)[12] is 9.63. Although water is only 10-20 times more basic than methanol, there is a large decrease in the acidity constant. These observations are consistent with the prediction from the theoretical model that the pK_a of acid is inversely proportional to the dielectric constant of the solvent. The effect of the solvent dielectric constant on the ionisation constants depends very much on the charges of the species involved. If the acid has a charge of +1, for example, NH_4^+, the dissociation constant of the acid has very limited sensitivity towards the change of solvent dielectric constant, because there is a positive charge on each side of the equilibrium. On the other hand, the dissociation constants of those acids which are neutral or have negative charge are greatly affected by the solvent dielectric constant, because of the change in charge upon ionisation. For neutral and charged acids, the general trend is for the acidity to increase with increasing dielectric constant of the solvent.

The rules above are sometimes not in very good agreement with experimental observations, for example, the acidity of picric acid (2,4,6-trinitrophenol) at 25°C is only 3000 times greater in water (pK_a = 0.43) than in methanol (pK_a = 3.90),[13] less than the difference observed for

acetic acid, moreover, it is only about 5 times less acidic than in DMSO (pK_a = -0.30), although the dielectric constant of DMSO is about half of that for water. The reason for the acidity of picric acid being less sensitive to the change of solvent is presumably due to the charge on the oxygen anion being highly delocalised over the large benzene ring and nitro groups, unlike the case for the carboxylate anion, where the charge is only delocalised over two oxygen atoms. The example above show that in addition to the basicity/acidity of the solvent and its dielectric constant, there are other interaction forces, such as ion-dipole, dipole-dipole, hydrogen bonding, etc., which may result in a specific solvent effect on the acid/base equilibria.

The ionising ability of a solvent increases with solvent ionic strength (*I*), especially for solutes which are susceptible to a strong electric field effect, in other words, have a greater polarisability. Adding salt can affect ionisation and dissociation constants differently, but in

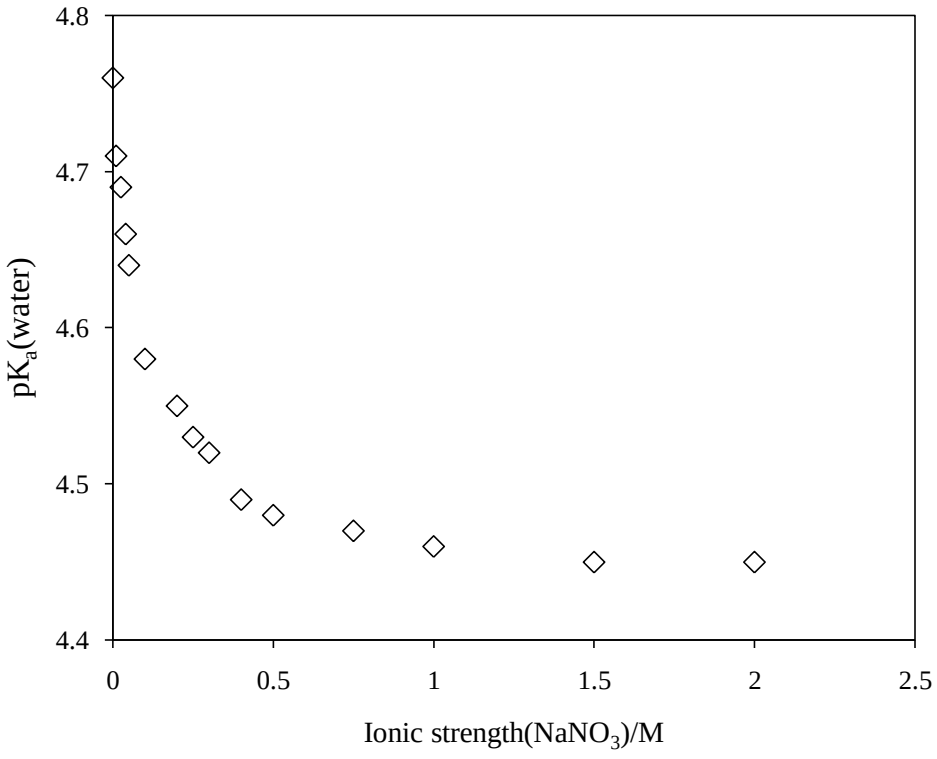
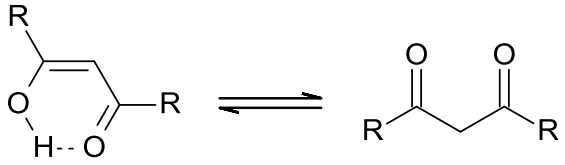


Figure 1 Aqueous pK_a of acetic acid decreases with the increase of ionic strength ($NaNO_3$) at 25 ^oC

general, without the presence of common ion effect and at low salt concentration, the ionisation and dissociation constant increases with increasing ionic strength. For example, the pK_a of acetic acid decreases from 4.76 in pure water to 4.45 when ionic strength (*I*) increases to 1.5M ($NaNO_3$) (**Figure 1**).

1.3.2 Tautomeric equilibria

The preferential solvation of different species in tautomeric equilibria, such as keto/enol, imine/enamine, azo/hydrazone, ring/chain equilibria, etc. can also give rise to solvent effects. Solvent effects on these equilibria are often key to the selectivity of organic reactions when ambident nucleophilic species are involved. Among all of the tautomeric equilibria, keto/enol equilibria have been most widely studied.[14] For example, in a symmetrical 1,3-diketone, there is a equilibrium between two possible tautomers (enol, and 1,3-diketo form) (**Scheme 3**):



Scheme 3

The keto/enol equilibrium constant K_{tauto} can be expressed as: K_{tauto} = [enol]/[diketo] and the values for acetylacetone and dimedone (5,5-dimethylcyclohexane-1,3-dione) in different solvent are shown in **Table 2**.

In solution, the 1,3-diketo form is the dominant species for the open chained acetylacetone, solvent effects on the equilibrium constant are relatively small in typical dipolar aprotic and dipolar protic solvents. The enol form only becomes significant in some nonpolar aprotic solvents, but there is still more than 70% of the 1,3-diketo form (in THF). Compared with the 1,3-diketo form, the enol is overall less polar due to an intramolecular hydrogen bond which also reduces its susceptibility to stabilisation by H-bonding from the solvent, whereas the 1,3-diketo form could be stabilised in this way. Thus, a change of solvent from a dipolar protic or dipolar aprotic to a nonpolar solvent favours the formation of intramolecular hydrogen bonding in the enol at the expense of the 1,3-diketo form. In contrast to the open chain

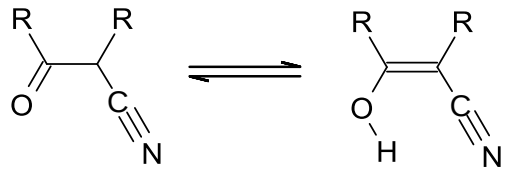
Table 2 Equilibrium constants of enol tautomers of acetylacetone and dimedone in different solvents at 20 °C[1]

Solvent (deuterated)	K_{tauto} (acetylacetone)	K_{tauto} (dimedone)
gas phase[a]	0.74	___
tetrahydrofuran	0.40	___
toluene	0.39	0.08
tetrachloromethane	0.29	___
1,4-dioxane	0.13	2.8
acetone	0.13	4.2
chloroform	0.09	0.05
methanol	0.07	148
water	0.07	19
dimethyl sulfoxide	0.05	94

[a]40 °C value.

acetylacetone, the cyclic dimedone has a significant amount of enol form but the variation with solvent is not as clear as with the open chained compound. The enol form of dimedone is favoured much more in dipolar solvents than in nonpolar solvents, presumably because the 1,3-diketo form is locked in the *cis*- arrangement with consequentially a high dipole moment and the enol form is unable to easily form an intramolecular H-bond and so is much more susceptible to H-bonding stabilisation from the solvent.[15]

An interesting example shows how intramolecular hydrogen bonding affects the enol/keto equilibrium in various solvents with different polarity. For β-ketonitriles, due to the linear structure of cyano group, the six-membered cyclic intramolecular hydrogen bond is unable to

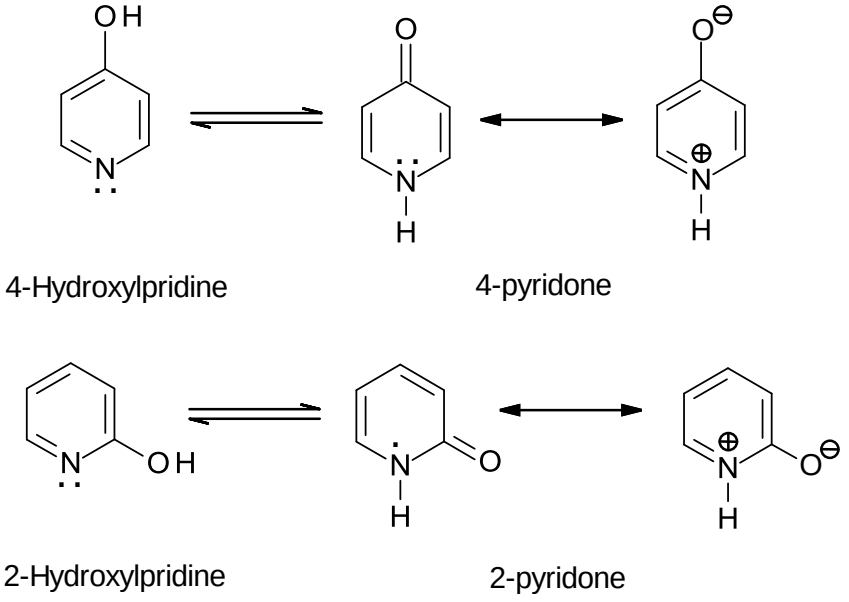


Scheme 4

form (**Scheme 4**). Without this stabilisation, therefore the intermolecular hydrogen bonding between enolic OH and solvent molecules are more likely to form in protic polar solvents than

nonpolar ones. In addition, the conjugation between the double bond and the cyano group further stabilises the enol form which also leads to some charge separation. Thus, the enol content increases as the solvent changes from nonpolar to polar.[16]

Similar solvent effects are also in lactim/lactam equilibria. One of the most classic examples is solvent effects on hydroxypyridine/pyridone equilibria (**Scheme 5**) in which hydroxypyridines dominate in the gas phase. However, the reverse situation is found in solutions, and increasing the solvent polarity significantly shifts the equilibrium towards the pyridone form. The difference in equilibrium constant in water and the gas phase is greater than 10^4 for 4-hydroxypyridine at 25 ^{o}C.[17] Due to resonance, both 2- and 4- pyridone is a charge separated species and so the keto form is more polar than the corresponding hydroxypyridine. Polar solvents significantly stabilise the charge distribution of the pyridone form.



Scheme 5

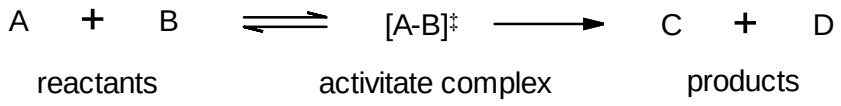
Besides the examples described above, solvent effects can also be observed in Brønsted acid/base, Lewis acid/base, conformational, and E/Z isomerisation equilibria, etc., all of which reveal the influences of solvation on relative molecular stabilities.

1.4 Solvent effects on the rates of organic reactions

The rate and order of chemical reactions can be considerably changed by a change of solvent, and in some extreme cases, rate accelerations as high as up to 10^9 can be achieved by a solvent change.[18] Studies of solvent effects on the rate of chemical reactions have a long and enlightening history, for example, as early as 1890, Menschutkin demonstrated that the rate of quaternisation of triethylamine by ethyl iodide was found to be very dependent on the reaction medium. Compared with the rate in n-hexane, the rate of the Menschutkin reaction is 4 times faster in ether, 280 times faster in methanol, and about 750 times faster in benzyl alcohol.[19] The choice of solvents is especially important for the chemical industry, where an appropriate choice of reaction medium can not only significantly reduce the cost of a product, but also can be eco-friendly to the environment. Therefore the establishment of theories and rules for solvent effects on reactions can facilitate the design and selection of a solvent for organic synthesis.

In principle, the way in which solvents can affect reaction rates can be rationalised in terms of transition-state theory[3,20] which describes the differential solvation of reactants and activated complexes leading to a change in the free energy of activation. Transition state theory is essential for a qualitative understanding of solvent effects on reactions, although it has limitation in some extreme cases, for example, when the rate of solvent reorganisation becomes rate-limiting. The latter has only been given attention recently due to rate measurement techniques becoming more advanced. It concerned with the non-equilibrium solvation of the activated complex that may occur in some fast or ultra-fast reactions, which is generally ignored in conventional transition state theory.[21] Under such circumstances, the rate of reaction will depend on the solvent dynamics or friction and so with the density, viscosity, internal pressure, etc.

1.4.1 Transition state theory[3,20]



Scheme 6

Consider a reaction between reactants A and B passing through an activated complex $[A\text{-}B]^{‡}$ to give products C and D (**Scheme 6**), in which the reactants are quasi-equilibrated with activated complex$[A\text{-}B]^{‡}$. The equilibrium constant can be given as follow:

$K^{‡}$ = $[A\text{-}B]^{‡}$ / [A][B], in which [A], [B] and $[A\text{-}B]^{‡}$ corresponding to the concentration of reactants and activated complex respectively. Transition state theory presumes that the formation of products, C and D, does not affect the equilibrium between reactants and activated complex and the free energy of the activated complex occupies the highest point during the reaction process and is defined as transition state, the activated complex is the corresponding chemical entity, and the structure of the activated complex is defined as transition state structure (**Figure 2**).

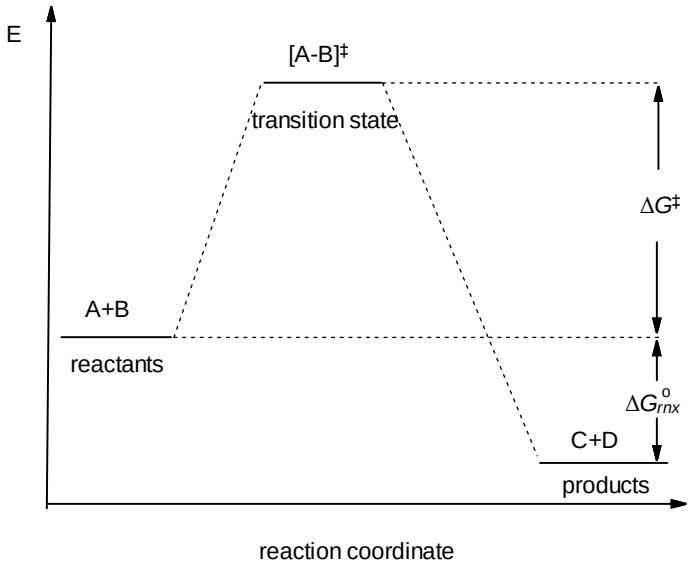


Figure 2

Figure 2 Single-dimensional reaction energy profile of the reaction (**Scheme 6**). $\Delta G^{‡}$: Gibbs energy of activation; $\Delta G_{rnx}{}^{o}$: Gibbs energy of the reaction.

The decomposition of activated complex to give the products proceeds with a fixed rate constant kT/h and so effectively rates of reactions vary as the concentration of the activated complex vary. Assuming that the reactants and activated complex are in thermal equilibrium with the solvent, a change in solvent will lead to a modification of the height of the reaction energy barrier by differential solvation of the activated complex and reactants. A change of

solvent that reduces the energy barrier for reaction can be realised by either decreasing the energy of the activated complex though solvation stabilisation or by increasing the energy of reactant state though solvation destabilisation. It is the net differential change in the free energies of solvation that determines whether a change in solvent results in an increase or decrease in the rate of reaction. The solvation effects on the activated complex and reactants could be in the same or opposite direction (**Figure 3**).

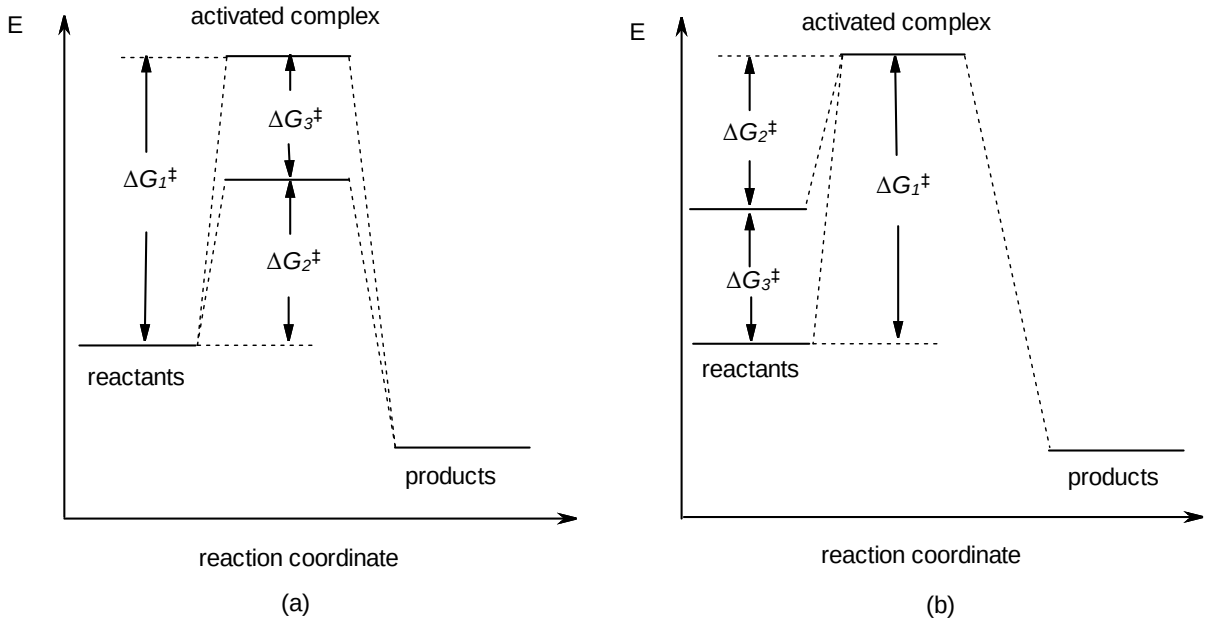


Figure 3

Figure 3 The reduction of the reaction energy barrier by differential solvation of (a) the activated complex, (b) the reactants. $\Delta G_1^{\ddagger}$: Gibbs free energy of activation of the reaction in solvent 1; $\Delta G_2^{\ddagger}$: Gibbs free energy of activation of the reaction in solvent 2; $\Delta G_3^{\ddagger}$: standard Gibbs transfer free energy for the reactants ($\Delta G^{R}_{1\rightarrow 2}$) or activated complex ($\Delta G^{\ddagger}_{1\rightarrow 2}$).

From the measurement of rate constants in different solvents and different temperatures, the activation parameters can be acquired and compared, thus enabling analysis of solvent effects on reaction rates.

1.4.2 Hughes-Ingold solvation 'rules'

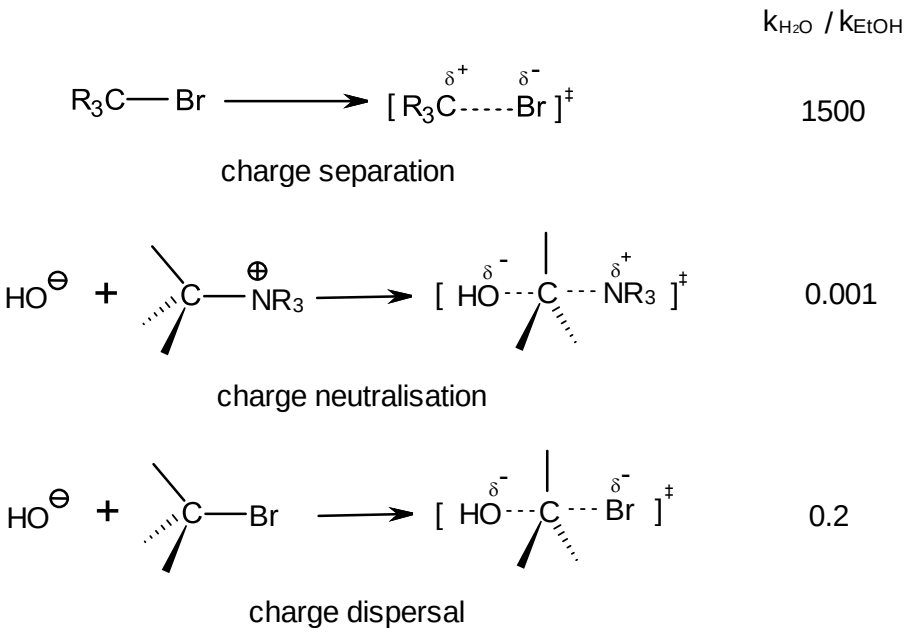
The structure of the activated complex in the transition state may be modified by changes in solvent. According to the Hammond postulate,[22] reactions can be described as proceeding through a reactant-like or a product-like transition state structure. These structures can vary in terms of bond formation/breaking and charge distribution. Like 'normal' molecules, the activated complexes are subjected to the interactions with solvent molecules and these may be stabilising or destabilising, which, in some cases, may even lead to a change in reaction mechanism. Generally, reactions proceed through activated complexes which can be grouped roughly into polar, isopolar and free-radical types. Polar types of activated complexes have a considerable charge separation which differs from the reactant state and normally exhibits the largest solvent effects. Hughes and Ingold[23] investigated solvent effects on a range of aliphatic nucleophilic substitution reactions, but only the pure electrostatic interactions between ions or dipolar molecules and solvent molecules in reactant and transition states were considered in their qualitative solvation model. Based on some simple assumptions and observations they concluded that the creation or destruction or dispersal of charge is expected to be subjected to an increase and decrease of solvation, respectively. The overall effect of the solvent on the rate of reactions of different charge types can be summarised as follows:

1. An increase in charge density ongoing from the reactants to activated complex will lead to an increase in rate in a more polar solvent.
2. A decrease in charge density ongoing from the reactants to activated complex will cause a decrease in rate in a more polar solvent.
3. A dispersion of charge ongoing from the reactants to activated complex results in a small or negligible decrease in rate with a change of solvent polarity.

Some examples[6] can be found that agree with these Hughes-Ingold rules (**Scheme 7**) and a more generalised summary of the solvent effects on aliphatic substitution reaction is given in **Table 3**.[24]

A further extension of the Hughes-Ingold rules was made by Westaway[25] regarding the solvent effects on the structure of activated complexes in S_N2 reactions. This solvation rule argued that the solvent effects on the transition state structure is primarily determined by the

interactions of solvent molecules with the incoming nucleophile and leaving group, and that the activated complex, penta-valent central carbon, is unlikely to have a strong interaction



Scheme 7

Table 3 Predicted solvent effects on rates of nucleophilic substitution reactions

Reaction type	Initial reactants	Activated complex	Charge alteration during activation	Effect of increased solvent polarity on rate
S_N1	R-X	$R^{\delta+}\cdots X^{\delta-}$	Separation of unlike charges	Large increase
S_N1	$R\text{-}X^+$	$R^{\delta+}\cdots X^{\delta+}$	Dispersal of charge	Small increase
S_N2	Y + R-X	$Y^{\delta+}\cdots R\cdots X^{\delta-}$	Separation of unlike charges	Large increase
S_N2	Y^- + R-X	$Y^{\delta-}\cdots R\cdots X^{\delta-}$	Dispersal of charge	Small increase
S_N2	Y + $R\text{-}X^+$	$Y^{\delta+}\cdots R\cdots X^{\delta+}$	Dispersal of charge	Small increase
S_N2	Y^- + $R\text{-}X^+$	$Y^{\delta-}\cdots R\cdots X^{\delta+}$	Destruction of charge	Large decrease

with solvent. The transition state of a reaction in which the nucleophile and leaving group have the same charge will not significantly be influenced by a change of solvent (Type I S_N2 reaction). On the other hand, a change in solvent will lead to a change of transition state energy for a reaction in which the nucleophile and leaving group bear different charges (Type

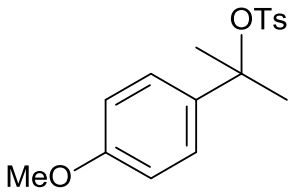
II S_N2 reaction). In essence, the Westaway solvation rule is a refinement of Hughes-Ingold rules, both of them established a good guide for predicting solvent effects on chemical reactions in a qualitative way.

Despite numerous examples that have been found to be consistent with Hughes-Ingold rules, it has its limitations. The model of Hughes-Ingold rules was built upon the assumption and simplification that only pure static interactions are considered, and they are not capable of evaluating solvent effects on reactions that have an isopolar activated complex. Moreover, the rules are based on a continuous solvation model, assuming the solvent molecules equilibrate thermodynamically with reactants and activated complexes, but this is not appropriate for some very fast reactions in which the rate limiting step is the solvent reorganisation. A very interesting and counterintuitive example challenges the validity of the rules. A theoretical study shows that the Gibbs free energy of activation for S_N1 ionisation of *t*-butyl halides in solution decreasing with increasing solvent polarity, which is in line with the rules. However, the study also shows a *decrease* in the stabilisation of the activated complexes with increasing solvent polarity. This indicates that the activated complex becomes less charged with increasing solvent polarity, which is not easily rationalised with the Hughes-Ingold model.[26] However, if the charged transition state structure is stabilised by a more polar solvent, then, according to the Hammond Postulate this should lead to a more reactant-like transition state *i.e*. less bond fission and less charge development in the transition state. In addition, Hughes-Ingold rules do not directly consider the contribution from the entropy of activation to the overall Gibbs free energy of activation, and regard the enthalpy of activation as dominant. However, solvent restriction will result from the interaction of solvent molecules with a charged activated complex, giving rise to a large entropy loss. For example, the activation parameters for S_N1 reaction in other solvents and water indicate that changes in the highly ordered water structure make the activation process entropy controlled.

1.4.3 Specific solvation effects on reaction rates

Besides pure electronic interactions, such as inductive and dispersion forces which exist between solvent molecules and reactants or activated complexes, there are some other specific intermolecular forces which are responsible for the solvent effects on the kinetics and mechanisms of reactions in solution. Hydrogen bonding forces are among one of the most

important specific interactions. In nucleophilic substitution reactions in which the attacking nucleophiles or leaving groups are ionic, hydrogen bonding forces are especially important for the understanding of solvent effects on the kinetics and mechanisms of these reactions. In this sense, protic solvents have a great advantage by forming hydrogen bonds with reactants and leaving group. This is especially the case when the reactants and leaving groups are negatively charged anions. Specific solvation of leaving anions by hydrogen bonding facilitates the decomposition of activated complexes to form products, thus increasing the rate of reaction. On the other hand, specific solvation of attacking anions by hydrogen bonding leads to a decrease in the relative nucleophilicity of nucleophiles. For example, the rate of neighbouring group assisted solvolysis of 4-methoxyneophyl tosylate (**I**) is tremendously varied by about



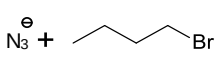
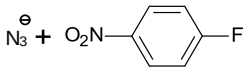
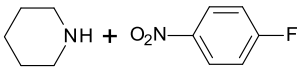
I

10^6-fold on changing solvent from diethyl ether to formic acid due to the difficulty of solvating the leaving tosylate anion by ether.[27] Counter-ions can also affect the nucleophilicity of anionic nucleophiles, especially in non-polar solvents.

Dipolar aprotic solvents, such as DMSO, acetonitrile and DMF, normally have large dipole moments and relatively high dielectric constants (**Table 1**). These solvents have no, or very limited, ability to act as hydrogen bond donors and are often called dipolar non-HBD solvents. Anions are poorly solvated in these solvents and hence are better nucleophiles than in, say, water leading to large rate enhancements in these solvents. As dipolar aprotic solvents are not good hydrogen bond donors, anionic nucleophiles are more 'free' than in protic solvents in which these nucleophiles are solvated by the hydrogen bonding and must be at least partially desolvated for reaction to occur. For example, the rate of S_NAr reaction between sodium azide and 4-nitrofluorobenzne in a typical dipolar aprotic solvent is about 10^4-10^7 times faster than in protic solvents and large rate enhancements are also seen for S_N2 reactions involving anions.[28] In contrast, the rate of S_NAr reaction between neutral secondary amines and 4-

fluorobenzene is not affected very much when the solvent is changed from protic to dipolar aprotic (**Table 4**).

Table 4 Relative rates of representative S_NAr, S_N2 reactions in protic and dipolar aprotic solvents at 25 ^oC[29]

solvents	**log ($k_{2,solvent}$ / $k_{2,MeOH}$)**		
			
MeOH	0	0	0
H_2O	0.8	N. A.	N. A.
$HCONH_2$	1.1	0.8	N. A.
acetonitrile	3.7	3.9	0.9
DMSO	3.1	3.9	2.3
DMF	3.4	4.5	1.8
acetone	3.6	4.9	0.4
HMPT	5.3	7.3	N. A.

It is worth noting that dipolar aprotic solvents also could influence the stability of activated complexes. Theoretical studies show that the intermediate Meisenheimer complex for the reaction of azide anion with 4-NFB is more stable relative to reactants in dipolar aprotic than protic solvents (**Figure 4**).[30]

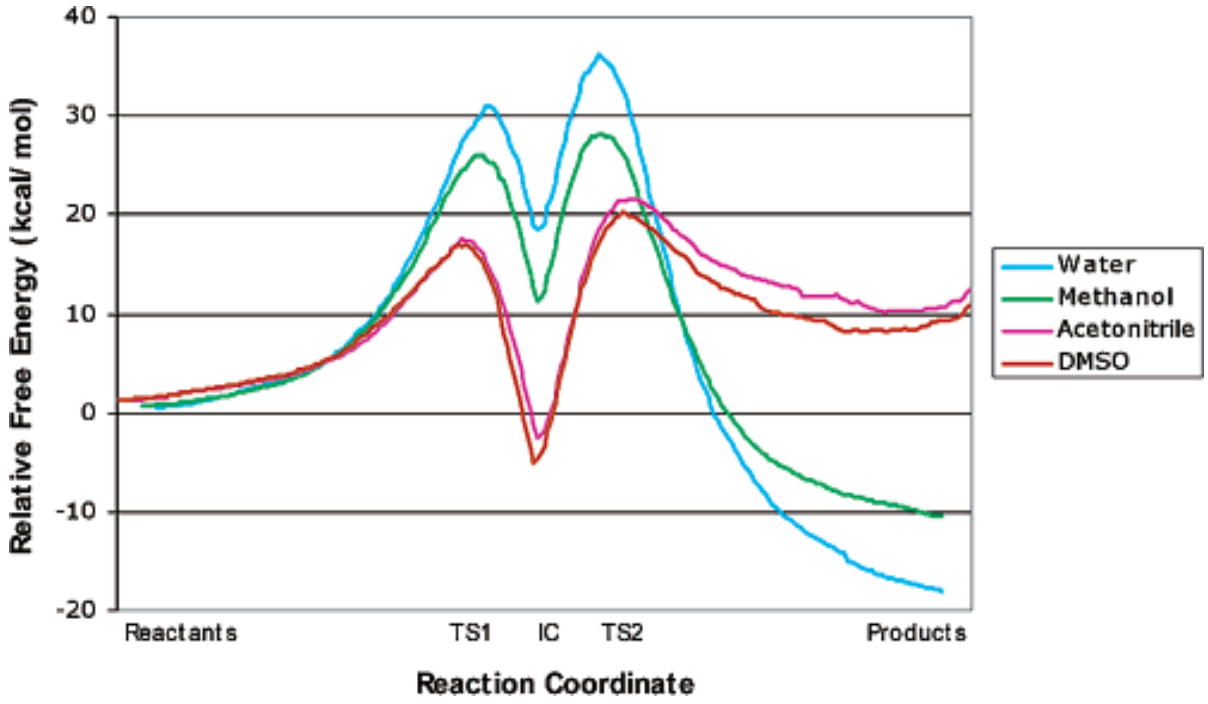


Figure 4 The QM/MM calculation of potential energy for the reaction of azide anion with 4-NFB in different solvents. TS1: transition state 1; TS2: transition state 2; IC: intermediate complex.

1.5 Solvent effects on UV spectra

In solution, the UV spectra of organic compounds may differ from one solvent to another in their wavelength of maximum absorption and extinction coefficient. These changes can be interpreted in terms of the changes of interaction between solute and solvent, which can alter the energy gap(s) between ground and excited state of solute molecule. In many cases, ionisation can play an important role on the UV absorption spectra of organic compounds and these spectral changes can allow the determination of dissociation constants.[31] Normally, solvent effects on the UV absorption spectrum are pronounced when the energy gap between the ground and excited state of the molecule is relatively large, whereas it is relatively small in benzene, polyenes, etc.

1.6 Empirical parameters of solvent polarity

It is not easy to measure solvent polarity but simple physical properties, such as dielectric constant or refraction index, are often used to correlate rate constants of reactions. For example, it was found that logarithms of relative rate for Menschutkin reaction shows good linear relationship with the Kirkwood function[32] $[(\varepsilon_r-1)/(2\varepsilon_r+1)]$ of the solvent (**Figure 5**).[33] Unfortunately, in most cases it has been found that no correlation between dielectric constant and logarithms of rate constants of solvent sensitive reactions. Obviously, the establishment of solvent scale need to combine all possible detailed intermolecular interaction forces between solvent and solute molecules, such as dipole-dipole, ion-dipole interactions, electrostatic forces, hydrogen bonding and EPD/EPA interactions, *etc*. No single macroscopic physical parameters could reflect the intermolecular forces on microscopic level.

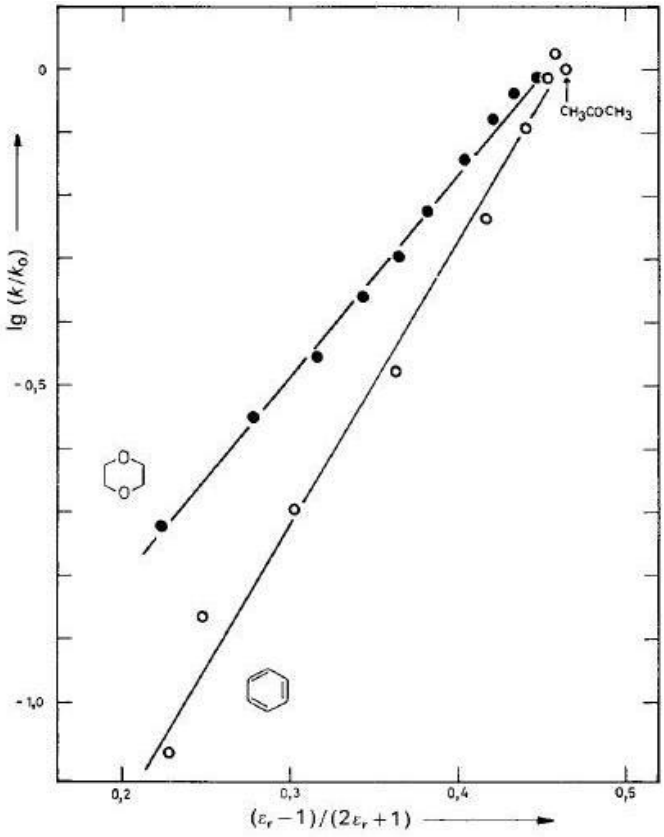


Figure 5 The correlation between $\lg(k/k_o)$ and the Kirkwood function $[(\varepsilon_r-1)/(2\varepsilon_r+1)]$ for the Menschutkin reaction between triethylamine and iodoethane at 40 ^oC in binary acetone/benzene and acetone/1,4-dioxane mixtures.

1.6.1 Grunwald-Winstein Equation[34]

Despite the difficulty and complexity to establish a satisfactory solvent polarity scale, Grunwald and Winstein made one of most ambitious attempts to correlate rate constant with empirical solvent polarity parameters. Based on the solvolysis rate of *t*-butyl chloride, they

$$Y = \log k^{t\text{-BuCl}} - \log k_0^{t\text{-BuCl}}$$

$$\log (k/k_0) = m \bullet Y + c$$

Equation 2

(**Equation 2**, Grunwald-Winstein equation, where $k_0^{t\text{-BuCl}}$: the solvolysis rate of *t*-butyl chloride in 80% (v/v) aqueous ethanol at 25 ^{o}C ($Y = 0$); $k^{t\text{-BuCl}}$: the solvolysis rate of *t*-butyl chloride in the solvent of interest at 25 ^{o}C).

found that polar solvents significantly accelerate the reaction and arbitrarily defined a *Y* parameter that describes the ionising power of solvent, and a substrate parameter *m* that senses the rate change to the ionisation power of solvent (**Equation 2**).

The correlation of *Y* and *m* is a type of linear free energy relationship (LFER), and is reasonably successful in correlating the rates of the S_N1 solvolytic reactions of various tertiary alkyl halides, secondary alkyl sulfonates. However, an unsatisfactory correlation is found for some solvolysis reactions with borderline mechanism between S_N1 and S_N2, such as the solvolysis of secondary haloalkanes. The main concern with the Grunwald-Winstein equation is whether the solvent intervenes in S_N1 solvolysis processes. Schleyer later showed that the solvolysis of *t*-butyl and 1- or 2-adamantyl chlorides and adamantyl tosylates occur without nucleophilic assistance from the solvent and can be best regarded as 'true' S_N1 process, although protic solvents can facilitate the expulsion of the leaving anion by strong

$$\log (k/k_0)_{RX} = m \bullet Y + l \bullet N + c$$

Equation 3

(**Equation 3**, modified Grunwald-Winstein equation to account for nucleophilic solvent assistance, where *l*: sensitivity of substrate to the solvent nucleophilic assistance; N: solvent nucleophilicity, in contrast to Y, ionising power of solvent).

hydrogen bonding.[35] However, studies also found that the solvolysis rates for *t*-butyl chloride and adamantyl chloride are very different in some nucleophilic solvents, which suggests partial nucleophilic assistance from some solvents.[36] In order to account for possible nucleophilic solvent assistance, the Grunwald-Winstein equation was later modified to a multiple parameter one (**Equation 3**).[37]

The Grunwald-Winstein solvent scale is applied mainly to S_N1 reactions, and the S_N2 Menschutkin reaction of tri-*n*-propylamine and iodomethane has been used to measure solvent polarity.[38]

1.6.2 Other spectroscopically obtained empirical parameters

Spectroscopic methods such as UV-Vis, IR, and NMR have been used to establish a solvent polarity scale. Several solvent scales were successfully established by using solvatochromic dyes as indicator.[39] Kosower set up a Z parameter as the molar transition energy based on 1-ethyl-4-methoxycarbonyl)pyridium iodide as model, a higher Z value corresponding to a more polar solvent. So far, about 60 commonly used solvents are included in Kosower Z scale.[40] Dimroth and Reichardt proposed an E_T (30) parameter based on the UV absorption of N-phenolate betaine dyes.[41] Due to the extraordinarily large range of solvatochromic absorption of betaine dyes, a much wider solvent polarity spectrum can be established, and so far, 360 more E_T (30) values have been measured. Based on solvent hydrogen bond acceptor basicity and hydrogen bond donor acidity, a method called solvatochromic comparison was introduced by Taft and Kamlet, using HMPT and methanol as a reference solvent for constructing hydrogen bond acceptor (β) and donor (α) ability, respectively, a dual parameters model for solvent relative HBD/HBA tendency was established.[42] Also a parameter π^* was introduced for the description of solvent dipolarity and polarisability, which was based on the solvent effects on $\pi \rightarrow \pi^*$ electron transitions of several nitroarmatic compounds. Those parameters reflect the solvent properties in different ways, and a combination of them sometimes can give good correlations in multiple parameter models.[43] However, it must be pointed out that there is no single method so far that can give an absolute accurate solvent scale, unsatisfactory correlations or limitations for each method are unavoidable which reflects the intriguing nature of solvent effects on chemical reactions.

2. Physical and chemical properties of liquid ammonia[44]

Ammonia has three covalent N-H bonds and a lone pair of electrons, and adopts a trigonal pyramidal shape as the valence shell electron pair repulsion theory predicted (**Figure 6**). In the

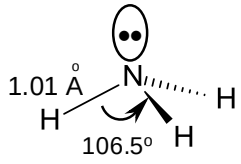


Figure 6 Structure of ammonia molecule

gas phase, the bond angle of ammonia (∠HNH) is 106.5°, smaller than that of methane (109.5°) and greater than that of water (105°), and the N-H bond length of ammonia is 1.01 Å, which is also in between of that for methane (1.10 Å) and water (0.96 Å). The ammonia molecule has the form of a low pyramid of height 0.360 Å,[45] and this configuration gives rise to the possibility of the nitrogen atom passing from its equilibrium position on one side of the plane of the hydrogen atoms through the plane to an equally stable position on the other side. The energy barrier for this nitrogen inversion is 24.7 kJ mol^{-1} at room temperature.[46] Because ammonia has three possible hydrogen bond donors but only one lone pair for H-bond acceptance, its arrangement in the liquid and solid phases is interesting. In the solid phase, X-ray diffraction indicates that each ammonia molecule is surrounded by six nearest neighbours though asymmetrical and nonlinear hydrogen bonds and each electron pair on a nitrogen atom can accommodate three hydrogen bonds.[47] While, in the liquid phase, an ammonia molecule is surrounded by an average of 11 molecules close to its boiling point.[48] However, interestingly, infra red spectroscopy of liquid ammonia at room temperature shows that less than 3 hydrogen bonds are formed,[49] in stark contrast with the X-ray results, which suggests that temperature and pressure effects are very important factor for the properties of liquid ammonia.

Table 5 lists some physical properties of liquid ammonia, which has a vapour pressure of 10 bar at room temperature. Its enthalpy of vapourisation (ΔH_{vap}) of 23.25 kJ mol^{-1} is intermediate between those of methane (8.19 kJ mol^{-1}) and water (40.65 kJ mol^{-1}), suggesting a moderate degree of association.

Table 5 Some physical properties of liquid ammonia[50]

critical temperature	132.4 ^{o}C
critical pressure	112.3 atm
vapour pressure of liquid	$\log_{10} P_{mm} = 9.95028 - (1473.17)/(T - 3.8603)\ 10^{-3}\ T$
enthalpy of formation	5.64 kJ mol^{-1}
enthalpy of vapourisation	23.25 kJ mol^{-1}
refractive index	1.325
electrical conductivity	1 × 10211 ohm^{-1} cm^{-1}
dielectric constant	22.70 (-50 ^{o}C), 18.94 (5 ^{o}C), 17.82 (15 ^{o}C), 16.70 (25 ^{o}C)

The lone pair of ammonia is of great importance in determining the properties of ammonia. It makes liquid ammonia one of the most basic molecular liquids and it enables ammonia to be a good electron donor and hydrogen bond acceptor. As ammonia has only one lone pair and the electronegativity of nitrogen (3.04) is smaller than that of oxygen (3.44), the properties of ammonia are also rather different from those of water. The most obvious difference between ammonia and water is boiling point. At one atmosphere, ammonia boils at -33.5 ^{o}C, compared with 100 ^{o}C for water. Despite the difference in properties between liquid ammonia and water, they are both classified as protic/amphiphilic solvent in a classical review[1] and are often listed together for comparison (**Table 6**).

At 25 ^{o}C the dielectric constant of water is about 4.7 times greater than that of liquid ammonia, which will make an obvious difference on the ionisation and dissociation of compounds in these two solvents. Specifically, the high dielectric constant of water facilitates the dissociation of ion-pairs while low dielectric constant ammonia favours the formation of ion-pairs but not their dissociation into free ions.[51] The autoprotolysis (self-ionisation) constant of ammonia is much lower than that of water, corresponding to a pK = 27.7. In addition, the internal energy of liquid ammonia is about -21 kJ mol^{-1}, which is around half the value for water.[52]As stated earlier, ammonia has only one lone pair of electrons and yet with three potential NH hydrogen bond donors, it cannot form a highly organised, web-like solvent

structure as in water. It is not surprising that liquid ammonia is highly soluble in water, to give a basic solution.

Table 6 Some physical properties of liquid ammonia and water

Physical property	**Liquid ammonia**	**Water**
Melting point (^{o}C)	-77.7	0
Boiling point (^{o}C)	-33.35	100
Dielectric constant (25 ^{o}C)	16.7	80
Dipole moment (D) (25 ^{o}C)	1.42	1.85
Density (g/ml) (25 ^{o}C)	0.606	0.997
Polarisability (Å^{3})	2.21	1.84
Autoprotolysis constant (25 ^{o}C)	2.0×10^{-28}	1.0×10^{-14}
Empirical polarity (E_{T30} /kcal mol^{-1})	51.7[a]	63.1

[a] Reference 53.

Liquid ammonia has a very strong tendency to donate lone pair electrons as indicated by its very high donor number (DN_{LNH3} = 59 kcal mol^{-1}), which is much greater than that for water (DN_{water} = 18 kcal mol^{-1}) and even HMPT (DN_{HMPT} = 38.8 kcal mol^{-1}),[54] and, as a consequence, it strongly solvates cations through a electron donation, as evidenced by ^{23}Na chemical shifts.[55] However, unlike water, it is not a good hydrogen bond donor[56] and does not significantly solvate anions, as shown by the high single ion transfer energies from water.[57] Many synthetically useful salts are highly soluble, particularly ammonium salts, e.g. NH_4N_3, 67.3g/100g at -36 ^{o}C, [58] and even a *ca*. 30 M NH_4NO_3 is possible in liquid ammonia at 25 ^{o}C.[44a] Some other salts, such as fluorides, and those with multiple negative charged anions, are difficult to dissolve in liquid ammonia at ambient temperature. For organic solutes, three factors may affect the solubility of a molecular substance in liquid ammonia: the magnitude of the dispersion forces, the polarity of the ammonia molecule, and the ability of solute to form hydrogen bonds. Generally speaking, most common organic compounds are more soluble in liquid ammonia then in water. Hydrocarbons are insoluble, but alkyl ethers, alcohols and amines are miscible with ammonia, and most importantly, the majority of aromatic compounds have a good or moderate solubility at ambient temperature. Solubility is obviously important for the potential application of liquid ammonia as an organic reaction medium.

The chemical properties of ammonia are closely associated with its physical properties. The lone pair of ammonia makes it a Lewis base and ammonia can accommodate a proton to form a tetrahedral ammonium cation. Due to electron donation from the lone pair, metal ions are coordinated by ammonia molecules. For examples, copper (II) cation forms tetraamminediaquacopper (II), $[Cu(NH_3)_4(H_2O)_2]_2^+$ complex in aqueous ammonia, silver (I) forms diamminesilver (I), $[Ag(NH_3)_2]^+$. Much attention has been given to the inorganic chemistry in liquid ammonia by Lagowski and others.[8,44c,59] One of the most extraordinary phenomenon is that alkali metals can be dissolved and ionised in liquid ammonia to form a solution of the metal cation and solvated electrons. Solutions of sodium or potassium in liquid ammonia are widely used as reducing agents in the organic synthesis (*vide infra*).[60]

3. Organic reactions and mechanisms in liquid ammonia

Since the commercial availability of liquid ammonia at the beginning of 19th century, chemical research in this unique solvent became popular. The early research work in this area was performed by Cady, Franklin and Kraus,[61] mainly covering on the physical and chemical properties of liquid ammonia, and especially through Kraus' and his many years of dedication to the chemistry of ammonia solutions, some fundamental data on liquid ammonia became available, such as the solubility of organic and inorganic chemicals, the conductivities of ammonia solutions, ionisation of metals in liquid ammonia,[62] etc., Audrieth,[63] Watt[64] and later Lagowski *et al*, investigated some fundamental organic and inorganic reactions in liquid ammonia. So far the largest body of literature related to liquid ammonia is on the reduction of organic compounds in alkali metal/ammonia solution, and the application of sodium/lithium amide in liquid ammonia as a strong base in synthesis. The last major review of the literature on organic reaction in liquid ammonia was edited by Smith in 1963.[65] Generally, the uses of liquid ammonia in organic reaction are divided into the following areas:

1. As a supporting medium that dissolves alkali metals for reduction purposes.
2. As a medium that dissolves alkali metals for the production of very strong bases.
3. As a reagent (solvolysis or amination) or medium for organic reactions.

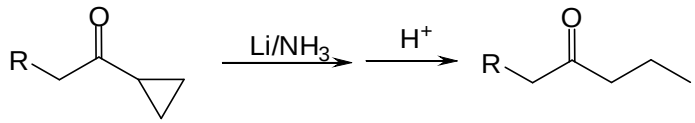
It should be pointed out that probably due to the limitation of equipment and the awkwardness of handling liquid ammonia at ambient temperature or above, most synthetic work has been done below or near the boiling point of ammonia.

3.1 As a solvent for reduction

The reduction of organic compounds with metals in liquid ammonia is a well-established synthetic technique. When an alkali metal is dissolved in liquid ammonia, a deep blue solution is formed. The colour is a characteristic of the solvated electron that is given up by metal in the medium, and these electrons can be donated to substrates to form radical anions and dianions, and the reduced product is generated after the protonation of the anion.

3.1.1 Cycloalkanes

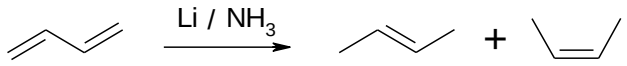
Generally speaking, alkanes are inert to the reducing conditions, but the α-keto-cyclopropanes can be reduced to the corresponding straight-chain ketone (**Scheme 8**).[66,67] The reaction probably proceeds through formation of the radical anion of the ketone followed by the interaction of radical with the ring and subsequent reduction and protonation of the carbanion.



Scheme 8

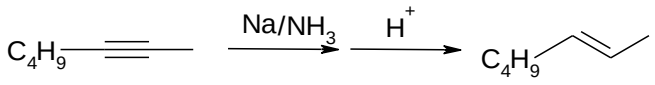
3.1.2 Conjugated alkenes and alkynes

Non-conjugated alkenes are difficult to reduce by alkali metals in liquid ammonia and, in fact, they are often the end product of the reduction of alkynes or conjugated alkenes and aromatic rings. Conjugated alkenes can be reduced easily to mono-alkenes, however, the reactive intermediate radical anion is active enough to undergo polymerisation or other radical reactions, and the stereochemistry could not be predicted due to the conformational instability of the allylic radical. For example, butadiene is reduced to a mixture of *cis*- and *trans*-2-butene with lithium in liquid ammonia, the ratio of the two isomers depends on the reaction temperature (**Scheme 9**).[68]



Scheme 9

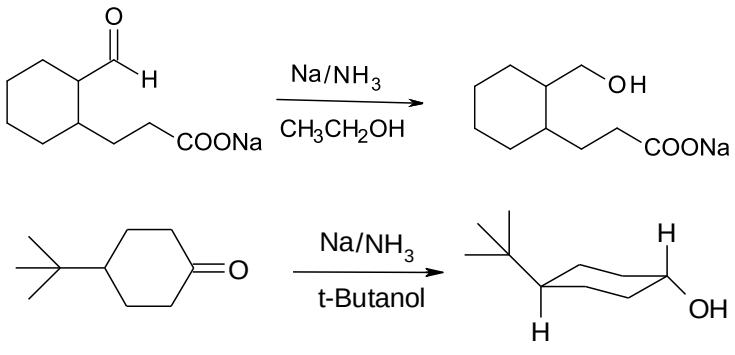
Alkynes are reduced predominantly to *trans*-alkenes, the stereochemistry of the reaction is dictated by the configuration of the intermediate radical anion or dianion, which prefers the *trans* form in order to minimise the interactions between the two newly-created negatively charged sp^2 centres. Thus, 2-heptyne is reduced via the dianion to give exclusively *trans*-2-heptene (**Scheme 10**).[69]



Scheme 10

3.1.3 Carbonyl groups

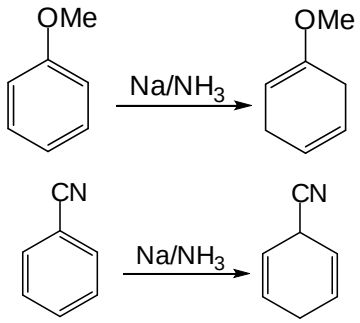
All carbonyl groups, with the exception of the salts of carboxylic acids, are reduced by alkali metals to hydroxyl groups in liquid ammonia. Due to the coupling of the reactive radical intermediate, the reduction of esters and aldehydes has very little synthetic use, however, if a proton donor, such as alcohol, is added to capture the reactive intermediate, the unwanted coupling reaction can be avoided, and the reduction can then be run successfully. The following are some typical examples (**Scheme 11**).[70,71]



Scheme 11

3.1.4 Aromatic Compounds

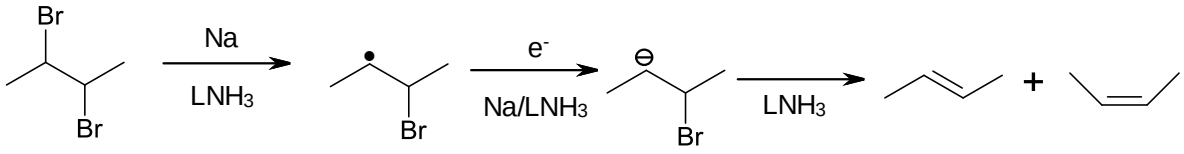
Possibly the best known of all alkali metal/ammonia reductions is the Birch reduction, the partial reduction of aromatic systems to 1, 4-dihydrocyclohexadienes.[72,73,74] The regio-selectivity of the Birch reduction depends on whether the substituent is electro-withdrawing or electro-donating. The intermediate radical anion tends to locate itself on the carbon *ortho* to an electro-withdrawing group and on the carbon *meta* to the electro-donating group in order to minimise the interactions.[75,76] This is best illustrated by the two examples below (**Scheme 12**).[77,78]



Scheme 12

3.1.5 Halogen-containing compounds

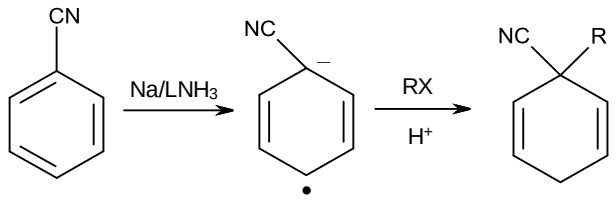
Most of the work in this area has involved the reduction of aromatic halides, and there are few examples of the reduction of aliphatic halides, although the following is an example of the reduction of 2, 3-dibromobutane in liquid ammonia (**Scheme 13**).[79]



Scheme 13

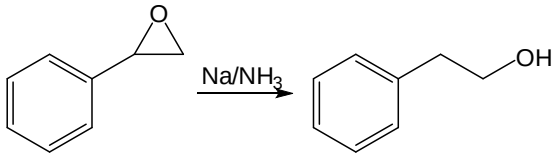
3.1.6 Nitro, nitrile groups and epoxides

Aromatic nitro groups are reduced to anilines, however, the yield is poor compared with conventional reduction methods, and is probably due to the reactive intermediate radical or radical anion involved.[80] Surprisingly, aromatic nitriles are not easily reduced to the corresponding amine, but, instead the aromatic ring is reduced. The intermediate radical anion



Scheme 14

attacks other substrates to give the nucleophilic substitution products which is synthetically useful (**Scheme 14**).[81] Alkali metal/ammonia reactions with epoxides open the ring and form alcohols, the stereochemistry of the process depends on the stability of the anion or dianion generated through the reduction. Interestingly, when styrene oxide undergoes the reduction with metal/liquid ammonia, 2-phenylethanol is the sole product (**Scheme 15**).[82]

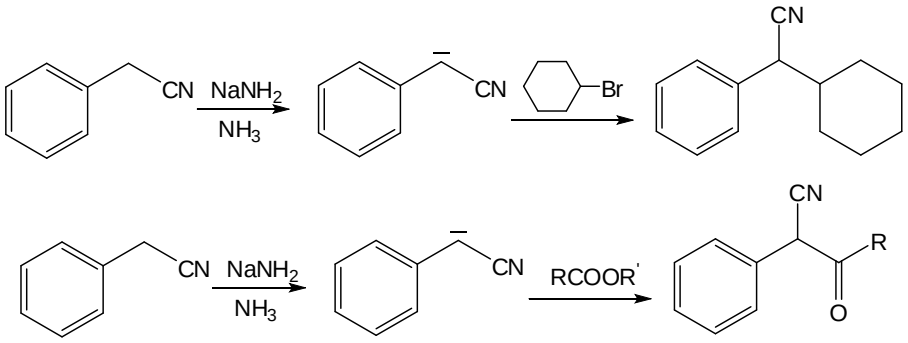


Scheme 15

3.2 Liquid ammonia as a solvent for the production and reaction of strong bases

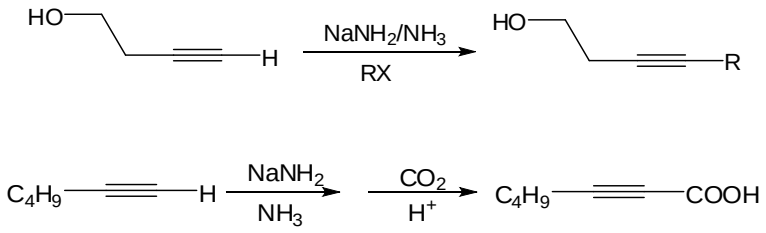
Generally speaking, alkali metal amides in liquid ammonia react as bases rather than as nucleophiles. There are many examples of carbanion formation using metal amides, the protons are abstracted in sequence of their pK_a value, and once a carbanion or dianion is formed, it can undergo inter- or intra-molecular nucleophilic substitution, or elimination reactions. For example, phenylacetonitrile in the presence of bromocyclohexane is deprotonated by sodium amide in liquid ammonia to form the carbanion, which then attacks

bromocyclohexane to give the alkylated product,[83] or the carbanion may attack a carbonyl group of ester in the same way as a Grignard reagent (**Scheme 16**).[84]



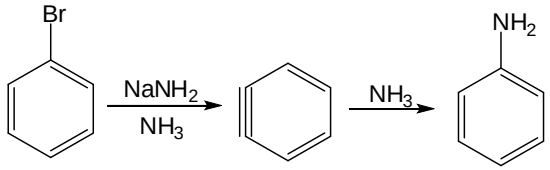
Scheme 16

Terminal alkynes also can be deprotonated by metal amides in liquid ammonia to form the corresponding anions, which can react with suitable electrophiles such as alkyl halides, ketones, or even carbon dioxide (**Scheme 17**).[85,86]



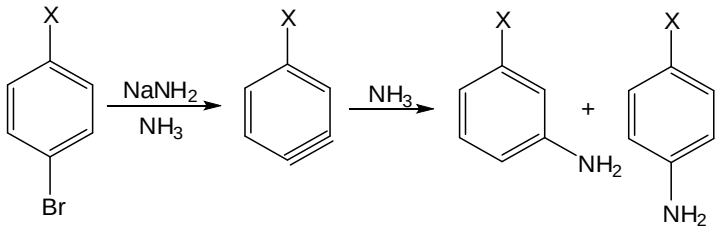
Scheme 17

Benzyne formation is a unique example of strong base-promoted elimination, which produces a highly reactive localized "acetylene" analogue within the benzene ring. Nucleophiles can add to this system to afford an anion intermediate which is then protonated to give substituted aromatic compounds (**Scheme 18**).[87]



Scheme 18

The regio-selectivity of the elimination-addition process is determined by the nature of the substituent group in the halobenzene. An electron-withdrawing group leads to para-addition of the nucleophile to the benzyne intermediate, whereas electron-donating group give a mixture of para and meta-substitution products for the reaction of 4-substituted bromobenzene with $NaNH_2$ at -33 ^oC (**Scheme 19** and **Table 7**).[88]

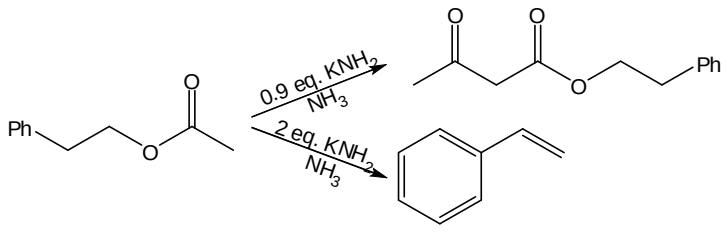


Scheme 19

Table 7 The product ratio of the reaction **Scheme 19**

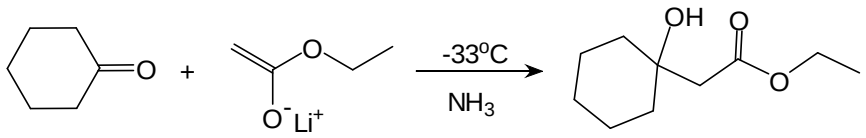
X	**products ratio**	
	para (%)	meta (%)
CN	95-100	0-5
OMe	50-55	45-50

A range of condensation reactions in the presence of sodium amide or potassium amide in liquid ammonia are known. Hauser *et al*. extensively investigated the Claisen condensation reaction in liquid ammonia.[89] For example, addition of 2-phenylethyl acetate to 0.9 equivalents of potassium amide in liquid ammonia at -33 ^oC gives 2-phenylethyl acetoacetate in a 39% yield, but with 2 equivalents excess of potassium amide, the major product is styrene, resulting from base catalyzed elimination (**Scheme 20**).[90]



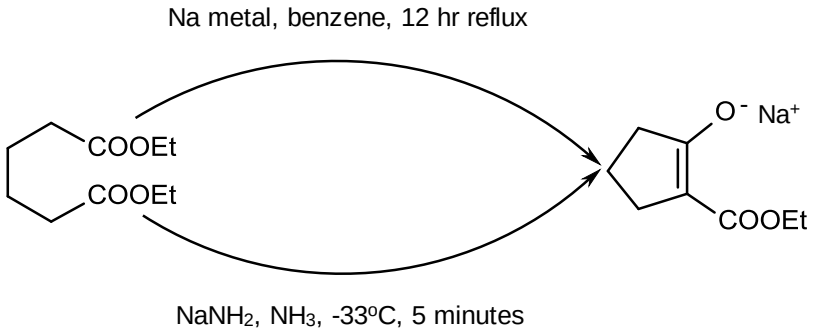
Scheme 20

Crossed Claisen condensation reaction between different esters in liquid ammonia is also possible, lithium salts are normally used to avoid the enolate exchange (**Scheme 21**).[91]



Scheme 21

Dieckmann condensation of diethyl adipate in liquid ammonia with one equivalent of sodium amide is completed in minutes (**Scheme 22**).[92]



Scheme 22

3.3 As a solvent for solvolysis

Solvolysis of substrates in liquid ammonia, involve ammonia as a reactant which leads to the replacement of an activated atom or group, for example, halogen, or alkoxy, by an amino group. Numerous solvolysis reactions in liquid ammonia are known, and some are widely used in preparative organic synthesis. However, the possible solvolysis of reactants must also be first considered as unwanted reaction for those reactions which use liquid ammonia as just a reaction medium, such as nucleophilic substitution or condensation, etc.

3.3.1 Alkyl and aryl halides

Alkyl halides undergo solvolysis in liquid ammonia to give primary, secondary, and tertiary amines, and in some cases, quaternary ammonium salts. For a given aliphatic group, the ease of solvolysis for alkyl halides generally lies in the order: iodides > bromides >> chlorides.[93]

The solvolysis of sterically hindered alkyl halides is very slow, in stark contrast with that in water. For example, the solvolysis of *t*-butyl chloride in liquid ammonia at 25 ^{o}C has a half life of about 150 days[94] versus 21 seconds in water.[34a] In addition, although ammonia is a basic solvent, tertiary alkyl halides and activated halides do not undergo elimination to give alkenes in liquid ammonia. Shatenshtein[94] investigated the kinetics of solvolysis of some saturated aliphatic halides in liquid ammonia at 25 ^{o}C (**Table 8**).

The data shows that the solvolysis rate of primary alkyl halides hardly changes with increasing size of the alkyl group beyond ethyl, but decreases markedly on passing from a primary to a branched alkyl chain halide, which suggests the solvolysis of alkyl halides in liquid ammonia occurs by an S_N2 mechanism.

Table 8 First order rate constants for the solvolysis of alkyl halides in liquid ammonia at 25 ^{o}C[94]

	10^4 k_{obs} (min^{-1})		
halides	**X=Cl**	**X=Br**	**X=I**
CH_3CH_2X	7.42	736	5020
$CH_3(CH_2)_2X$	3.98	578	1870
$CH_3(CH_2)_3X$	3.15	576	1550
$CH_3(CH_2)_4X$	2.49	414	—
$CH_3(CH_2)_5X$	3.74	496	—
$CH_3(CH_2)_6X$	3.05	529	—
$CH_3(CH_2)_7X$	1.53	275	1420
$(CH_3)_2CH(CH_2)_2X$	2.21	248	750
$(CH_3)_2CHX$	0.119	9.7	182
$CH_3CH_2CHXCH_3$	0.077	—	—
$(CH_3)_3CX$	0.033	—	—
$C_6H_5CH_2Cl$	544	—	—

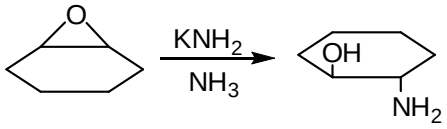
For a given halide, increasing the size of alkyl group in the alkyl halide tends to favour increased formation of primary over secondary amine (**Table 9**),[95] the latter product being the result of the first formed primary amine, in preference to ammonia, reacting subsequently with the alkyl halide. This is also indicates an S_N2 mechanism, as the amine becomes bulkier, its substitution reaction to form a secondary amine decreases. Inactivated aromatic halides, without the presence of a catalyst, generally do not react with liquid ammonia at room temperature or even higher,[94] but some heteroaryl halides do slowly solvolyse, for example, 2-chlorobenzthiazole gives 2-aminobenzthiazole in liquid ammonia at 20 ^{o}C.[96]

Table 9 The solvolysis of alkyl halides with different size of alkyl group in liquid ammonia at 25 ^{o}C after 24 hours

solvolysis product / halides	primary amine (%)	secondary amine (%)
n-Amyl chloride	10	80
n-Octyl chloride	45	43
n-Dodecyl chloride	90	trace

3.3.2 Epoxides

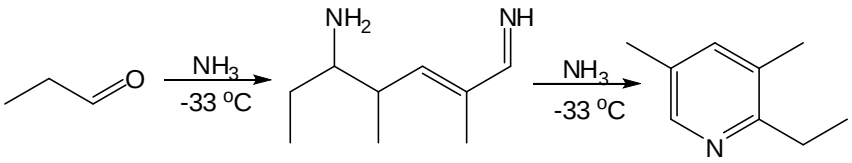
The opening of epoxides to give β-hydroxyamines occurs in aqueous ammonia and from metal amide attack in liquid ammonia. For example, cyclohexene oxide is converted into *trans*-2-amino-cyclohexanol by potassium amide in liquid ammonia (**Scheme 23**).[97]



Scheme 23

Due to the resistance of epoxides towards the solvolysis in just liquid ammonia, the solvolysis rates can be very slow, and some researchers claimed that there was no sign of solvolysis of styrene oxide in liquid ammonia at room temperature.[98]

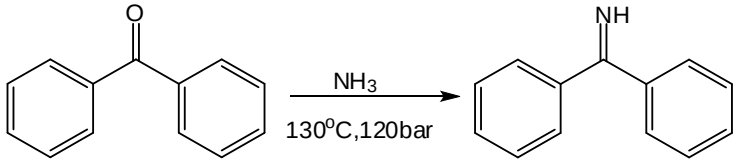
3.3.3 Aldehydes and ketones



Scheme 24

The solvolysis of aldehydes in aqueous ammonia is well known. The solvolysis of propionaldehyde and *n*-heptaldehyde in liquid ammonia at its boiling point, surprisingly gives pyridine derivatives as products. Probably the reaction proceeds via an imine intermediate in an aldol-type condensation (**Scheme 24**).[99]

In the presence of calcium chloride and ammonium chloride, acetone undergoes a series of condensation reactions at 0 °C in liquid ammonia.[100] Acetophenone gives a very low yield (3%) of acetophenone imine on heating with ammonia at 180 °C for 4 hours, but the yield can be improved to 30% by the addition of ammonium chloride as a catalyst.[101] Benzophenone



Scheme 25

fails to react with liquid ammonia at room temperature over several weeks, whereas fluorenone under the same conditions gives a quantitative yield of fluorenone imine.[102] Under forcing conditions, benzophenone can be converted to the corresponding imine with high yield (**Scheme 25**).[103](*vide infra*)

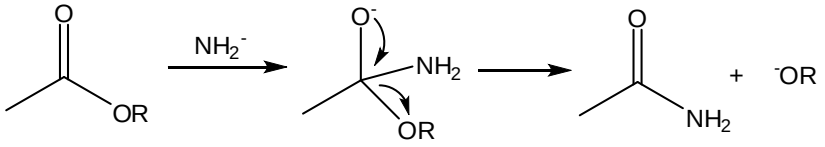
3.3.4 Esters

Many carboxylic esters undergo solvolysis in liquid ammonia to give the corresponding amide. The reaction is slow with the alkyl esters of simple aliphatic and aromatic carboxylic acids, but the solvolysis may be accelerated by increasing the temperature or by adding the

ammonium salts. In liquid ammonia, four trends are clearly observed for the solvolysis of ester:[104]

1. The reaction rate is accelerated by the presence of electro-withdrawing α-substituents which increase the electrophilicity of the carbon atom of the ester carbonyl group.
2. The reaction rate is decreased by the presence of α, β-double bond which decreases the electrophilicity of the carbonyl group by conjugation;
3. Aryl esters undergo the solvolysis reaction more rapidly than their aliphatic analogues.
4. The solvolysis rate is increased greatly by added the metal amide.

All of the above suggest that the ammonolysis of esters occurs by an addition-elimination mechanism (**Scheme 26**).



Scheme 26

The catalytic effect of ammonium salts is probably due to either the partial protonation of the carbonyl oxygen by ammonium cation, which increase the electrophilicity of carbonyl carbon, or protonation of the leaving alcohol presumably analogous to that in the acid-catalysed hydrolysis of esters. **Table 10** gives the quantitative outcome of the solvolysis of esters in liquid ammonia in the absence or presence the ammonium salt.[105]

Obviously, esters having electron-withdrawing groups as α-substituents solvolyse more quickly and added NH_4Cl salt has very little effect on the rate of solvolysis, whereas less reactive esters are subject to a pronounced catalytic effect with NH_4Cl salt.

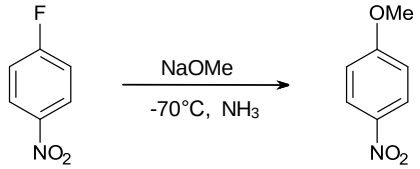
Table 10 The solvolysis of esters at 0 °C in liquid ammonia with (B) and without (A) ammonium chloride

esters	yield of amide (%)[a]			
	after 24 hours		after 48 hours	
	A	**B**	**A**	**B**
$NCCH_2CO_2C_2H_5$	97	96	99	100
$H_2NCOCH_2CO_2C_2H_5$	67	91	93	98
$C_2H_5OCOCH_2CO_2C_2H_5$	9	79	63	95
$C_6H_5CHOHCO_2C_2H_5$	44	63	62	79
$C_2H_5OCH_2CO_2C_2H_5$	5	53	38	77
$C_6H_5CH_2CO_2C_2H_5$	0.6	2	1.2	4.7
$CH_3CO_2C_2H_5$	0	1	0	3

[a] Data in columns A and B correspond to yields in the absence and presence respectively of ammonium chloride. (0.025mole ester, 0.2g ammonium chloride was added as catalyst)

3.4 As a solvent for nucleophilic substitution reactions

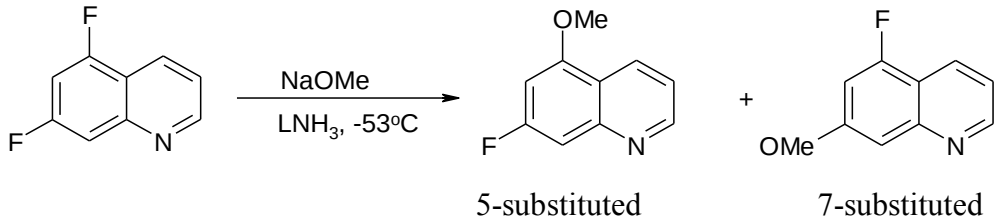
The research in this area is mainly concerned with aromatic nucleophilic substitution (S_NAr). Shteingarts *et al.* have investigated the kinetics and regioselectivity in liquid ammonia.[106,107] For example, the reaction of sodium methoxide with 4-NFB was carried out in liquid ammonia at -70°C. The extrapolated reaction rate was claimed to be nine orders of magnitude faster in liquid ammonia than in methanol (**Scheme 27**).[101,102]



Scheme 27

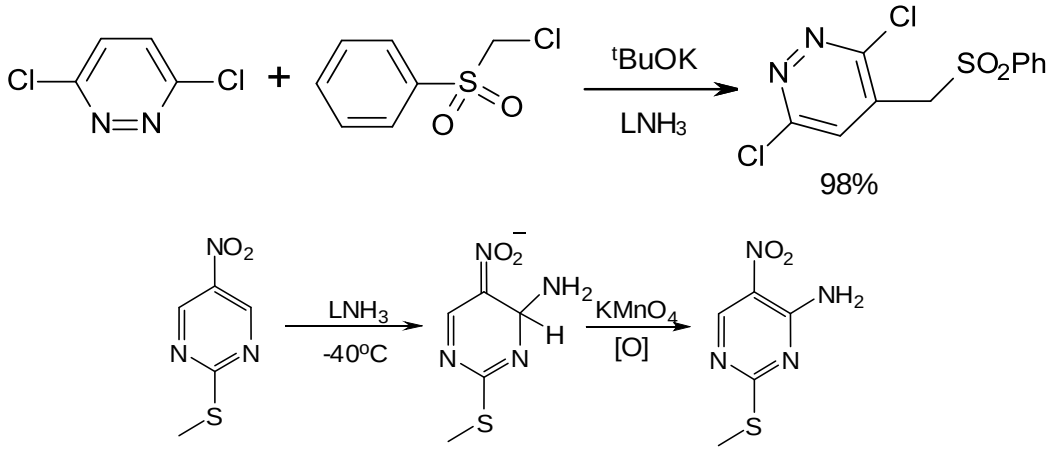
The selectivity of aromatic nucleophilic substitution in liquid ammonia is also claimed to be better than in conventional solvents, for example, the reaction of sodium methoxide with 5,7-difluoroquinoline at -53 °C in liquid ammonia yields a mixture of 5 and 7 substituted product

in a ratio of 8:1, the same reaction in DMSO at 25 ^{o}C gives a ratio of 6:1(**Scheme 28**). Interestingly, the selectivity of the reaction seems to decrease with increasing reaction temperature.[108]



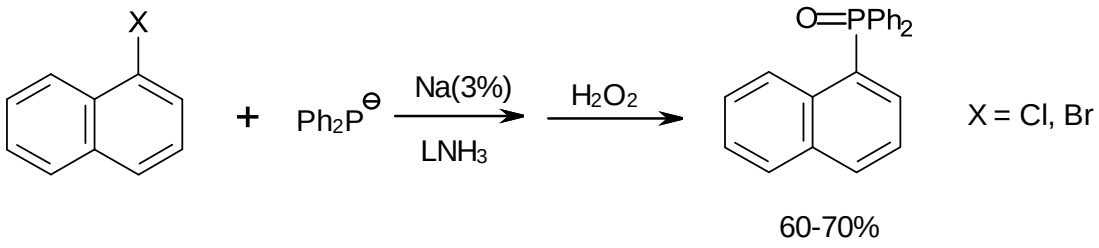
Scheme 28

Vicarious nucleophilic substitution reaction (VNS) and oxidative nucleophilic substitution of hydrogen (ONSH) also can be performed in liquid ammonia to give some interesting and useful functionalised heterocycles (**Scheme 29**).[109,110]



Scheme 29

Some unactivated aryl halides can react with nucleophiles to form C-C, C-N, C-P and C-S bonds under photo irradiation or using alkali metals as radical initiators in liquid ammonia, the reactions follow an $S_{NR}1$ mechanism.[111] For example, 1-naphthyl halides react with triphenylphosphine in liquid ammonia under ultrasound or sodium metal to give naphthyldiphenylphosphine oxide in moderate yields after the reaction mixture treated with 40% H_2O_2 (**Scheme 30**).[112]



Scheme 30

4. The project

The choice of solvent is still a significant problem in industrial organic synthesis. Ever increasing health and environmental concerns have resulted in some previously common solvents, for example chloroform, being proscribed, whilst others, still commonly used in research syntheses, are generally avoided at the manufacturing scale. Dipolar aprotic solvents (DMSO, DMF, DMAc, and NMP) are used in around 10% of cases. They are expensive and there are toxicity concerns with some of them. They are all difficult to recycle due to their water miscibility, and are frequently disposed of by incineration. No single alternative solvent is likely to solve these problems. Liquid ammonia is a promising candidate to replace dipolar aprotic solvents in a number of applications. Although liquid ammonia is among the least expensive bulk chemicals[113] and is a promising candidate to replace dipolar aprotic solvents in a number of industrial processes, its application as a common solvent is relatively unusual. Historically it has been used only where its use was essential, because of handling difficulties. It can be quantitatively recovered from water by distillation under pressure. There is an extensive literature on the physical and chemical properties of liquid ammonia,[64,114] on the reduction of organic compounds in alkali metal/ammonia solution[115] and the application of alkali metal amides in liquid ammonia as strong bases in synthesis.[116] However, there is little about the detailed kinetics and mechanisms of aromatic and aliphatic nucleophilic substitution in liquid ammonia, and the description of liquid ammonia solvent effects on organic reactions are also rare. To the best of our knowledge, there are no systematic studies on the mechanisms of organic reactions in liquid ammonia. Present research in liquid ammonia is much associated with theoretical studies on the solvent effects. Therefore, it is imperative to establish some

fundamental facts and concepts about the effect of liquid ammonia solvent on the behaviour of organic reactions.

The purpose of this project is to investigate the solvent effects of liquid ammonia on the kinetics and mechanisms of some fundamental reactions and to examine the scope of this solvent in synthesis, and so provide some of the physical organic chemistry required to support synthetic programmes.

Experimental Page

1. Materials

1.1 General

Liquid ammonia was purchased from BOC Ltd., has 99.98% purity with minimal levels of moisture (<200 ppm) and other impurities (<5ppm oil).[117] Ammonia was distilled once from the cylinder to a burette, and no further purification procedure was made before using as reaction solvent.

All organic and inorganic were purchased from commercial providers, and were used directly without further purification unless otherwise noted. (1S,2S)-(+)-N-(4-toluenesulfonyl)-1,2-diphenylethylenediamine(S,S-TsDPEN, 99.5%) was from Johnson Matthey Catalysis & Chiral Technologies. The general solvents were from commercial providers and were Reagent or HPLC grade and were used without further purification.

1.2 Synthesis and purification of organic compounds for starting materials and products characterisation

^{1}H NMR and proton decoupled ^{13}C NMR spectra were acquired with a Bruker Avance 400 (400 MHz, 100.1 MHz, respectively). Proton and carbon chemical shifts are reported on the δ scale relative to tetramethylsilane (δ_H = 0.00 ppm) and $CDCl_3$ (δ_C = 77.00 ppm) respectively as internal standards. Mass spectra were obtained with Agilent 6890 GC and 5973 MS detector. Melting points were measured using a Mettler Toledo STAR SW 9.01 DSC instrument.

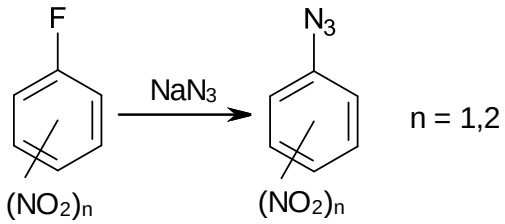
1.2.1 Preparation of sodium phenoxides[118] and triazolate salts[119]

Sodium phenoxides: phenol (2.4 g, 25 mmol) was dissolved in diethyl ether or THF (20ml), under argon. Sodium metal (0.46 g, 20 mmol) was cut into small pieces and added into the above solution in several portions at room temperature. After all the sodium was added, the reaction was refluxed overnight. Solvent was removed under vacuum, and the residual solid was repeatedly washed with petroleum ether (40-60) until no phenol was detected by GC in the washing eluent. The solid was dried under vacuum and used without further purification. Phenoxide salts are hygroscopic and susceptible to oxidation, therefore all the salts were kept in well-sealed bottle and stored under argon. Other phenolates were prepared by the similar method.

Sodium triazolate: NaOH (0.6 g, 15 mmol) and 1,2,4-triazole (1.0 g, 15 mmol) were dissolved in water (10 ml). The solution was maintained at room temperature for 4 h, and then cooled to 0 ^{o}C for 2 hours. The crystalline precipitate was filtered and repeatedly washed with ether, and dried under vacuum at 100 ^{o}C to give 1.0 g white solid (72% yield).

Sodium benzotriazolate: similar to the method for the preparation of sodium phenoxides.

1.2.2 Preparation of nitroazidobenzenes (Scheme 31)



Scheme 31

CAUTION: As organic azides are potentially explosive, it must be handled with care. All aryl azides have been stored in the freezer in the dark.

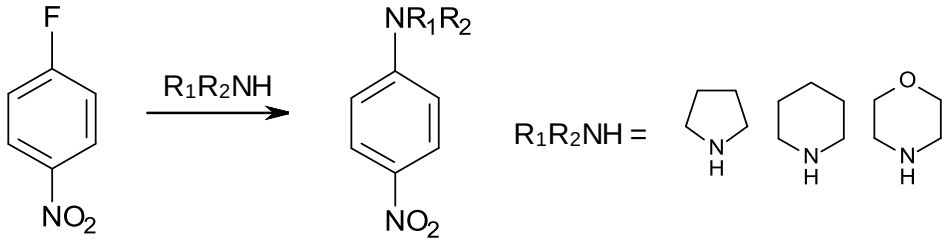
4-NAB: NaN_3 (0.39 g, 6 mmol) was added in portions to 4-NFB (0.71 g, 5mmol) in DMF (15ml) with stirring, the reaction temperature was maintained at 65 ^{o}C overnight, and the reaction mixture then poured into ice-water (50ml). The yellow precipitate was extracted with DCM (3 × 15ml), and the organic layer was dried over anhydrous Na_2SO_4. After solvent was removed under vacuum, a yellow solid (0.71 g, 87% yield) was obtained. The solid was recrystallised twice from water-ethanol (2:1) to give 0.58 g (71% yield) yellow solid with a purity of 98.5% (GC). Melting point: 74-75 ^{o}C[120]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, 2H), 8.25 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.1, 126.5, 143.9, 147.1;[121] MS (EI, 70 eV): *m/z* (%) = 164.1(M^+, 53.8), 136.1 (51.5), 90.1 (63.0), 63.1 (100), 50.0 (17.6).

2-NAB: NaN_3 (0.39 g, 6 mmol) was added in portions to 2-NFB (0.71 g, 5mmol) in DMF (15ml) with stirring, then heated to 60 ^{o}C and held there overnight. The reaction mixture was then poured into ice-water (50ml). The yellow precipitate was extracted with DCM (3 × 15ml), and the organic layer was dried over anhydrous Na_2SO_4. After solvent was removed under vacuum, a yellow solid (0.79 g, 96% yield) was obtained. The solid was recrystallised

twice from water-ethanol (2:1) to give 0.67g (82% yield) of yellow crystals with a purity of 99% (GC). Melting point: 63-65 ^{o}C;[122] ^{1}H NMR (400 MHz, $CDCl_3$): 7.28-7.39 (m, 2H,), 7.66 (m, 1H), 8.17 (q, 1H);[123] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.5, 125.2, 126.3, 134.3, 134.8, 140.9;[124] MS (EI, 70 eV): *m/z* (%) = 164.1(M^+, 43.8), 136.1 (61.5), 105.1 (100), 50.1 (52.5).

2,4-Dinitroazidobenzene: NaN_3 (0.20 g, 3 mmol) was added in portions to 2,4-dinitrofluorobenzene (0.37 g, 2mmol) in DMF (10ml) solution with stirring, held at 40 ^{o}C overnight, and poured into ice-water (20ml). The yellow precipitation was observed, the mixture was extracted with DCM (2 × 10ml), and the organic layer was dried over anhydrous Na_2SO_4. After solvent was removed under vacuum, a deep orange solid was obtained. The solid was recrystallised from water-ethanol (2:1) to give 0.23 g (56% yield) orange powder with a purity of 97% (GC). Melting point: 67-68 ^{o}C;[125] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, 1H), 8.48 (m, 1H), 8.81(d, 1H);[126] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.5, 127.4, 135.8, 147.2, 148.9; MS (EI, 70 eV): *m/z* (%) = 209.1 (M^+, 7.1), 181.1 (96.5), 51.1 (100).

1.2.3 Preparation of 1-(4-nitrophenyl)pyrrolidine, piperidine and morpholine (Scheme 32)



Scheme 32

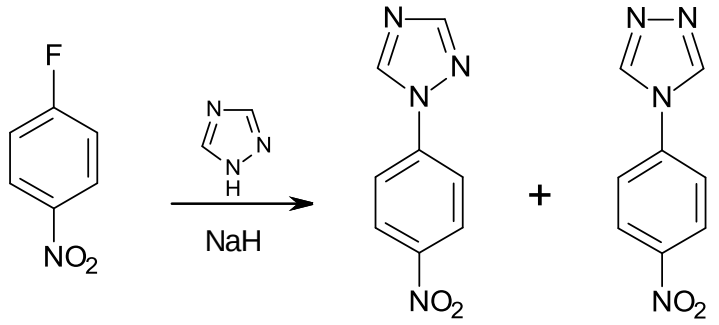
1-(4-nitrophenyl)pyrrolidine: pyrrolidine (1.8 g, 25 mmol) and 4-NFB (2.8 g, 20 mmol) were dissolved in DMF (25ml) under argon, the reaction temperature was maintained at 70 ^{o}C overnight. The reaction mixture then poured into 50ml ice-water, the yellow precipitation was filtered and washed with water, then dissolved in DCM (10ml). The filtrates was extracted with DCM (2 × 10ml) and organic layer was combined and washed with water until no DMF was detected in the organic layer by GC. The solvent was removed under vacuum to afford 2.5g of yellow solid (64% yield). Melting point: 176-177 ^{o}C;[127] ^{1}H NMR (400 MHz, $CDCl_3$):

δ = 2.05-2.20 (m, 4H, CH_2), 3.38-3.47 (m, 4H, CH_2N), 6.48 (d, 2H, aromatic), 8.13 (d, 2H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 47.9, 110.4, 126.4, 136.5, 151.8.[128] MS (EI, 70 eV): *m/z* (%) = 192.1 (M^+, 100), 191.1 (92.9), 136.1 (23.9), 120.0 (7.1), 104.0 (7.1), 90 (9.7), 77.0 (10.6).

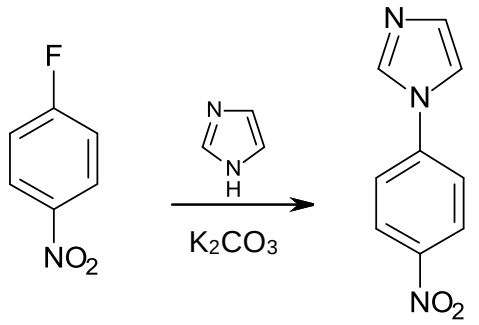
1-(4-nitrophenyl)piperidine: pyrrolidine (2.1 g, 25 mmol) and 4-NFB (2.8 g, 20 mmol) were dissolved in DMF (25ml) under argon and kept at 70 ^oC overnight. The reaction mixture then poured into ice-water (50ml), the yellow precipitation was filtered off and washed with water, then dissolved in DCM (10ml). The filtrates was extracted with DCM (2 × 10ml) and organic layer was combined and washed with water until no DMF was detected in organic layer by GC. The solvent was removed under vacuum to afford 2.8 g yellow solid (68% yield). Melting point: 104-105 ^oC[129]; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.67 (m, 6H, CH_2), 3.45 (m, 4H, CH_2N), 6.76-6.80 (d, 2H, aromatic), 8.06-8.11 (d, 2H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 25.3, 48.3, 112.2, 126.2, 137.2, 154.9.[128] MS (EI, 70 eV): *m/z* (%) = 206.1 (M^+, 89.4), 205.1 (100), 176.1 (8.0), 165.1 (15.9), 159.1(23.9), 150.0 (18.6), 120.0 (13.3), 77.0 (11.5).

1-(4-nitrophenyl)morpholine: morpholine (2.1 g, 25 mmol) and 4-NFB (2.8 g, 20 mmol) were dissolved in DMF (25ml) under argon and kept at 70 ^oC overnight. The reaction mixture then poured into 50ml ice-water, the yellow precipitation was filtered off and washed with water, then dissolved in DCM (10ml). The filtrates was extracted with DCM (2 × 10ml) and organic layer was combined and washed with water until no DMF was detected in organic layer by GC. The organic layer was dried over anhydrous Na_2SO_4, and solvent was removed under vacuum to afford 1.8 g yellow solid (44% yield). Melting point: 152-154 ^oC[130]; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.32-3.40 (m, 4H, CH_2), 3.83-3.89 (m, 4H, CH_2N), 6.80-6.87 (d, 2H, aromatic), 8.10-8.17 (d, 2H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2, 47.9, 110.8, 126.6, 137.1, 151.7.[128] MS (EI, 70 eV): *m/z* (%) = 208.0 (M^+, 86.7), 150.0 (100), 120.0 (40.8), 104.0 (12.4), 77.0 (21.2).

1.2.4 Preparation of 1-(4-nitrophenyl)-1*H*-1,2,4-triazole, 4-(4-nitrophenyl)-4*H*-1,2,4-triazole and 1-(4-nitrophenyl)-1*H*-imidazole (Schemes 33 and 34)



Scheme 33



Scheme 34

1,2,4-Triazole (2.4 g, 35 mmol) was dissolved in 40 ml DMF, NaH (1.2 g, 50 mmol) were added and mixture was stirred for 1 hour. 4-nitrofluorobenzne (4.9 g, 35 mmol) was added dropwise at ambient temperature for 4 hours. The reaction mixture was poured into 100ml ice-water and the precipitate was isolated by filtration. The residue was dissolved in DCM, the insoluble solid was filtered off and collected, recrystallised from water-ethanol (1:1) to give 1.2g of pale white powder as 4-(4-nitrophenyl)-4*H*-1,2,4-triazole. The filtrate, DCM layer was washed with water until no DMF was observed in washing eluent by GC analysis. The organic layer was dried over anhydrous Na_2SO_4, and solvent was removed under vacuum to afford 2.8g of pale yellow solid (60% total yield) as 1-(4-nitrophenyl)-1*H*-1,2,4-triazole.

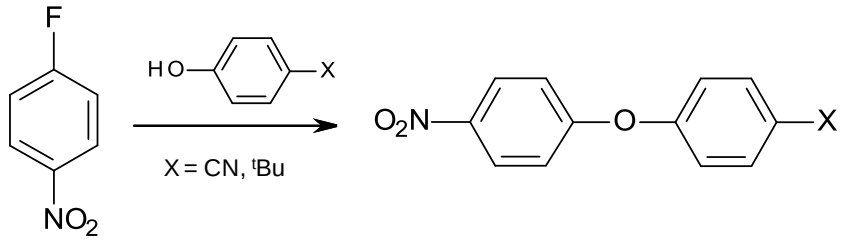
1-(4-nitrophenyl)-1*H*-1,2,4-triazole: Melting point: 194-195 ^{o}C; [131] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93-7.97 (m, 2H, Ph), 8.18 (s, 1H, triazole), 8.41-8.49 (m, 2H, Ph), 8.74 (s, 1H,

triazole);[132] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.9, 125.7, 141.3, 146.1, 153.5; MS (EI, 70 eV): *m/z* (%) = 190.1 (M^+, 100), 163.1 (30.4), 136.0 (37.6), 90.1 (54.0), 80.1 (15.5), 63.1 (44.2), 50.1 (14.6).

4-(4-nitrophenyl)-4*H*-1,2,4-triazole: Melting point: >300 ^{o}C (decomp.) ^{1}H NMR (400 MHz, DMSO-d_6/$CDCl_3$): δ = 8.14 (m, 2H, Ph), 8.54 (m, 2H, Ph), 8.86 (s, 2H, triazole); ^{13}C NMR (100 MHz, DMSO-d_6/$CDCl_3$): δ = 122.8, 126.6, 142.0, 141.8, 147.3. MS (EI, 70 eV): *m/z* (%) = 190.1(M^+, 100), 160.1 (33.6), 136.1 (40.2), 90 (45.6), 63.1 (28.8), 30.0 (10.6).

1-(4-nitrophenyl)-1*H*-imidazole: a mixture of imidazole (0.34 g, 5 mmol) and 4-NFB (0.71 g, 5 mmol) in 15ml DMF was added K_2CO_3 (1 g, 7.5 mmol) and stirred at 75 ^{o}C for overnight. The reaction mixture was poured into 50ml ice-water and the precipitate was collected and washed with water. The solid then recrystalled from ethanol water (2:1) to give 0.81 g (86% yield) pale white solid. Melting point: 202-204 ^{o}C;[133] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (s, 1H, imidazole), 7.38 (s, 1H, imidazole), 7.58 (d, 2H, Ph), 7.98 (s, 1H, imidazole), 8.42 (d, 2H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.6, 121.4, 126.2, 134.9, 131.9, 142.2, 146.7.[134]

1.2.5 Preparation of 4-substituted phenyl 4-nitrophenyl ether (Scheme 35)



Scheme 35

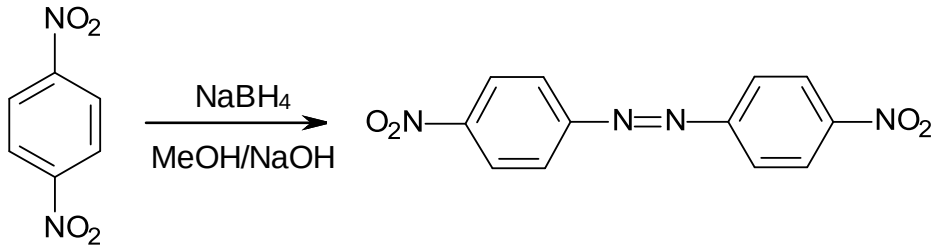
4-substituted phenols (5 mmol), 4-NFB (5 mmol) and K_2CO_3 (1 g, 7.5 mmol) in DMF (15ml) was stirred at 85^{o}C for 5 hours. The reaction mixture was poured into ice-water (50ml) and extracted with DCM, then the organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the solid was recrystallised twice from water-ethanol (1:1).

4-cyanophenyl 4-nitrophenyl ether: 1.1 g light yellow solid (91% yield). Melting point: 161-162 ^{o}C;[135] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13-7.19 (m, 4H), 7.73 (d, 2H), 8.29 (d, 2H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ = 108.4, 118.3, 119.0, 126.2, 134.6, 143.9, 159.0, 160.9.[136] MS (EI, 70 eV): *m/z* (%) = 240.0 (M^+, 100), 210.0 (30.1), 166.0 (16.8), 140.0 (27.4), 102.0 (16.8), 75.0 (10.6), 50.0 (10.6).

4-*tert*-butyl phenyl 4-nitrophenyl ether: 0.91 g pale yellow solid (67% yield). Melting point: 58-59 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H), 7.00 (m, 4H), 7.46 (d, 2H), 8.19 (d, 2H);[137] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.6, 35.6, 117.8, 120.7, 125.4, 127.9, 130.3, 142.5, 154.8, 164.1.

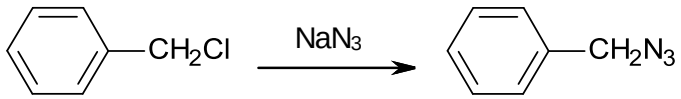
1.2.6 Preparation of 1,2-bis(4-nitrophenyl)diazene (Scheme 36)[138]



Scheme 36

1,4-dinitrobenzene (0.34 g, 2mmol) was dissolved together with NaOH (1.0 g, 2.5 mmol) in methanol (10ml) at 60 ^oC, the solution was stirred and a 5 ml methanol solution of $NaBH_4$ (0.1 g, 2.5 mmol) was added dropwise, the progress of the reaction being monitored by GC until no 1,4-dinitrobenzene was observed. Solvent was removed under vacuum and the residue syrup was washed with water and extracted with toluene, the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the deep brown solid was recrystallised from toluene/ethanol (5:1) twice to give 0.22 g (41% yield) of dark orange crystals. Melting point: 225-227 ^oC;[139] ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, 4H), 8.46 (d, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.1, 124.9, 150.2, 156.0;[138] MS (EI, 70 eV): *m/z* (%) = 272.0 (M^+, 36.1), 242.1 (8.4), 150.0 (55.9), 122.0 (100), 92.0 (44.9), 75 (42.3), 74 (40.9), 64 (10.6), 51 (4.4).

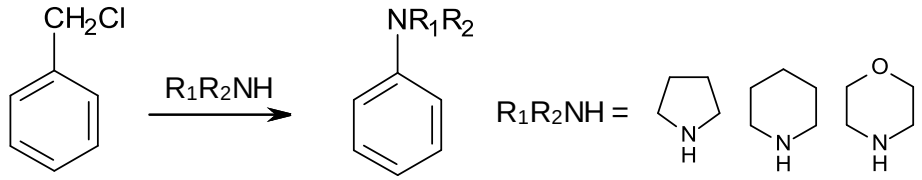
1.2.7 Preparation of benzyl azide (Scheme 37)



Scheme 37

NaN_3(2.5g, 38.5mmol) was added to benzyl chloride (3.78 g, 30 mmol) in DMF (25ml) with stirring at room temperature, then the temperature was raised to 70 ^oC and maintained overnight. The reaction mixture was poured into ice-water (100ml) and extracted with DCM (3 ×20ml), and then organic layer was washed with water until no DMF was detected by GC analysis. The organic layer was dried over anhydrous Na_2SO_4 and solvent removed under vacuum. The oily residue was distilled (58-60 ^oC / 3mmHg) to give a colourless liquid (2.6g, yield 65%). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.38 (s, 2H, CH_2N_3), 7.36 (m, 5H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6, 128.5, 128.5, 128.7.[140]

1.2.8 Preparation of N-benzylpyrrolidine, N-benzylpiperidine and N-benzylmorpholine (Scheme 38)



Scheme 38

Secondary cyclic amine (15 mmol) and benzyl chloride (15 mmol) in acetonitrile (30ml) were added together with Na_2CO_3 (2.1 g, 20 mmol), reaction temperature was 85 ^oC for 5 hours, the reaction mixture was poured into 50ml ice-water, and extracted with DCM (3×10ml). Combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum. The crude product purified by flash column (hexane/ethyl acetate = 5:1).

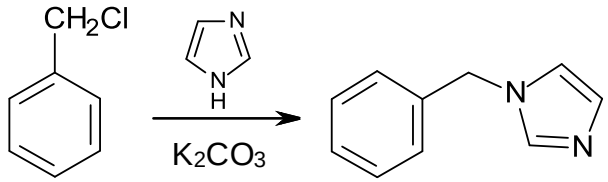
N-benzylpyrrolidine: 2.1 g colourless oil (yield 87%), ^1H NMR (400 MHz, $CDCl_3$): δ = 1.71-1.83 (m, 4 H, CH_2), 2.42-2.52 (m, 4 H, NCH_2), 3.51(s, 2H, CH_2Ph), 7.31 (m, 5H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4, 54.3, 60.8, 127.2, 128.2, 129.2, 139.5;[141] MS (EI, 70 eV): *m/z* (%) = 161.2(M^+, 54.0), 160.2 (77.0), 132.1 (7.1), 91.1 (100), 84.1 (56.6), 70.1 (39.8), 65.1 (20.8).

N-benzylpiperidine: 1.9 g colourless oil (yield 72%), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44-1.48 (m, 2 H, CH_2), 1.60 (m, 4H, CH_2), 2.41 (m, 4H, NCH_2), 3.52 (s, 2H, CH_2Ph), 7.32 (m, 5H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 25.7, 54.4, 63.6, 127.1, 128.2, 128.9, 138.5.[142]

N-benzylmorpholine: 2.3 g light yellow oil (yield 88%), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (t, 4 H, NCH_2), 3.51 (s, 2H, CH_2), 3.72 (t, 4H, OCH_2), 3.51 (s, 2H, CH_2Ph), 7.34 (m, 5H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.6, 63.4, 66.9, 127.2, 128.3, 128.9, 138.9.[143]

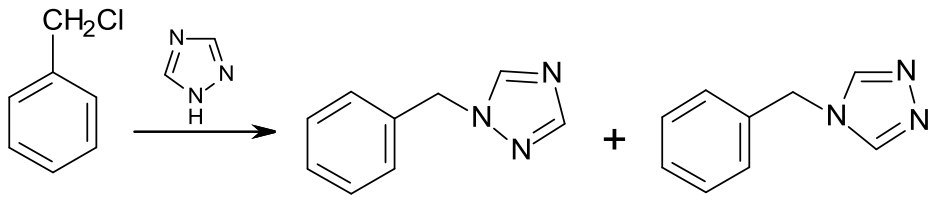
1.2.9 Preparation of 1-Benzylimidazole (Scheme 39)



Scheme 39

Imidazole (1.4 g, 20mmol) and benzyl chloride (2.5 g, 20mmol) added together with K_2CO_3 (3.5 g, 25mmol) in THF (25ml), the reaction mixture was stirred under reflux overnight. After filtration of solid, solvent was removed under vacuum to afford a yellow solid as crude product. The solid was dissolved in DCM (30ml), washed with brine (3×15ml), and dried over anhydrous Na_2SO_4. After removing the solvent under vacuum, yellow crystals (1.5 g, 47% yield) with a melting point 74-75 ^{o}C were obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.15 (s, 2 H, $PhCH_2$), 6.88 (s, 1H, imidazole), 7.07 (s, 1H, imidazole), 7.15 (d, 2H, benzene), 7.31-7.33(m, 3H, benzene), 7.54 (s, 1H, imidazole); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.8, 127.2, 128.3, 128.9, 129.8, 136.2, 137.4.[144]

1.2.10 Preparation of 1-benzyl-1,2,4-triazole and 4-benzyl-1,2,4-triazole (Scheme 40)



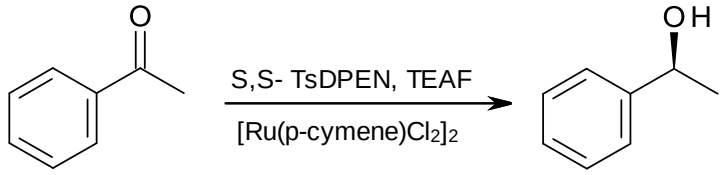
Scheme 40

Sodium 1,2,4-triazolate salt was prepared according to the literature,[119] and used directly without further purification. Sodium 1,2,4-triazolate salt (2.3 g, 25mmol) and benzyl chloride (3.2 g, 25mmol) was added to acetonitrile (25ml), the reaction was stirred vigorously under heterogeneous conditions at 85 ^{o}C and the progress of the reaction was monitored by GC analysis. After 5 hours, the solvent was removed under vacuum to give yellow solid (2.97 g) as crude products (the molar ratio between 1-benzylated and 4-benzylated triazole was 6.9:1 based on GC analysis). The solid was washed with hot ethyl acetate (3×15ml), and filtrates were evaporated in vacuo to give a light yellow solid. The solid residue was purified using flash column with DCM/hexane = 6:1 as eluent to give 2.2 g 1-benzyl-1,2,4-triazole as white solid with a melting point 55-56 ^{o}C and 0.25 g 4-benzyl-1,2,4-triazole as white powder with a melting point 107-108 ^{o}C (62% total yield).

1-benzyl-1,2,4-triazole: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.34 (s, 2 H, $PhCH_2$), 7.25-7.28 (m, 2H, Ph), 7.33-7.40 (m, 2H, Ph), 7.91 (s, 1H, triazole), 8.06 (s, 1H, triazole); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.6, 128.0, 128.8, 128.9, 129.1, 134.6, 143.1, 152.2. MS (EI, 70 eV): *m/z* (%) = 159.1(M^+, 39.2), 158.1 (51.1), 132.1 (46.8), 105.1 (11.5), 91.1 (100), 65 (17.7).[145]

4-benzyl-1,2,4-triazole: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.20 (s, 2H, $PhCH_2$), 7.19-7.23 (m, 1H, Ph), 7.36-7.43 (m, 1H, Ph), 8.19 (s, 1H, triazole); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.1, 127.6, 129.0, 129.4, 134.2, 142.9. MS (EI, 70 eV): *m/z* (%) = 159.1 (M^+, 44.3), 158.1 (7.0), 132.1 (6.4), 91.1 (100), 65 (12.2).[145]

1.2.11 Preparation of (S)-α-methyl benzyl alcohol (Scheme 41)

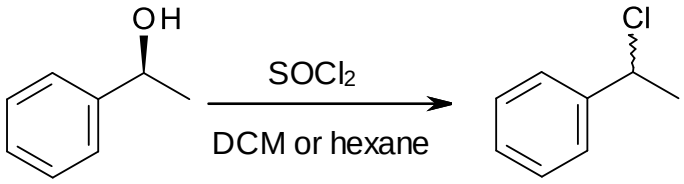


Scheme 41

A 25ml vessel was pre-charged with $[Ru(p\text{-cymene})Cl_2]_2$ (27.5 mg, 0.0375 mmol) and of S,S-TsDPEN[(1S,2S)-(-)-N-(4-toluenesulfonyl)-1,2-diphenylethylenediamine] (23 mg, 0.075mmol), TEAF (7.5ml, a mixture of formic acid and triethylamine in molar ratio of 5:2) was added slowly in several portions until the catalysts were fully dissolved, then the remainder was quickly added followed by acetophenone (1.81 g, 15mmol). The solution was maintained at 35 ^{o}C overnight. The reaction mixture was washed with 1M NaOH (10 ml) solution, then extracted with DCM, the organic layer was washed with 1M HCl (2×10ml), and then with water several times, and dried over anhydrous Na_2SO_4. The solvent was remove under vacuum, and the crude product was purified over silica gel column [ethyl acetate/n-hexane=1:2.5 (v/v)] to give 1.8 g (S)-α-methyl benzyl alcohol as colourless oil (yield 98.5%, 99%ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (3H, d, CH_3), 2.04 (1H, br. s), 4.85 (1H, q, CH), 7.26-7.38 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 70.5, 125.5, 127.8, 128.6, 145.7.[146]

GC condition for the analysis of (R, S)-α-methyl benzyl alcohol:
Inlet temperature: 150 ^{o}C; detector temperature: 150 ^{o}C;
Column: Varian Chrompack CP-Chiral-Dex CB (25.0m×250μm×0.25 μm);
Oven temperature: Isothermal, 120 ^{o}C for 35mins;
Inlet pressure: 14 psig;
Retention time of alcohol enatiomers:
(S)-α-methyl benzyl alcohol: 20.6mins;
(R)-α-methyl benzyl alcohol: 23.6mins.

1.2.12 Preparation of (S)-α-methyl benzyl chloride (Scheme 42)



Scheme 42

A 25 ml vessel with ice-bath was charged with thionyl chloride (1.2 g, 10 mmol) and 10ml DCM or n-hexane, (S)-α-methyl benzyl alcohol (0.61g, 5 mmol, 99%ee) in 5 ml DCM was added dropwise with caution so that the reaction temperature remained below 0 ^{o}C and the reaction mixture agitated vigorously and was under argon during whole process. After adding of alcohol, the reaction temperature was allowed to reach the ambient temperature. The reaction completed after the reaction mixture agitated vigorously at room temperature for an hour. The solvent was removed under vacuum to give a colourless liquid (0.57, 81% yield, 40.1%ee) as crude product. The crude product was used directly without further purification.[147] The enantiomeric excess of chloride was independent on the reaction solvent used. The stability of the chloride was monitored by GC, the results shows that the chloride is stable at room temperature, no decomposition or racemisation was observed after days at room temperature. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92 (3H, d, CH), 5.16 (1H, q, CH_3), 7.28-7.51 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.6, 58.9, 126.6, 128.3, 128.6, 142.9; MS (EI, 70 eV): *m/z* (%) = 140 (M^+, 48.7), 125 (25.2), 105 (100), 77 (39.8), 63, (9.7), 51 (22.1).

GC conditions for the analysis of (R, S)-α-methyl benzyl chloride:
Inlet temperature: 120 ^{o}C; detector temperature: 120 ^{o}C;
Column: Varian Chrompack CP-Chiral-Dex CB (25.0m×250μm×0.25 μm);
Oven Temperature: Isothermal temperature fixed at 100 ^{o}C for 20 mins;
Inlet pressure: 14 psig;
Retention time of the chloride enantiomers:
(S)- α-methyl benzyl chloride: 12.1mins;
(R)- α-methyl benzyl chloride: 11.5mins.

GC condition for the analysis of (R, S)-α-methyl benzylamine:

Inlet temperature: 100 ^{o}C; detector temperature: 100 ^{o}C;

Column: Varian Chrompack CP-Chiral-Dex CB (25.0m×250μm×0.25 μm);

Oven Temperature: Isothermal temperature fixed at 100 ^{o}C for 35 mins;

Inlet pressure: 10 psig;

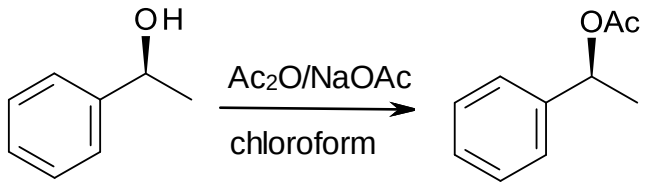
Retention time of the amine enantiomers:

(S)- α-methyl benzylamine: 29.16mins;

(R)- α-methyl benzylamine: 30.02mins.

The structures of amines were confirmed by authenticated samples and GC-MS.

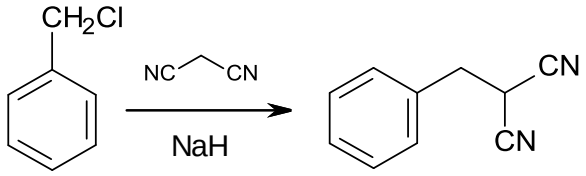
1.2.13 Preparation of (S)-α-methylbenzyl acetate (Scheme 43)



Scheme 43

To a 50ml 3-neck round bottom flask was charged chloroform (25 ml) and (S)-α-methylbenzyl alcohol (1.25 g 10 mmol), acetic anhydride (1.53 g, 15 mmol) and ammonium acetate 1 mmol. The reaction was held at 75 ^{o}C for about 40 hours, until all the alcohol was consumed. (GC was used for the monitoring the progressing of the reaction). The reaction mixture then treated with saturated $NaHCO_3$, extracted with DCM. Organic layer was died over anhydrous Na_2SO_4, and solvent was removed under vacuum to give 1.2g colourless liquid (73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (d, 3H), 2.10 (s, 3H), 5.90 (q, 1H), 7.28(s, 1H), 7.29-7.36 (m, 1H), 7.38 (d, 3H);[148] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 22.3, 72.3, 126.1, 127.9, 128.5, 141.7, 170.4;[149] MS (EI, 70 eV): *m/z* (%) = 164.0 (M^+, 27.9), 122.0 (100), 105.0 (75.2), 104.0 (96.5), 77.0 (34.1), 43.0 (35.4).

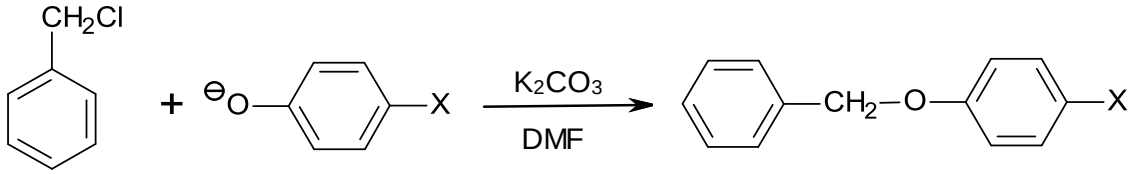
1.2.14 Preparation of 2-benzylmalononitrile (Scheme 44)



Scheme 44

Malononitrile (0.87 g, 13 mmol) and benzyl chloride (1.1 g, 8.7 mmol) were dissolved in 20ml THF with stirring at room temperature, NaH (0.53 g, 13 mmol, 60%w/w in mineral oil) was added in portions. The temperature was increased to 65 ^{o}C and held for 4 hours. After washing with water, then extracted with DCM (3 × 20ml), the organic layer was dried over anhydrous Na_2SO_4, and solvent was removed under vacuum. The residue was purified using a flash column (DCM/hexane = 6:1) to give 0.91g (45% yield) as colourless prisms. Melting point: 89-90 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): 3.38(d, 2H), 5.15(t, 1H), 7.36-7.46(m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.8, 35.0, 114.6, 128.4, 129.3, 129.8, 135.2.[150] MS (EI, 70 eV): *m/z* (%) = 156.0 (M^+, 15.0), 91.1 (100), 77.1 (4.0), 65.1 (13.3), 77.0 (3.5), 5 1.1 (6.2).

1.2.15 Preparation of 4-substituted phenyl benzyl ether (Scheme 45)



X = Cl, OMe, Me, CN, NO_2, COOMe, ^{t}Bu

Scheme 45

Benzyl chloride (10 mmol) was dissolved in DMF (25 ml) with stirring, and the 4-substitttuted phenoxide (10 mmol) and K_2CO_3 (2.0 g, 14 mmol) were added, the mixture was stirred at 80 ^{o}C for 12 hours. The reaction mixture was poured into ice-water (50 ml), the precipitate were filtered and washed with water. The filtrate was extracted with DCM (3×15ml) and the organic layer was combined and washed with water until no DMF could be detected by GC.

The organic layer was dried over anhydrous Na_2SO_4, solvent was removed under vacuum, and the solid residue recrystallised from ethanol/water (1:1) twice before used as standards.

4-methylphenyl benzyl ether: 1.7 g white solid (86% yield), melting point: 41-42 ^oC; [151] ^1H NMR (400 MHz, $CDCl_3$): 2.29(s, 3H), 5.05 (s, 2H), 6.87(d, 2H), 7.09(d, 2H), 7.31-7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 70.1, 114.8, 127.4, 127.9, 128.7, 129.3, 129.8, 130.2, 137.3, 157.0.[151]

4-chlorophenyl benzyl ether: 1.8 g white solid (83% yield), melting point: 72-73 ^oC;[152] ^1H NMR (400 MHz, $CDCl_3$): 5.04 (s, 2H), 6.89 (d, 2H), 7.23(d, 2H), 7.31-7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 70.1, 116.2, 125.7, 127.4, 128.0, 128.7, 129.3, 136.5, 157.9.[151]

4-methoxyphenyl benzyl ether: 2.0 g white solid (92% yield), melting point: 68-70 ^oC;[153] ^1H NMR (400 MHz, $CDCl_3$): 3.77 (s, 3H), 5.01 (s, 2H), 6.75-6.93 (m, 4H), 7.31-7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7, 70.6, 114.6, 115.8, 127.6, 127.8, 128.6, 137.6, 152.9, 153.1, 154.[151]

4-cyanophenyl benzyl ether: 1.7 g white crystal (72% yield), melting point: 92-92.5 ^oC (very sharp);[154] ^1H NMR (400 MHz, $CDCl_3$): 5.14 (s, 2H), 7.03-7.06 (d, 2H), 7.36-7.48 (m, 5H), 7.59-7.62 (d, 2H); [155] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 70.3, 104.2, 115.6, 119.3, 127.5, 128.5, 128.8 ,134.1, 135.7,162.0.[156]

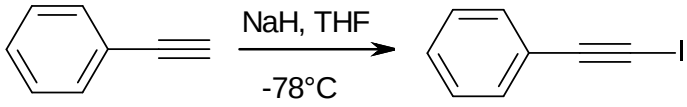
4-*tert*-butylphenyl benzyl ether: 1.8 g white powder (76% yield), melting point: 62-63 ^oC;[157] ^1H NMR (400 MHz, $CDCl_3$): 1.29(s, 9H), 5.04 (s, 2H), 6.87 (d, 2H), 7.27-7.34 (m, 5H), 7.41(d, 2H);[158] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6, 37.6, 69.6, 114.8, 127.3, 127.7, 128.3, 129.0, 129.6, 130.1, 137.5, 156.5.

4-carbomethoxyphenyl benzyl ether: 1.7 g white crystal (71% yield), melting point: 99.5-100 ^oC (sharp);[159] ^1H NMR (400 MHz, $CDCl_3$): 3.86(s, 3H), 5.10 (s, 2H), 7.00 (d, 2H), 7.31-7.46 (m, 5H), 7.98(d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.3, 71.1, 114.6, 122.7, 127.5, 129.1, 131.6, 136.3, 162.5, 166.9.[160]

4-nitrophenyl benzyl ether: 1.6 g yellowish solid (70% yield), melting point: 106-107 ^{o}C;[161] ^{1}H NMR (400 MHz, $CDCl_3$): 5.18(s, 2H), 7.04 (d, 2H), 7.38-7.42 (m, 5H), 8.23(d, 2H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 70.6, 114.8, 125.9, 127.5, 128.5, 128.9, 135.5, 141.7, 164.1.[156]

1.2.16 Preparation of (iodoethynyl)benzene (Scheme 46)[162]



Scheme 46

Phenylacetylene (520 mg, 5 mmol) was dissolved in THF (5 ml) at -10 ^{o}C with a cooling bath, and, with vigorous stirring, NaH (240 mg, 60%wt in mineral oil, 6 mmol) was added and the reaction temperature was further lowered down to -78 ^{o}C. A solution of iodine (1.0 g, 8 mmol) in THF (15 ml) was added dropwise at -78 ^{o}C, and then the temperature was allowed to rise to ambient and the mixture left overnight for 14 hours. The reaction mixture was poured into saturated $Na_2S_2O_3$ solution (35ml), extracted with diethyl ether (3×15ml) and the organic layer dried over anhydrous Na_2SO_4. Solvent was removed under vacuum, and the residue was purified on a flash column (DCM/n-hexane = 4:1) to give 430mg (38% yield) yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.25-7.31 (m, 3H), 7.38-7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.6, 94.6, 123.8, 129.1, 132.7.[163] MS (EI, 70 eV): *m/z* (%) = 228.0 (M^+, 100), 175.9 (3.5), 126.9 (5.3), 101.1 (24.8), 75.1 (26.5), 5 1.1 (8.8).

2. Pressure equipments

Note: Use of these pressure equipments with liquid ammonia must follow the safety protocols which are described in the Appendix D: Safety Protocols.

2.1 Glassware design

2.1.1 Ammonia tank (B) and burette (C)

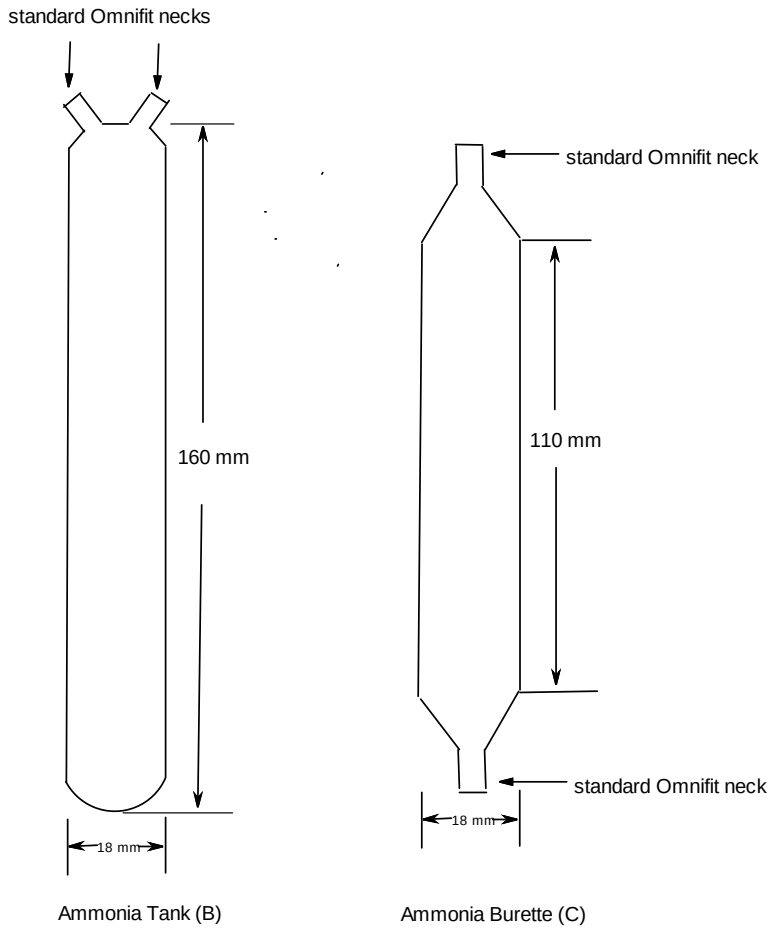


Figure 7 The design of ammonia tank (B) and burette (C)

The ammonia tank (B) and burette (C) were made of glass by a professional glassware company (HGL Ltd., Southampton, UK). The ammonia tank was uncalibrated has a volume capacity of about 40ml, while that for burette is about 30 ml. The burette was calibrated and had a minimum volume unit of 0.5 ml. All the necks had a standard Omnifit® which allows

connection to standard Omnifit® valves, connectors and septa. Both B and C were pressure tested up to 35 bar (**Figure 7**).

2.1.2 Reaction vessel (D)

The reaction vessel (D) also was made of glass and has a volume capacity of 15 ml. It has 2 Omnifit® necks and a standard GL14 neck which can be fitted with a GL14 lid (the GL14 lid has a PTFE coated silicone rubber septa which is inert to the attack from ammonia).

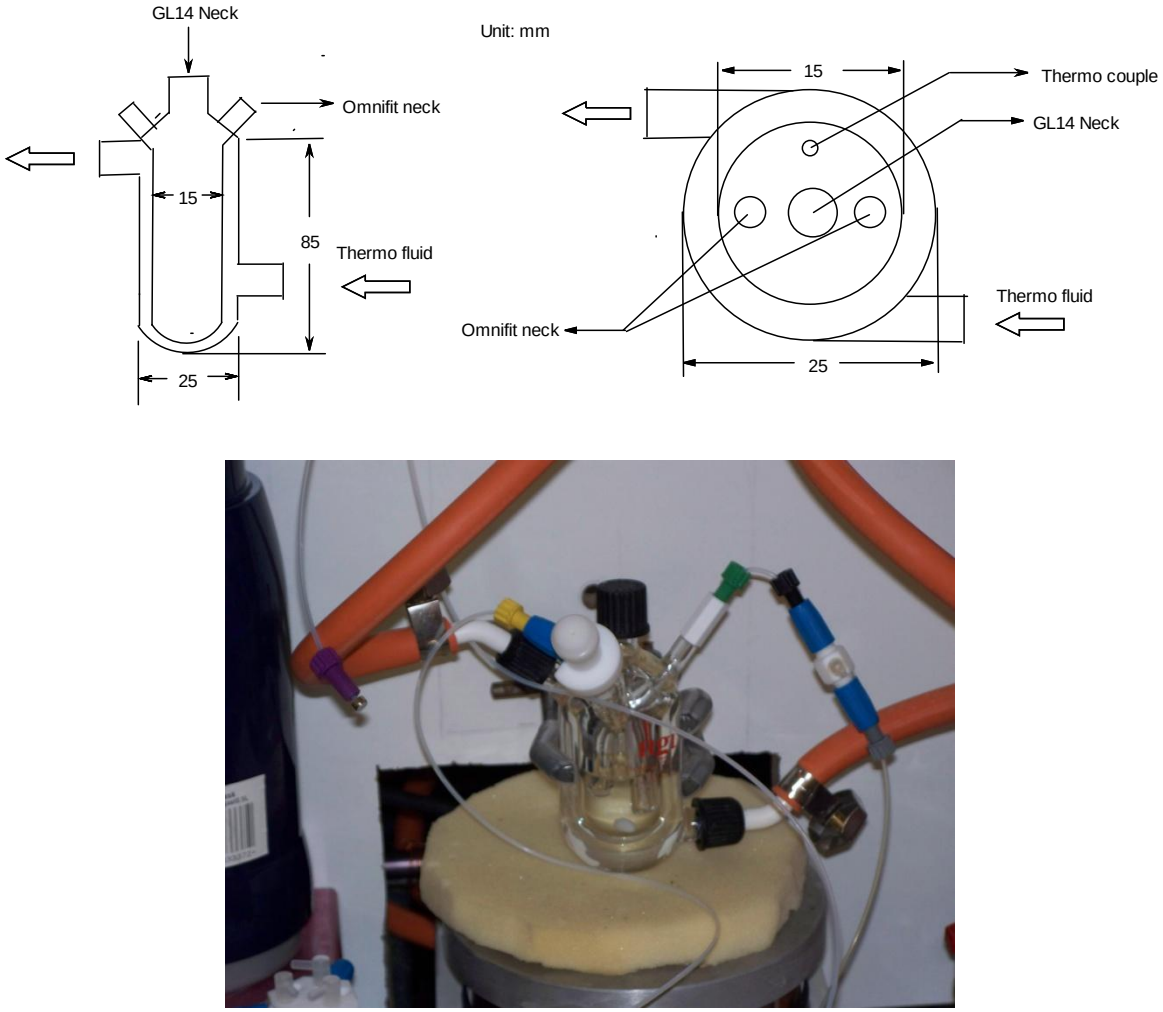


Figure 8 The design of reaction vessel (D).

The reaction vessel also has a jacket which allows connecting with thermo regulators. The vessel was pressure tested up to 35 bar and the maximum working temperature of the reactions in the vessel was 45 ^{o}C. The Omnifit® necks allow the reaction vessel (D) connects to

Omnifit® valves, septum and tubing, Swagelok connections, ammonia burette (C), pressure UV-cell, IR-cell, and pressure NMR tube (**Figure 8**).

2.2 Pressure glassware set-up

As shown in **Figure 9**, ammonia cylinder (A) is connected to ammonia tank (B) through Omnifit® connectors and PTFE tubing (1/16 inch O.D.), which condenses ammonia gas from A into B which is cooled by dry-ice or liquid nitrogen. Then liquid ammonia in B is warmed to room temperature and is transferred from B to ammonia burette (C) by opening and closing the Omnifit® valves. The burette (C) is connected to the reactor (D) through several Omnifit® 3-way and 2-way valves in order to keep the pressure balanced between the reactor and the burette during the liquid ammonia transfer from (C) to (D), thus the required amount of liquid ammonia then can be accurately dispensed from (C) to (D).

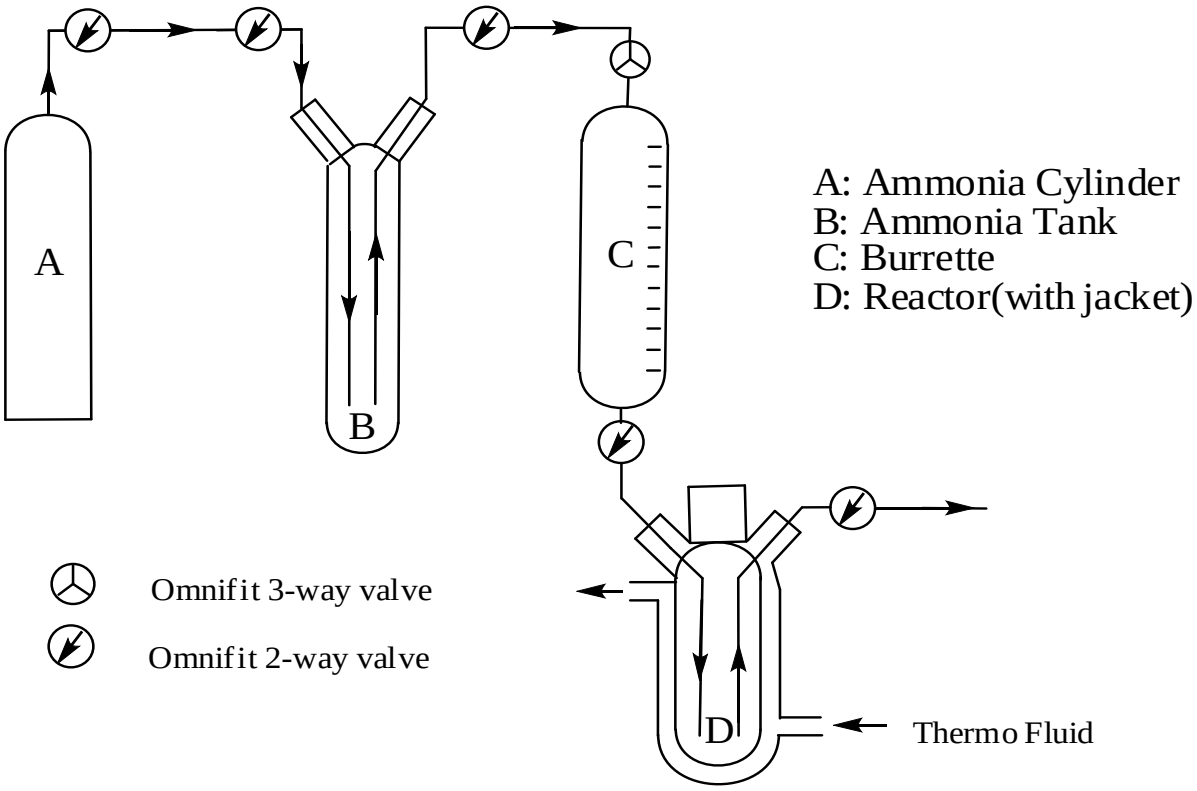


Figure 9 Diagram of the set-up of pressure equipment for the studies in liquid ammonia. B, C and D are fixed into a 60 × 40 cm wooden board by clamps. B and C are placed inside a wooden protection box with a Perspex sheet as front window and a protection sheet is placed in front of D when A is charged with liquid ammonia. The maximum working temperature allowed for the system is 45 ^{o}C (18 bar).

2.3 Pressure UV cells and NMR tubes

2.3.1 Pressure UV cells

Pressure UV cells were based on a design by Gill and were on loan from Syngenta. (**Figure**

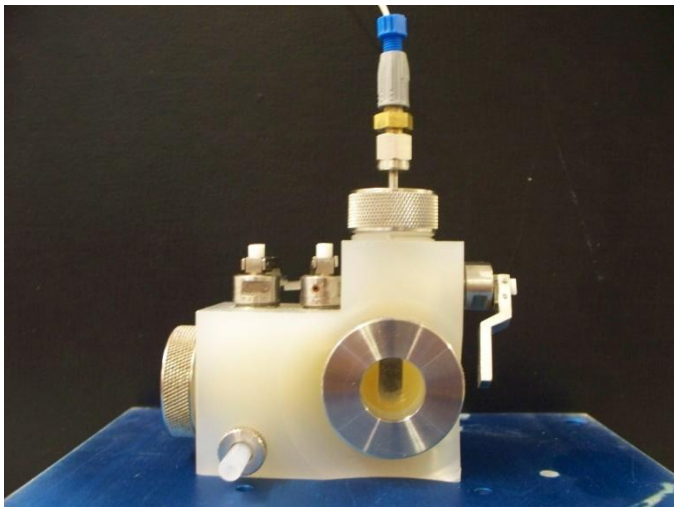


Figure 10 A picture of pressure UV cell

10).[164] The body of the pressure UV cell is made of PTFE, and with an inlet and outlet controlled by Kel-F valves, the windows of the UV cell are made from CaF_2, the path length between two windows is 10mm. The top of the UV cell has a standard Swagelok which can be connected to the Omnifit® valves, thus the cell can be connected with D (**Figure 8**) and allows the liquid ammonia solution to be transferred from D to the cell.

2.3.2 Pressure NMR tubes

Pressure NMR tube rated to 200 psi (14 bar) was purchased from Wilmad-Lab Glass® with an O.D. of 5mm, a tube length of 7 inches and was the thin-walled (0.38mm) model which was specially designed for 500Hz NMR instruments (Model 522-PV-7).[165] The top inlet valve of the pressure NMR tube has a standard Swagelok connection which allows the connection to Omnifit® valve, thus ammonia solution can be transferred from the pressure vessel (D) to the tube (**Figure 11**).

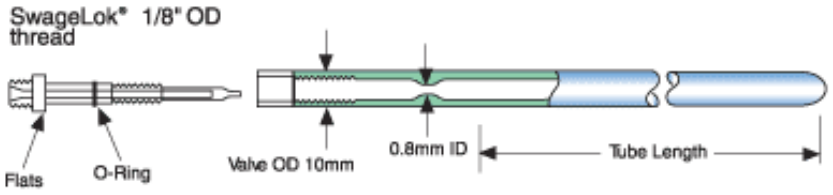


Figure 11 A diagram of pressure NMR tube

2.3.3 Pressure syringe

Pressure syringe was from SGE which has a total volume capacity of 1ml, the minimum volume unit of the syringe is 0.01 ml. The top of the pressure syringe has a standard Swagelok fitting and a gas tight PTFE on/off valve that enables to connect with various apparatus, such as pressure reaction vessels (D), UV cells and NMR tubes. Frequently it was used to inject one

Figure 12 A picture of high pressure syringe

of ether solutions of the reactant into the pressure vessel (D) through an Omnifit® septum, therefore it also equipped with a special side-hole needle which has a length of 71 mm and an O.D. of 1.07mm. The pressure syringe was pressure rated to 500 psi (33 bar) (**Figure 12**).

2.4 Pressure tube reactors

Several pressure tube reactors were made from standard 1/4 inch O. D. Swagelok stainless steel tubing (316L seamless, ammonia resistant), the length of these tube reactors was varied from 10-20cm. Both ends of these reactors had standard Swagelok fittings which can be sealed with Swagelok caps. These tube reactors had been tested to be able to hold pressure up to 1200 bar by the provider. Due to requirements form the Swagelok Fittings Protocols, the individual reactor only can be used under pressure for 10-15 times. The working temperature for these reactors was from 50-110 ^{o}C. Due to liquid ammonia has a very high coefficient of expansion with temperature, great care must be taken to avoid overfilling these pressure tube reactors. Ammonia expands by 20% on heating from 25 ^{o}C to 100 ^{o}C (volumetric coefficient of expansion for liquid ammonia is 2.45×10^{-3} K^{-1}, the largest among some common liquids).

3. Instruments

3.1 Thermo regulator

Thermo regulator was a Huber-Unistat Tango Nuevo which enables the temperature control of pressure vessel (D) accurately (±0.01 ^{o}C) in a range of -40-200 ^{o}C. The instrument has a Pt-100 thermo sensor which can be used as a temperature probe to measure the actual temperature difference between thermo fluid and reaction vessel. The temperature control also can be monitored by the computer. Normally the temperature that required for the investigation kinetics in liquid ammonia is range between -10- 45 ^{o}C.

3.2 Analytical instruments

GC instrument was an Agilent 7980, the column for general kinetic study was an Agilent J&W Scientific 19091J-433 HP5 (30 m × 0.25 mm × 0.25 μm); the column for the chiral product analysis was a Varian Chrompack CP-Chiral-Dex CB (25 m × 250μm × 0.25 μm). The general GC analysis conditions were:

Injection and detector temperature were 250 ^{o}C. Carrier gas was helium at constant pressure 14 psi, GC oven started at 50 ^{o}C for 1.5mins then ramped with a temperature increasing rate of 20 ^{o}C/min to 280 ^{o}C and held the temperature for 2 mins.

GC-MS was an Agilent 6980 with a 5973 MS selective detector (EI, 70 eV), the column was an Agilent J&W Scientific DB-1701(30m × 0.25mm × 0.25μm), the general GC-MS analysis condition:

Injection and detector temperature were 250 ^{o}C. Carrying gas was helium at constant pressure 8 psi, GC oven started at 50 ^{o}C for 1.5mins then ramped with a temperature increasing rate of 20 ^{o}C/min to 280 ^{o}C and held the temperature for 2 mins.

HPLC instrument was an Agilent 1200 series with a fraction collector for purification and products of interest. The column used for general kinetic investigation was an Agilent Zorbax Extend C-18 (4.6 mm × 150 mm × 5μm). The general HPLC condition:

Mobile phase: 75% methanol/25% water, flow rate was 1ml/min, the column temperature was set at constant 30 ^{o}C, and the UV detector was normally set at 254 nm and 365 nm.

UV-Vis instrument was a Varian Cara 300 series and the pressure cells were fitted inside by modification of the chamber.

Melting points were obtained from a Mettler Toledo DSC (STAR SW 9.01) instrument.

NMR Instruments were Bruker Avance DPX 400 and 500 MHz NMR spectrometers.

4. General procedures

4.1 Kinetics

4.1.1 Nucleophilic substitution

Generally, the kinetic measurement for nucleophilic substitution reactions in liquid ammonia were carried out under pseudo first order conditions. The concentration of nucleophile was at least 10 times greater than those for substrates. Ether solutions of substrates, for example, benzyl chloride, 4-nitrofluorobenzne, etc., were prepared firstly. Normally, the concentration of these ether solutions was 0.5 M or 1 M and 0.1-0.2 ml of these solutions was injected into

10 ml liquid ammonia, therefore all the kinetic measurements were made in liquid ammonia containing 1-2% (v/v) diethyl ether. Normally nucleophiles were pre-charged in the reaction vessel (D), together with internal standard, for example, biphenyl or ethyl phenyl ether, etc. Generally, 10ml liquid ammonia was released from burette (C) to reaction vessel (D), and the concentration of nucleophiles was varied from 0.1M to 1M. With the temperature control from thermo regulator and vigorous stirring, liquid ammonia solution was allowed to equilibrate with system temperature for 1 hour before the diethyl ether solution of substrate was injected through the pressure syringe. The sample (0.5 ml) was released into a 3 ml sample vial at the required time interval by opening and closing two way Omnifit® valves, and the reaction was stopped with quenching agent, such as saturated NH_4Cl solution, 1M HCl or 1M NaOH, depending on the nature of the reaction. The aqueous solution was extracted with 1-2ml DCM or toluene, the organic layer was separated, dried over anhydrous Na_2SO_4, and analysed by GC, or HPLC. The peak area of starting material and product acquired from GC or HPLC instrument were normalised against the peak area of internal standard (**Equation 4**). The reaction profiles were obtained by plotting the normalised area against time by Microsoft Excel.

$$\text{Normalised area} = \frac{\text{Peak area of reactants or products}}{\text{Peak area of internal standard}}$$

Equation 4

The data then transferred to the commercial data fitting software, such as Berkeley Madonna or Scientist 3.0,[166] and the pseudo first order rate (k_{obs}) was obtained by following both starting material and product through data fitting. **Table 11**, **Figures 13** and **14a, b** give a typical example of data processing and fitting.

Table 11 The GC area and normalised area for the reaction between 0.01 M 4-NFB and 0.1 M sodium phenoxide in liquid ammonia at 25 ^{o}C (I = 0.2M $NaNO_3$)[a]

time (mins)	area 4-NFB	area product	area IS	NA 4-NFB	NA product
0	2238.4	0	2373.1	0.943	0
0.33	133.5	20.8	159.7	0.836	0.130
0.67	149.6	42.5	190.9	0.784	0.223
1.0	129.7	58.1	179.0	0.725	0.325
1.5	106.7	77.0	163.7	0.652	0.470
2.0	116.7	121.3	203.5	0.573	0.596
2.5	103.4	149.6	207.1	0.499	0.722
3.0	125.8	224.6	271.5	0.463	0.827
5.0	95.9	345.8	305.9	0.314	1.130
7.0	79.4	503.3	365.8	0.217	1.376
10.0	33.6	481.2	305.0	0.110	1.578
15.0	9.9	459.2	265.1	0.037	1.732
20.0	4.0	558.6	312.6	0.013	1.787
31.0	0	591.2	329.6	0	1.794

[a] IS = internal standard; NA = normalised area.

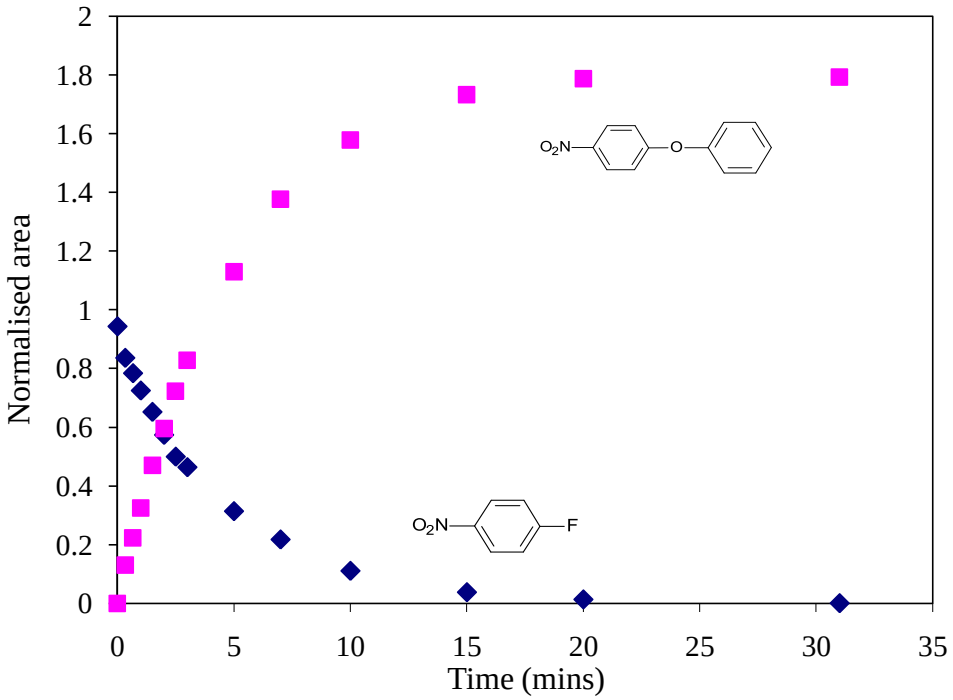


Figure 13 Reaction profile for the reaction between 0.01 M 4-NFB and 0.1 M sodium phenoxide in liquid ammonia at 25 ^{o}C (I = 0.2 M $NaNO_3$)

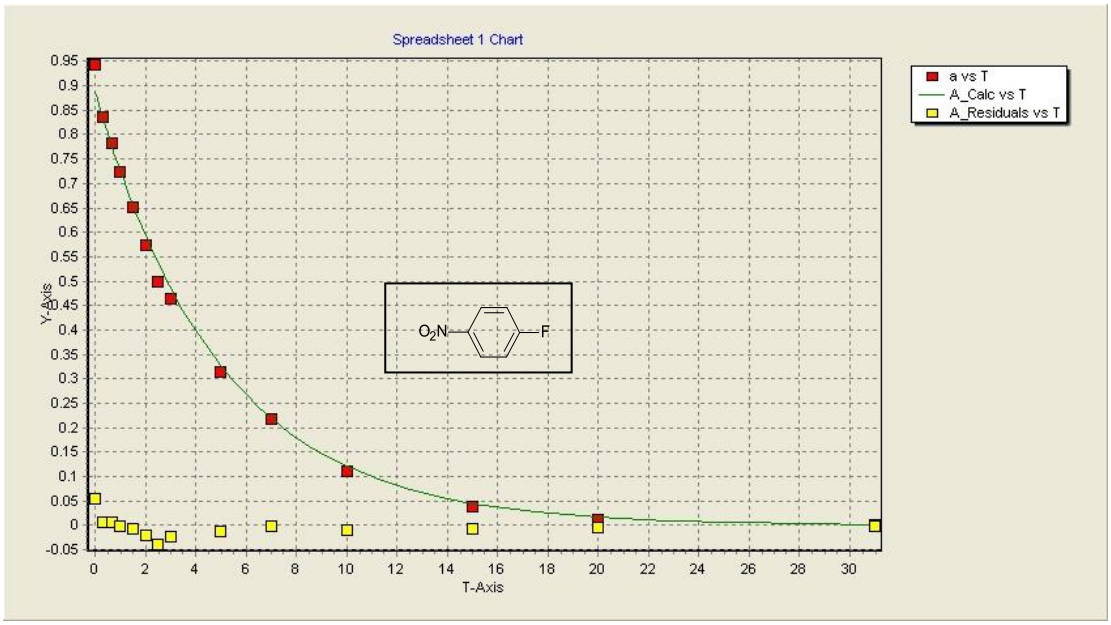


Figure 14a Scientist 3.0 data fittings for the reaction between 0.01 M 4-NFB and 0.1 M sodium phenoxide in liquid ammonia at 25 ^{o}C (I = 0.2M $NaNO_3$), following the decreasing of 4-NFB.

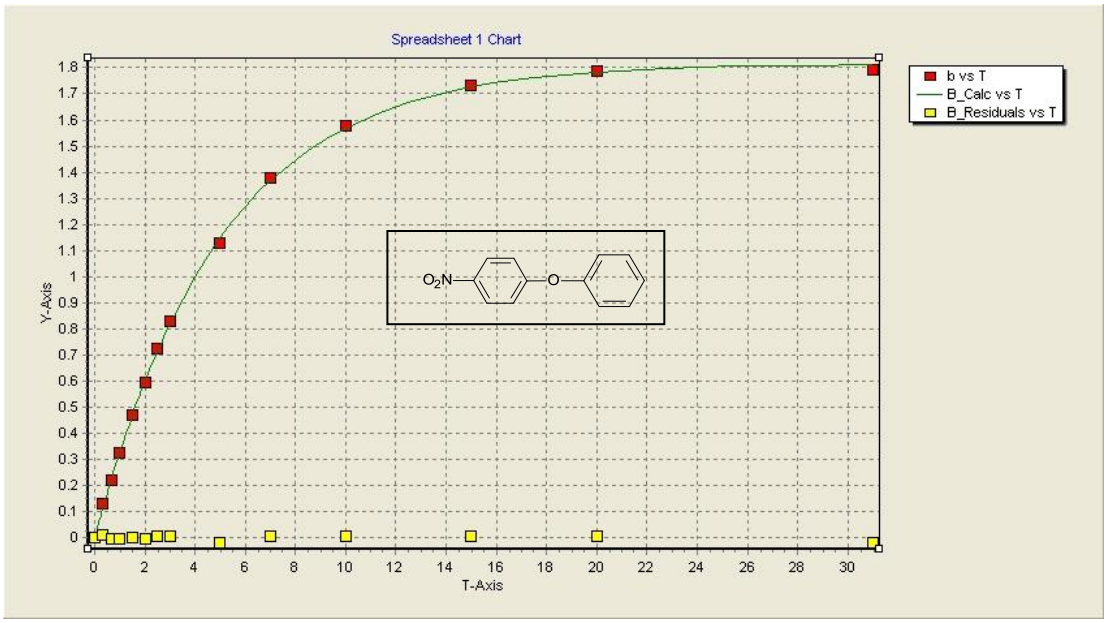
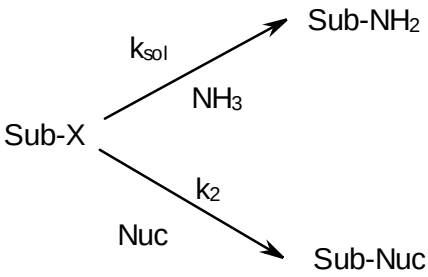


Figure 14b Scientist 3.0 data fittings for the reaction between 0.01 M 4-NFB and 0.1 M sodium phenoxide in liquid ammonia at 25 ^{o}C (I = 0.2M $NaNO_3$), following the increasing of 4-nitrophenyl phenyl ether.



Scheme 47

$$-d[Sub]/dt = k_{obs}[Sub]$$

$$-d[sub]/dt = k_{sol}[NH_3][Sub] + k_2[Nuc][Sub]$$

$$k_{obs} = k_{sol}[NH_3] + k_2[Nuc]$$

$$k_2 = \frac{k_{obs} - k_{sol}[NH_3]}{[Nuc]}$$

Equation 5

Due to the background solvolysis of substrate (**Scheme 47**), the second order rate constant of nucleophilic substitution reaction (k_2) was obtained from the slope of pseudo first order (k_{obs}) against concentration of nucleophile ([Nuc]), or calculated based on pseudo first order (k_{obs}), the concentration of nucleophile ([Nuc]) and background solvolysis rate (k_{sol}) according to **Equation 5**.

Because the rates of some reactions were too fast to be accurately measured by sampling method, for example, pseudo first order reaction between thiophenoxide and benzyl chloride, or the reaction samples which could not be satisfactorily quenched, for example, the reactions between 4-nitrofluorobezene, benzyl chloride and secondary cyclic amines, the kinetic of these reactions were acquired by a competition method, so the rate constants were obtained

$$\frac{\text{Mole of nucleophilic product}}{\text{Mole of solvolysis product}} = \frac{k_{sol}[NH_3]}{k_2[Nuc]}$$

Equation 6

from the molar ratio of products through the product analysis (**Equation 6**). If the background solvolysis rate is so slow compared with nucleophilic substitution rates, for example, solvolysis rate of 4-NFB is negligible compared with nucleophilic substitution

$$\frac{\text{Mole of nucleophilic product 1}}{\text{Mole of nucleophilic product 2}} = \frac{k_{2,Nuc1}[Nuc_1]}{k_{2,Nuc2}[Nuc_2]}$$

Equation 7

reaction rate of 4-NFB with phenoxides, alkoxides, therefore, the rates of some very fast reactions, such as thiophenoxide with 4-NFB, can be measured by referencing to the known nucleophilic substitution reaction rates according to **Equation 7**. Rates measured by the competition method were the average of at least 3 individual runs.

4.1.2 Solvolysis

General procedure for the solvolysis was similar to that described for nucleophilic substitution. The substrates were prepared as standard diethyl ether solutions and injected into reaction vessel (D) which was pre-charged with 10 ml of liquid ammonia and internal standard. The samples were quenched with 1M NaOH and extracted with DCM or toluene, the organic layer was dried over anhydrous Na_2SO_4 and analysed by general GC or HPLC methods. The substrate concentration was varied from 0.01M to 0.02 M, and the solvolysis rate is independent of substrate concentration due to constant concentration of ammonia.

The kinetics of some relatively slow reactions, for example, solvolysis of 4-NFB, were measured by both sampling and UV methods. The concentrations of substrates in UV kinetic study were range from 2.5×10^{-5} M to 5×10^{-4}M depending on the molar extinction coefficient of the substrate. The initial rate of solvolysis reaction was obtained according **Equation 8**, where A: absorbance of reactant or product; ε_{max}: the molar extinction coefficient at maximum absorbance wavelength; C_0: the initial concentration of the substrate.

$$k_{sol} = \Delta A/(\varepsilon_{max}\Delta t \bullet C_0)$$

Equation 8

4.2 Ionisation of phenols by UV-Vis study

Standard solution of phenols (0.05M or 0.1M) were prepared in ether, then 50-100 μL of this solution was injected into the pressure vessel (D) using a SGE syringe. If adjustment of the ionic strength was required, the salt was also pre-charged in the vessel. With stirring, 10 ml of liquid ammonia was released from burette (C) and the liquid ammonia solution was left to equilibrate at room temperature for 1 hour. Then the solution was transferred into the pressure UV cell. The UV spectra of phenols in acidified, basified water and ether were also acquired and compared with these in liquid ammonia. The concentration range of phenol was from 10^{-5} M to 10^{-3}M depending on the absorbance intensity of the phenol. The UV spectra were recorded at ambient temperature with the dual beam method and the absorbance of phenol was relative to the solvent blank.

4.3 Ionisation of amines, carbon acids by NMR study

A liquid ammonia solution of amine or carbon acid was prepared as described above, the concentration of substrate being in the range 0.1M to 1M. A small amount of deuterated standard (2.5%) such as DMSO-d_6, toluene-d_8, or benzene-d_6 was also added to the solution to provide a the deuterium lock, the solution was transferred into a pressure NMR tube, and the NMR spectrum was recorded in a Bruker 500 MHz NMR (125 MHz for carbon) instrument. For the study of ionisation of carbon acids, in order to confirm the deprotonation, a known amount of acetonitrile, THF or benzene was added in the liquid ammonia solution as the internal reference. The NMR spectra of amines and carbon acids were also recorded in normal deuterium solvent, normally D_2O, $CDCl_3$ and DMSO-d_6, and compared with these in liquid ammonia. In some cases, strong base was required to deprotonate the carbon acid, so the NMR solvent was HMPT with benzene-d_6 as deuterium lock. In the case of weak quaternary carbon signal, a small amount of shiftless relaxation reagent $Cr(acac)_3$, was added in order to shorten the spin-lattice relaxation times (T_1) of quaternary carbon nuclei.[167] Proton and carbon chemical shifts were on the δ scale relative to DMSO (δ_H = 2.50 ppm, δ_C = 39.50 ppm) or benzene (δ_H = 7.36 ppm, δ_C = 128.30 ppm) as internal standards. ^{19}F NMR chemical shift was relative to $CFCl_3$ (δ_F = 0.00 ppm) as reference. The NMR spectra in normal solvents were acquired from a Bruker 400 MHz NMR instrument.

4.4 Copper (I) catalysed amination of aryl halides and 1,3-dipolar cycloaddition

A thick walled GC sample vial (2 ml total volume capacity, from Agilent) was pre-charged with copper salt and the required amount of reactants and additives. The vial was pre-cooled in a cold bath (ethanol slurry, -35 to -50 ^oC), then 1ml liquid ammonia was released into the vial carefully, and the vial was quickly sealed with an aluminum cap which has a strong and inert PTFE septa. Without stirring, the vial was allows to rise to ambient temperature and kept in a protection jar. After the required time interval, the vial was cooled with liquid nitrogen and decapped, upon the vapourisation of ammonia, the reaction mixture was treated with 1M NaOH then extracted with DCM or toluene, the organic layer was dried over anhydrous Na_2SO_4, and analysed by general GC or HPLC methods. The high temperature reactions, for example, copper catalysed amination of aryl bromides and chlorides at 100 ^oC or higher, were performed in the pressure tube reactors, and the procedure was similar to those introduced

above. The heating apparatus was a GC oven (Agilent 5890) which can accurately control the temperature for those reactions that require high temperature conditions (normally range from 50-120 ^{o}C) in liquid ammonia.

1. Acidity and spectral studies of compounds in liquid ammonia Page

1.1 UV-Vis studies

Due to the difficulties of easily handling liquid ammonia without the necessary pressure equipment at room temperature, the studies on the UV-Vis spectra of organic compounds in liquid ammonia above its boiling point are rare. However, UV investigations of liquid ammonia solutions of alkali metals below ammonia boiling point have been widely studied.[168] Being a good electron donor but with limited ability to form hydrogen bonds, liquid ammonia affects UV-Vis spectra of organic compounds showing very different shapes, wavelengths of maximum absorption and intensities from other solvents. For example, the UV spectrum of 4-nitrophenol in liquid ammonia shows a large bathochromic shift of λ_{max} from its ether solution due to ionisation (**Figure 1.1**).

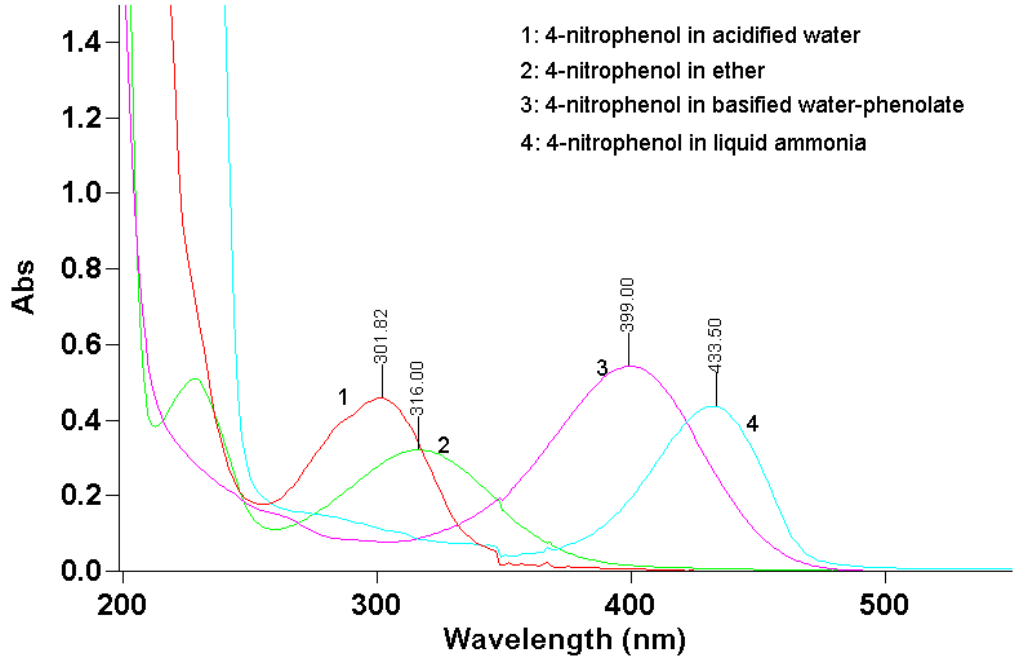


Figure 1.1 UV absorbance of 4-nitrophenol in different solvents at room temperature, pH = 1 for acidified water, pH = 13 for basified water.

1.1.1 UV-Vis spectra of aromatic nitro compounds

The dielectric constant of liquid ammonia is quite different from that for water and the extinction coefficients of compounds are generally greater in liquid ammonia compared with those in water and also ether under the similar conditions, although the maximum wavelength of absorption of some nitrobenzene derivatives changes little on going from water to liquid ammonia (**Table 1.1**).

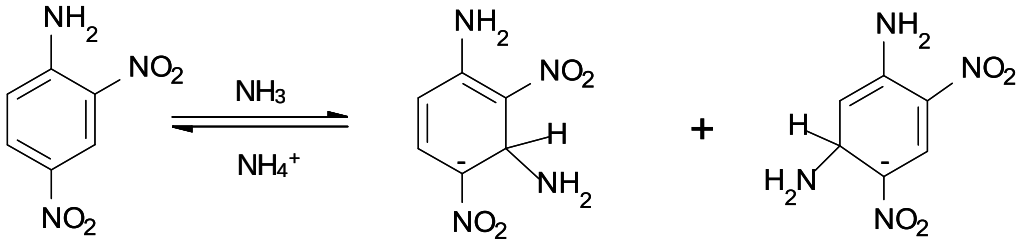
Table 1.1 Molar extinction coefficients (ε_{max}) and wavelength of maximum absorbance (λ_{max}) of nitrobenzene compounds in LNH_3 compared with ether at room temperature

compound	λ_{max}(nm)		ε_{max}($M^{-1}cm^{-1}$)	
	ether	LNH_3	ether	LNH_3
2-NFB	282	295	3000	5150
4-BFB	260	267	6950	8350
2-nitroaniline	358	410	3900	4100
4-nitroaniline	348	386	13700	14200
2-NAB	393	413	5850	5900
4-NAB	304	383	10350	3500
2,4-dinitroaniline	378	537	4600	6100
1,3-dinitrobenzene	300	555	1350	3950

The compounds in **Table 1.1** are either stable in liquid ammonia or their solvolysis rates in liquid ammonia at room temperature are relatively slow. The wavelength of absorption maximum of 4-NFB, 4-nitroaniline and 4-NAB is significantly shorter than the corresponding ortho analogue and may indicate a stronger resonance effect from the ortho nitro group, which decreases the energy gaps between the ground and excited states. Conversely the extinction coefficients are greater for the para-isomers. The absorption spectra of 1,3-dinitrobenzene and 2,4-dinitroaniline in liquid ammonia show several absorptions (257, 353, 387, 537 nm), which are more complicated than those in ether and water (220 and 300 nm). One possible interpretation is that 2,4-dinitroaniline is attacked by a solvent molecule to form stable a Meisenheimer σ-complexes (**Scheme 1.1**), which are written as anions rather than zwitterions, as we have shown that the aminium ions exist as free bases in liquid ammonia.[219b]

The formation of Meisenheimer σ-complexes between highly activated benzenes and a nucleophile is well known, and has been shown spectroscopically,[169] including NMR.[170]

Generally speaking, the UV-Vis absorption of a typical Meisenheimer σ-complex is in a range between 450-600 nm,[171] but sometimes fall in the range of the visible spectrum (380-750 nm)



Scheme 1.1

and therefore often colour is observed during the formation of the adducts. 10^{-5} to 10^{-4}M Liquid ammonia solution of 1,3-dinitrobenzene appears a pink red colour, while that of 2,4-dinitroaniline is dark green at room temperature. The absorption of 2,4-dinitroaniline at 537 nm thus can be assigned to one or both of the intermediates (**Scheme 1.1**). The similar absorption at 555 nm for 1,3-dinitrobenzene also can be regarded as due to a Meisenheimer σ-complex. There is no new product formed after vapourisation of liquid ammonia solution of 2,4-dinitroaniline and 1,3-dinitrobenzene and it appears that the Meisenheimer σ-complex is formed rapidly but reversibly and removal of the ammonia solvent results in its reversion to starting material. The stable Meisenheimer σ-complexes of electron deficient arenes have been previously demonstrated in liquid ammonia,[172] however, in the presence of a strong base,[173] i.e., $NaNH_2$, or a strong oxidation agent,[174] i.e., $KMnO_4$, the decomposition of intermediates occurs to yield the amination product in liquid ammonia.

1.1.2 Ionisation of phenols

$$HA + NH_3 \underset{}{\overset{K}{\rightleftharpoons}} A^- + NH_4^+$$

Equation 1.1

Liquid ammonia is a basic solvent with a very low self-ionisation constant (pK = 27.6 at 25 ^oC) and the ionisation of acids in this solvent generates equivalent amounts of the conjugate base and the ammonium ion (**Equation 1.1**). The low dielectric constant of liquid ammonia indicates that most ionic species will be strongly associated in this solvent and conductivity

data shows that ion-pairing occurs even at low concentrations and probably larger aggregates form at higher concentrations.[175] There have been several methods used to determine ionisation and dissociation constants of acids in liquid ammonia including spectroscopic, conductivity and NMR,[176] however, to our knowledge, there has been no systematic evaluation of substituent effects on any one class of acids. We are interested in the relationship between ionisation constants in liquid ammonia compared with other solvents and their variation with substituents to aid the interpretation of linear free energy relationships in liquid ammonia (*vide infra*).

1.1.2.1 Ionisation without salt effect

The λ_{max} and ε_{max} of some phenols in liquid ammonia at room temperature are compared with those in ether, basic and acidic water, (**Table 1.2**) and the results show the expected bathochromic shift and intensified absorption upon ionisation.

Table 1.2 Molar extinction coefficients (ε_{max}) and wavelengths of maximum absorbance (λ_{max}) of phenols in LNH_3 at room temperature

phenol	pK_a[a]	λ_{max} (nm)				ε_{max} ($M^{-1}\cdot cm^{-1}$)			
		Et_2O	H_2O pH=1	H_2O pH=13	LNH_3	Et_2O	H_2O pH=1	H_2O pH=13	LNH_3
4-methoxyphenol	10.21	290	287	306	296	2650	2800	2780	3530
phenol	9.99	274	270	287	275	1980	1370	2600	2340
4-chlorophenol	9.20	283	285	294	287	1833	1890	2150	1885
3-chlorophenol	9.02	276	274	292	279	2215	1850	2835	2440
4-carbomethoxyphenol	8.47	251	255	295	319	25050	20360	28010	28200
3-nitrophenol	8.35	346	340	398	440	2320	2210	3930	4210
4-cyanophenol	7.95	244	243	274	298	16450	17220	22710	35200
2,4-dibromophenol	7.79	287	285	307	331	4240	3360	5670	4260
2,4-dichlorophenol	7.65	286	283	305	325	4880	3120	4850	6240
3,5-dichlorophenol	7.51	282	279	297	320	3265	2295	4425	5470
5-methyl-2-nitrophenol	7.41	282	295	417	441	8765	4275	6004	9640
2-nitrophenol	7.23	272	278	418	444	7410	5985	4620	9140
4-nitrophenol	7.14	302	316	399	434	13165	9155	15990	39060

[a] Aqueous pK_a, ref.177.

The λ_{max} of phenol and 3-chlorophenol are similar to those in acidified water, while those for 4-cyano, 3,5-dichloro, 2-nitro, 4-nitrophenol exhibit large bathochromic shifts along with intensified absorption and are similar to the corresponding spectra in basified water. The

difference in the wavelength of maximum absorption, $\Delta\lambda_{max}$, between that in acidic water and liquid ammonia increases dramatically when the corresponding aqueous pK_a of phenol drops below 8 (**Figure 1.2**). This clearly indicates that phenols with aqueous $pK_a < 7.0$ are fully ionised in liquid ammonia at room temperature, but not those with $pK_a > 8.5$. It is also worth noting that the molar extinction coefficients of the phenolate ions are, except for 2,4-dibromophenol, significantly greater in liquid ammonia compared with those in water. For examples, phenols with electron-withdrawing group at *para* position normally have greater extinction coefficient, such as shown by 4-nitro, 4-cyano and 4-carbomethoxyphenol. Interestingly, although both *ortho, meta* and *para*-nitrophenol are fully ionised in liquid ammonia, the molar extinction coefficients are very different in the order *para* >> *ortho* > *meta*.

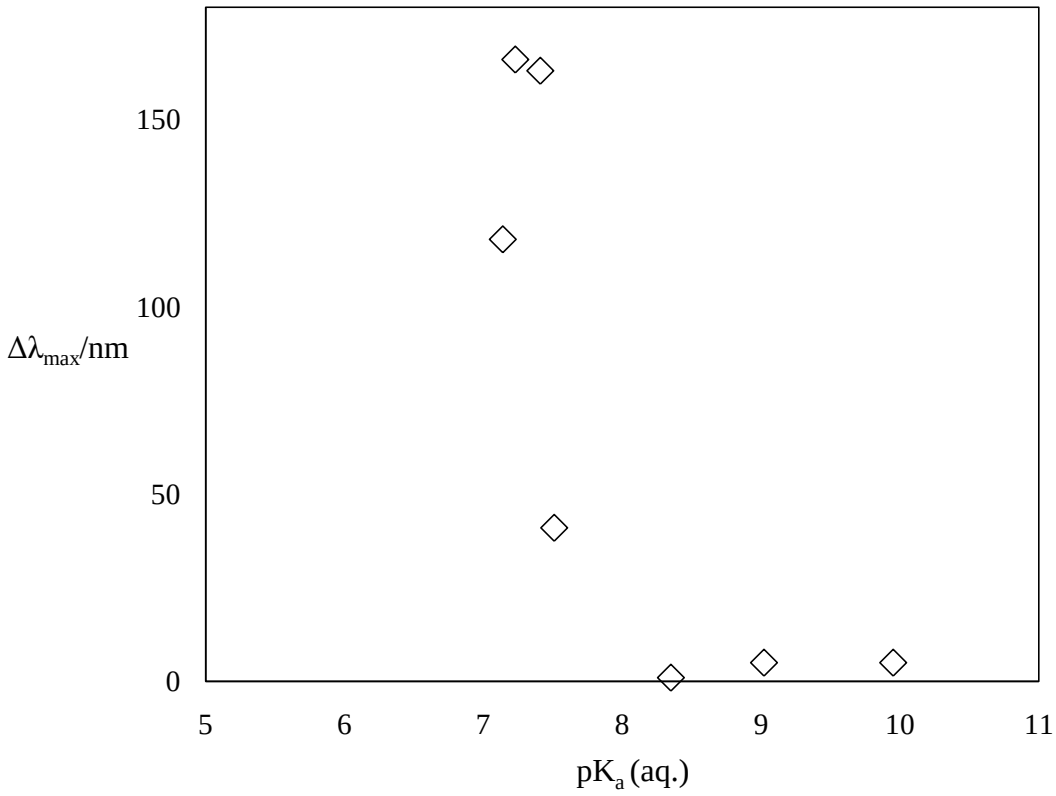


Figure 1.2 A plot of the bathochromic shift ($\Delta\lambda_{max}$) of phenols in acidified water (pH = 1) and liquid ammonia against the corresponding aqueous pK_a of the phenol. ($\Delta\lambda_{max} = \lambda_{max,\ LNH3^-} - \lambda_{max,\ acidified\ water}$).

1.1.2.2 Ionisation of phenols with added salts

1.1.2.2a. Measurement of the apparent pK_a of phenols

Salt effects on the ionisation of acids in solution are well known, as salts can influence the activity coefficients of the solutes thus changing the ionisation and dissociation process.[178] Normally the acidity of acids increases with the ionic strength of the medium. In liquid ammonia, the UV spectra of phenols change with the ionic strength with respect to the positions of the absorption bands, the peak shapes and intensities. For example, the absorption of 4-chlorophenol at λ_{max} (326 nm) increases gradually with the increasing concentration of added $KClO_4$ (0 to 0.6M) in liquid ammonia, and finally reaches a maximum which does not increase by further added salt (**Table 1.3**, **Figures 1.3** and **1.4**). This phenomenon suggests that under sufficient ionic strength, the phenol can be forced to fully ionise in liquid ammonia, and so the molar extinction coefficient of fully ionised species can be determined.

Table 1.3 The absorbance of 4-chlorophenol (10^{-4} M) at λ_{max} (326 nm) with various salt concentrations (I = 0 to 0.6M, $KClO_4$) in liquid ammonia at 25 ^{o}C

I **($KClO_4$)/M**	**absorbance (326nm)**
0	0.0561
0.05	0.155
0.1	0.222
0.2	0.281
0.3	0.304
0.5	0.305
0.6	0.309

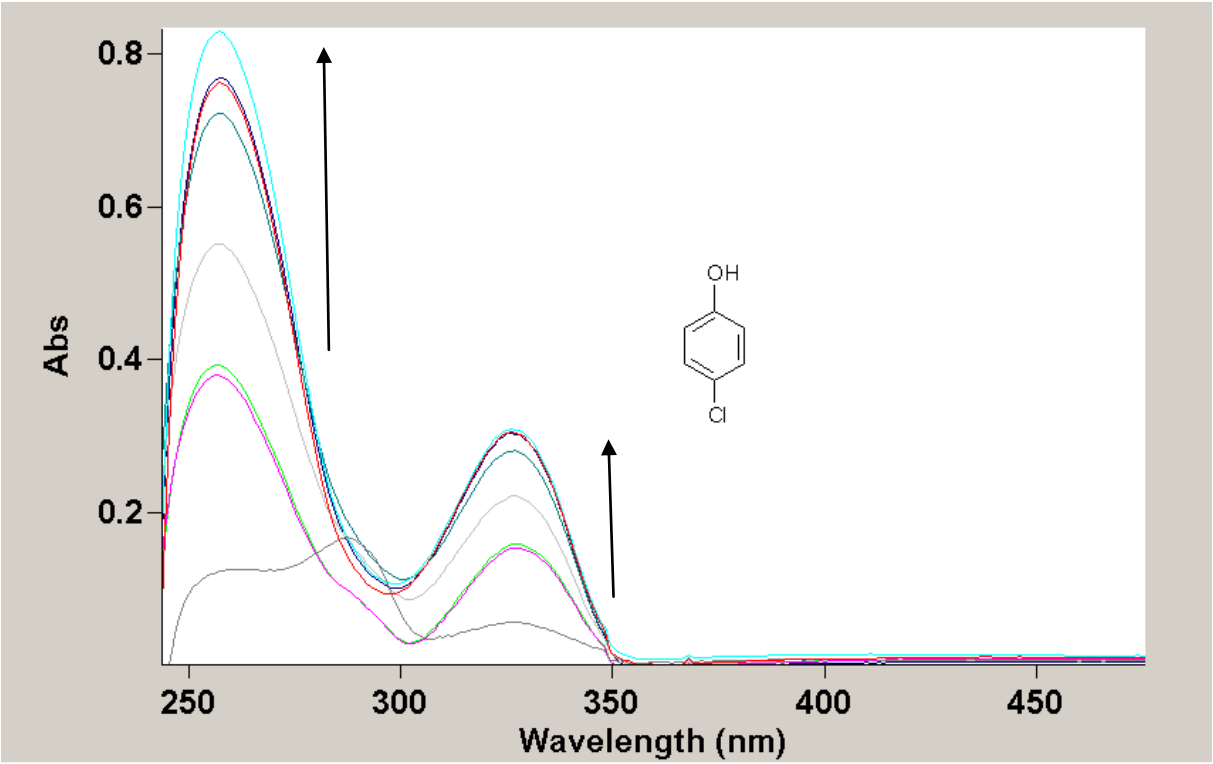


Figure 1.3 The absorbance of 4-chlorophenol (10^{-4}M) increases at λ_{max} (326 nm) with increasing concentrations of added salt ($KClO_4$, I = 0 to 0.6M) in liquid ammonia at room temperature and reaches a maximum.

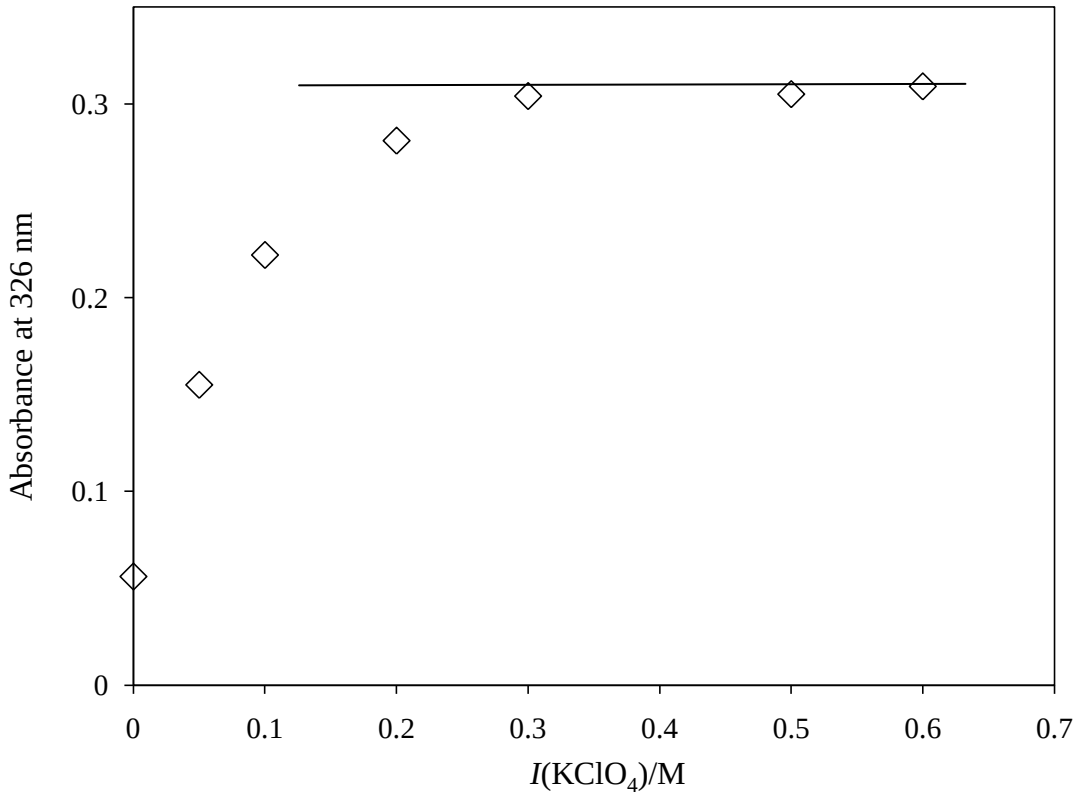


Figure 1.4 The absorption of 4-chlorophenol at λ_{max} (326 nm) as a function of added salt ($KClO_4$) in liquid ammonia at room temperature.

Furthermore, the saturation absorbance of phenol is independent of nature of salt, for example, 3-chlorophenol (10^{-4}M) can be forced into fully ionised species with NaCl or $KClO_4$ in liquid ammonia and reaches the same saturation absorbance (Appendix A: **Tables A1** and **A2**, **Figures A1** to **A4**).

The sensitivities of the change in absorbance to ionic strength vary with the aqueous pK_a of the phenol. The salt effect on the UV absorbance of phenols becomes more pronounced when the aqueous pK_a of phenol is closer to 8.5. For example, the absorption of 4-nitrophenol (aqueous pK_a = 7.14) does not change with added salt, even under relative high salt concentration (Appendix A: **Figure A5a**), while those for 3- and 4-chlorophenol (aqueous pK_a = 9.02 and 9.20 respectively) are very sensitive to the added salt in liquid ammonia (*vide supra*). This is compatible with phenols of aqueous $pK_a < 8$ being already fully ionised in the absence of added salt.

Using these observations and extinction coefficients of the substituted phenoxide ions, and the absorbance at λ_{max} in liquid ammonia, the apparent ionisation constant for phenol (pK_a) under different concentration of added salt can be calculated, taking the activity coefficients ($\gamma_{+,-}$) at low concentrations as unity (**Equation 1.2**).

$$pK_a = -\log \frac{[PhO^-][NH_4^+]}{[PhOH]}$$

Equation 1.2

Empirically, a reasonable linear relationship is found between these constants and the square root of the ionic strength ($I^{1/2}$) and this allows an estimate of the apparent pK_a for substituted phenols at zero ionic strength (**Table 1.4**, for details see: Appendix A: **Tables A3** to **A9**; **Figures A5** to **A11**).

Table 1.4 Apparent pK_a of some phenols in LNH_3 at room temperature

phenol	**pK_a in water** [a]	**pK_a in LNH_3 ($I = 0$)**
4-methoxyphenol	10.27	6.62
phenol	9.99	6.02
1-naphthol	9.37	4.97
4-chlorophenol	9.20	4.69
3-chlorophenol	9.02	4.50
4-carbomethoxy phenol	8.47	4.04
3-nitrophenol	8.36	3.61
4-nitrophenol	7.14	1.10

[a] Aqueous pK_a value is from reference 177.

Interestingly, there is a linear relationship between these apparent pK_a values and the corresponding aqueous ones with a slope of 1.68 (**Figure 1.5**). This compares with similar plots of the acidity constants in other solvents, for example, those in dipolar aprotic solvents acetonitrile and DMSO, against the corresponding values in water give slopes of 2.00 and 1.84,[179] respectively (**Figure 1.5**, Appendix A: **Tables A41** and **A42**), and these slopes are very different from those in protic solvents such as methanol, which gives a slope of 1.15

(Appendix A: **Table A43** and **Figure A25**).[180] The 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 delocalization through the substituent. The similarity of slopes for apparent pK_a of phenols in liquid ammonia, DMSO and acetonitrile against that in water indicate that liquid ammonia behaves like a dipolar aprotic solvent in its effects upon ionisation of organic acids.

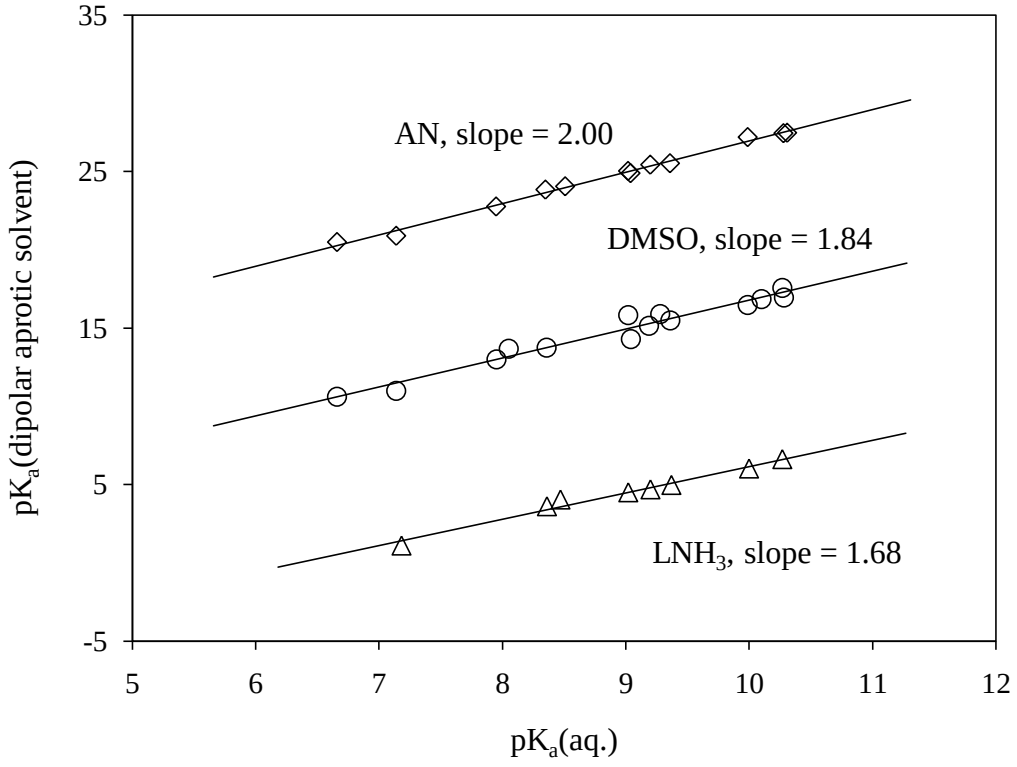


Figure 1.5 Plots of the pK_a of phenols in liquid ammonia (LNH_3), DMSO and acetonitrile (AN) against the corresponding aqueous pK_a

1.1.2.2b. Separation of ionisation and dissociation constant

The apparent pK_a of phenols as described above are actually the product of the two constants K_i, for ion pair formation, and K_d, for dissociation to the free ions (**Scheme 1.2** and **Equation 1.3**). The degree of dissociation is dependent on the concentration of ammonium ions and the

$$ArOH + NH_3 \overset{K_i}{\rightleftharpoons} [\,ArO^- NH_4^+\,]_{ip} \overset{K_d}{\rightleftharpoons} ArO^- + NH_4^+$$

$$K_i = \frac{[\,ArO^- NH_4^+\,]_{ip}}{[ArOH]} \qquad K_d = \frac{[NH_4^+]\ [ArO^-]}{[\,ArO^- NH_4^+\,]_{ip}}$$

Scheme 1.2

$$\text{Apparent } pK_a = -\log(K_i \bullet K_d)$$

Equation 1.3

addition of the latter generally decreases the UV absorption of the phenoxide ion which then levels out when only the ion-pair is present. At higher concentrations of ammonium ions, the absorbance then increases again in line with that expected from the ionic strength effect

$$Abs. = \frac{K_i(K_d + [NH_4^+])}{[NH_4^+] + K_i(K_d + [NH_4^+])} \cdot \varepsilon \cdot [ArOH]_t$$

Equation 1.4

described earlier. The values of K_i and K_d can be approximated from **Equation 1.4**, where $[ArOH]_t$ is the total amount of phenol present, and if it is assumed that the extinction coefficients of the phenoxide ions are the same for the ion pair and the free ion.[181] For example, the absorbance of 5.0×10^{-5}M 4-carbomethoxyphenol, which is about 70% ionised in liquid ammonia, decreases markedly with even small concentrations of NH_4Cl (up to 0.05M) and then levels out but the absorbance subsequently increases with further increasing NH_4Cl concentrations (up to 0.2M). Interestingly, the absorbance increases with higher NH_4Cl concentrations is not as marked as seen with other salts (**Figure 1.6**), similar observations were found with 4-nitrophenol (Appendix A: **Table A12, Figure A14**). The rapid decrease in absorbance at low concentration of ammonium ions is due to the suppression of the dissociation step (Appendix A: **Table A10, Figure A12**), while later slower increase at higher

NH_4^+ concentrations can be regarded as a general salt effect increasing ionisation but which is counterbalanced by the specific ion effect on dissociation.

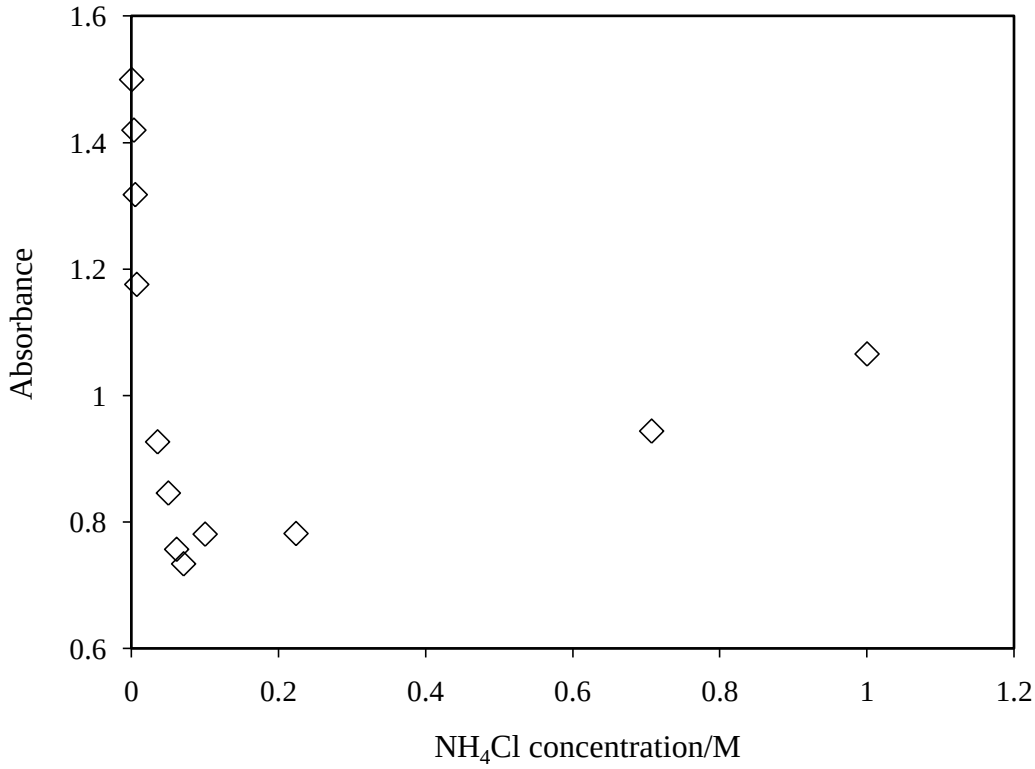


Figure 1.6 Change in absorbance at 315nm of 4-carbomethoxy phenol (5×10^{-5}M) with NH_4Cl in liquid ammonia at room temperature

At the minimum of absorption, presumably there is no free phenoxide ion in solution and all phenoxide ions are ion-paired with NH_4^+. Based upon this assumption and together with the mass balance of the process and molar extinction coefficient of the ionised species, a model can be established to separate the K_i and K_d by data fitting in Excel (for the detailed model building and derivations, see Appendix B: **Derivation 1**). It is also necessary to assume that the extinction coefficient is the same for the phenoxide ion whether it is in the ion-pair or 'free' and that it is independent to the nature of its counter ion. A similar titration of phenols by NH_4Cl but under constant ionic strength (I = 0.2M, NaCl) in liquid ammonia showed that phenoxide absorbance decreased more slowly than with just ammonium chloride and varying ionic strength, although the minimum absorbance is the same (Appendix A: **Tables A10** to **A13, Figures A12** to **A15**).

The dissociation constant K_d for the equilibrium between the ion-pair and free ions increases with ionic strength, whereas the ionisation constant K_i is almost independent (**Table 1.5**) and it appears that the effect is greater for the weaker acid. At low ionic strength (I<0.2M), K_i >> K_d, which indicates that ionised phenols mainly exist as ion pairs in liquid ammonia at room temperature, and is consistent with relatively low dielectric constant of liquid ammonia. However, the dissociation constant of the ion-pair to the free ions, K_d, is very dependent on

Table 1.5 The equlibium constants K_i and K_d of some phenols in liquid ammonia at room temperature

phenol	C_{phenol}	K_d		K_i	
		no ionic strength control	(I=0.2M, NaCl)	no ionic strength control	(I=0.2M, NaCl)
4-cabomethoxyphenol	5×10^{-5}M	1.2×10^{-4}M	5.0×10^{-2}M	0.65M^{-1}	0.63M^{-1}
4-nitrophenol	2.5×10^{-5}M	1.5×10^{-2}M	0.11M	5.6M^{-1}	1.9M^{-1}

the ionic strength of the medium, the difference between K_i and K_d decreases with increasing salt concentration, so that a significant amount of phenoxide ion exists as the 'free' ion.

For 4-nitrophenol at I = 0.2M (NaCl), K_i = 1.9M^{-1} and K_d = 0.11M whereas at low ionic strength (the concentration of ammonium ion added varying from 0 to 5×10^{-3}M) K_i = 5.6M^{-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 (**Equation 1.3**), in good agreement with the value of 1.10 obtained by extrapolation to zero ionic strength (**Table 1.5**). The linear relationship between the apparent pK_a of phenols in liquid ammonia and those in water (**Figure 1.5**) probably reflects a good correlation between K_d and the aqueous pK_a.

The suppression of the concentration of free phenoxide ion by adding ammonium salts is also reflected in the kinetics of their reactions as reported in the following sections. The half life of the pseudo first order reaction between phenoxide and benzyl chloride is significantly increased by adding small amount of NH_4Cl in the reaction system, and no reaction at all is observed if the NH_4Cl concentration is very high.

Attempts to measure the ionisation of aminium ions by examining the effect on the UV absorbance by adding amines to phenols in liquid ammonia were unsuccessful. For example, adding 0.1M triethylamine or piperidine to 3-chlorophenol (1mM) showed less than 5% increase in absorption at the λ_{max} of the phenoxide ion, indicating that the pK_a of triethylammonium ion in liquid ammonia is < -1 (Appendix B: **Derivations 2**).

1.2 NMR studies in liquid ammonia

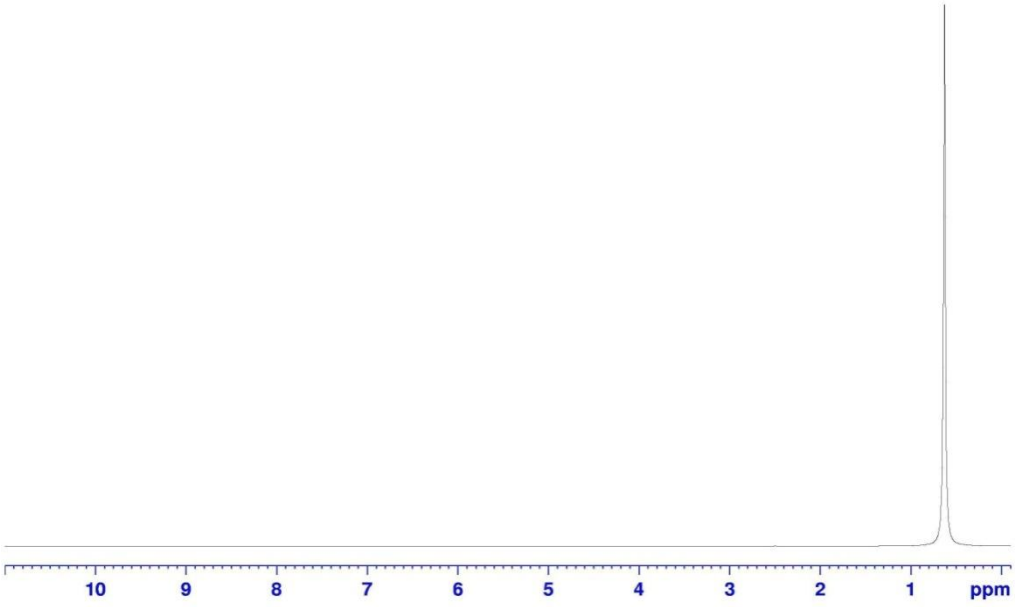


Figure 1.7 ^{1}H NMR spectrum of ammonia blank at room temperature (500 MHz)

^{1}H NMR studies to investigate the ionisation of organic compounds in liquid ammonia are not new,[182] but are rare, especially at room temperature, again probably due to equipment availability. Another reason maybe the assumption is that the ammonia solvent peak would be very large and broad, which would limit the scope of ^{1}H NMR spectrum in liquid ammonia. However, although the ^{1}H NMR spectrum of liquid ammonia solvent at room temperature (**Figure 1.7**) does show a large ammonia singlet peak at 0.65 ppm (referenced to DMSO-d_6, δ = 2.50 ppm), it is surprisingly sharp and the downfield region is very clean. However, due to the large solvent peak, any compound with a chemical shift below 1.00 ppm may be difficult to identify but ^{1}H NMR spectra in liquid ammonia still can be useful for the majority of

organic compounds. The ^{1}H NMR spectra of 0.1M and 1M NH_4Cl solution show that solvent peak shifted downfield to 0.70 and 1.0 ppm (**Figure 1.8**), respectively, but still a sharp singlet as expected.

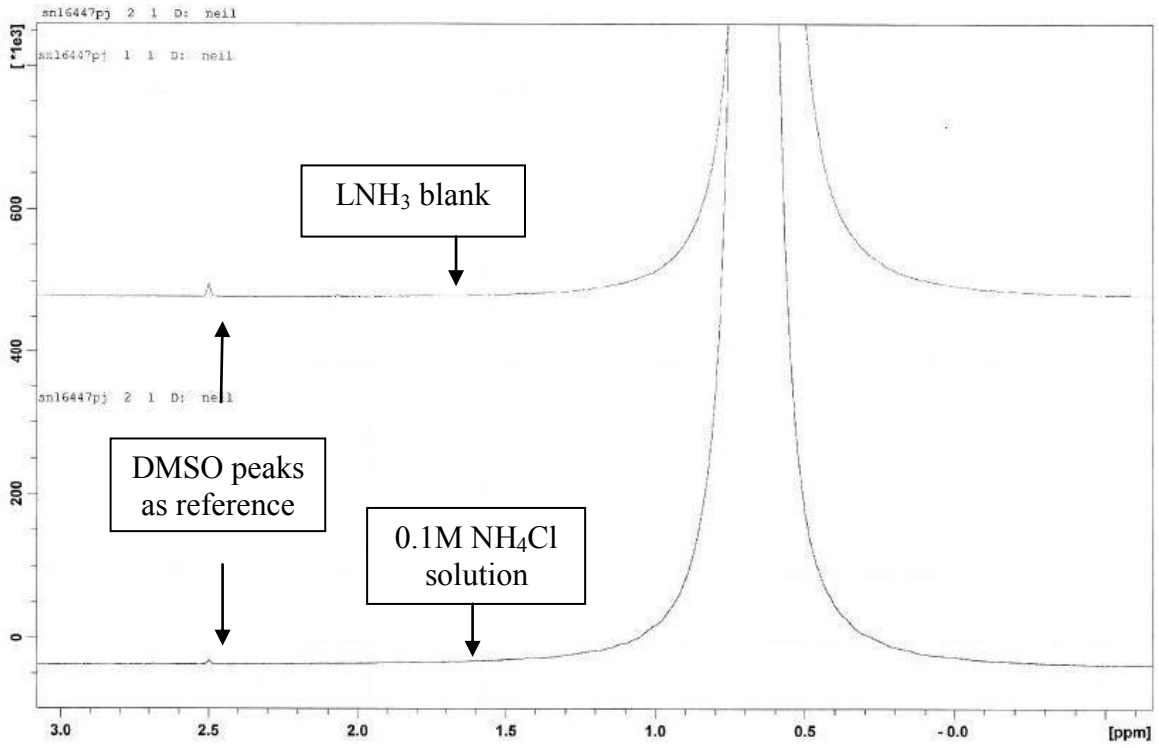
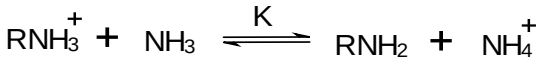


Figure 1.8 The superimposition of the ^{1}H NMR spectra of ammonia blank and 0.1M NH_4Cl liquid ammonia solution at 25 ^{o}C

1.2.1 Ionisation of aminium salts

The ionisation of aminium ions in liquid ammonia were investigated using ^{1}H NMR at 25 ^{o}C. The control spectra were the chemical shift differences of the protonated and free base forms of the amine seen in other solvents. For example, 0.1M trifluoroethylamine hydrochloride (aqueous pK_a = 5.8) in liquid ammonia shows the same ^{1}H NMR spectrum as the free base indicating that it is fully deprotonated. Surprisingly, 0.1M benzylamine hydrochloride (aqueous pK_a = 9.33) and 1M piperidine hydrochloride (aqueous pK_a = 11.27) also show the same ^{1}HNMR spectrum as their free bases indicating that they also are fully deprotonated in liquid ammonia (**Tables 1.6**, **1.7** and **1.8**, Appendix C: **Figures N1** to **N7**). These observations agree with the UV-Vis studies of mixtures of phenols and amines which showed that amines



Equation 1.5

do not deprotonate phenols in liquid ammonia. The equilibrium for the dissociation of aminium ions in liquid ammonia (**Equation 1.5**) must lie well over to the right, suggesting that ammonia solvent stabilises the ammonium ion (NH_4^+) more than the aminium ions (RNH_3^+), or put another way, in liquid ammonia, ammonia is a much *stronger* base than other amines, which is different from the situation in water.

Table 1.6 ^{1}H NMR shift of trifluoroethylamine and trifluoroethylamine hydrochloride in DMSO-d_6 and in liquid ammonia at 25 ^{o}C

	trifluoroethylamine	**trifluoroethylamine hydrochloride**
DMSO-d_6	δ 3.13(q, 2H)	δ 3.17(q, 2H)
LNH_3	δ 3.15(q, 2H)	δ 3.18(q, 2H)

Table 1.7 ^{1}H NMR shift of benzylamine, benzylamine hydrochloride and triethylbenzylammonium chloride in DMSO-d_6 and in liquid ammonia at 25 ^{o}C

	benzylamine	**benzylamine hydrochloride**	**triethylbenzylammonium chloride**
DMSO-d_6	δ 3.71(s, 2H), 7.11-7.37(m, 5H)	δ 4.00(s, 2H), 7.32-7.53(m, 5H)	δ 1.30(t, 9H), 3.20(q, 6H), 4.59(s, 2H), 7.47-7.58(m, 5H)
LNH_3	δ 3.69(s, 2H), 7.12-7.26(m, 5H)	δ 3.69(s, 2H), 7.14-7.29(m, 5H)	δ 1.36(t, 9H), 3.20(q, 6H), 4.69(s, 2H), 7.49-7.62(m, 5H)

Table 1.8 ^{1}H NMR shift of piperidine and piperidine hydrochloride in DMSO-d_6 and in liquid ammonia at 25 ^{o}C

	piperidine	**piperidine hydrochloride**
DMSO-d_6	δ 2.64(t, 4H), 1.36-1.54(m, 6H)	δ 2.96(t, 4H), 1.52-1.71(m, 6H)
LNH_3	[a] δ 2.61(t, 4H), 1.35-1.41(m, 6H)	[a] δ 2.59(t, 4H), 1.34-1.41(m, 6H)
LNH_3	[b] δ 2.61(t, 4H), 1.35-1.43(m, 6H)	[b] δ 2.57(t, 4H), 1.31-1.38(m, 6H)

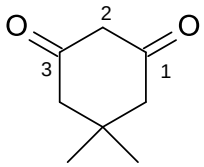
[a] 0.1M. [b] 1M.

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 (*vide infra*).

1.2.2 Ionisation of carbon acids

Several conventional carbon acids with different aqueous pK_a are studied in liquid ammonia by ^1H and ^{13}C NMR at 25 ^oC. The NMR spectra are compared with those in other solvents, such as DMSO-d_6 or $CDCl_3$ in order to confirm the ionisation of these carbon acids in liquid ammonia.

Dimedone (5,5-dimethylcyclohexane-1,3-dione) (1)



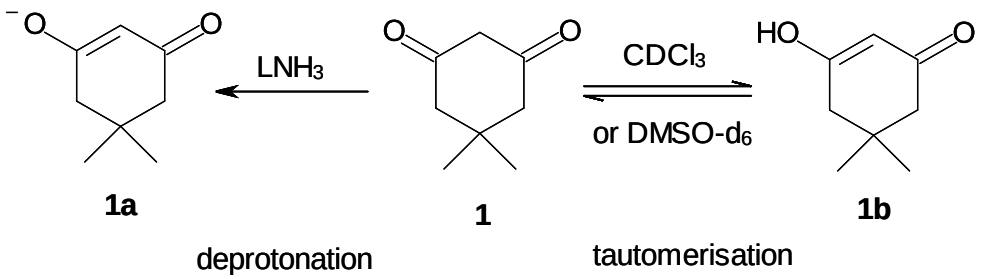
1

Table 1.9 ^1H NMR spectra of dimedone (**1**) in various solvents at 25 ^oC (Appendix C: **Figure N8)**

solvent	**^1H NMR shift (ppm)**
$CDCl_3$	1.09 (s, 3H); 1.11 (s, 3H); 2.31 (s, 2H); 2.54 (s, 2H); 3.35 (s, 1H); 5.51 (s, 1H)
DMSO-d_6	0.99 (s, 6H); 2.21 (s, 4H); 5.20 (s, 1H)
LNH_3	0.89 (s, 6H); 1.84 (s, 4H); 4.62 (s, 1H)

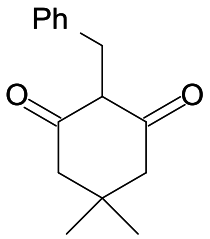
Table 1.10 ^{13}C NMR of dimedone (**1**) in various solvents at 25 ^oC (Appendix C: **Figure N9)**

solvent	**^{13}C NMR shift (ppm)**
$CDCl_3$	28.2; 30.9; 32.7; 54.1; 57.28; 103.0; 191.4; 203.8
DMSO-d_6	28.4; 32.6; 102.8
LNH_3	29.5; 31.5; 50.4; 99.0; 192.4



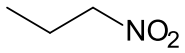
Scheme 1.3

Dimedone (**1**) has an aqueous pK_a of 5.25 and, as expected, the ^1H NMR and ^{13}C NMR spectra of dimedone (**1**) in $CDCl_3$ and DMSO-d_6 indicate that it is unionised in these two solvents, although the ratio between enol (**1b**)/1,3-diketone (**1**) significantly changes with the properties of the solvent (**Scheme 1.3**).[183] However, dimedone (**1)** is deprotonated to its mono-anion form (**1a**) in liquid ammonia (**Scheme 1.3**). ^1H NMR and DEPT135 spectra of **1** in liquid ammonia (**Tables 1.9 and 1.10,** Appendix C: **Figure N10**) show only one proton attached to carbon 2 between the two carbonyl groups, and the carbon shift of the carbonyl carbons (carbon 1 and 3) is about 10 ppm smaller than that for a normal carbonyl group which comes about 200 ppm. These observations in liquid ammonia are not due to the enol form, where intramolecular hydrogen bonding can cause the upfield shift of carbonyl groups as seen for open chained 1,3-diketones, such as acetylacetone in $CDCl_3$ which has a carbon shift of 192 ppm in its enol form.[184] Intramolecular hydrogen bonding in the enol form of dimedone (**1**) is not possible. The ionisation of **1** in liquid ammonia also supported by the synthetic experiment, in which equal molar reaction of **1** and benzyl chloride in liquid ammonia affords only mono-substituted product **1c**, without the aid from strong bases.



1c

1-Nitropropane (2)



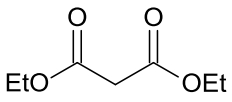
2

Table 1.11 ^{1}H NMR of 1-nitropropane (**2**) in various solvents at 25 ^{o}C (Appendix C: **Figure N11**)

solvent	**^{1}H NMR shift (ppm)**
$CDCl_3$	1.03 (t, 3H); 2.03 (m, 2H); 4.36 (t, 2H)
DMSO-d_6	0.91 (t, 3H); 1.91 (m, 2H); 4.51 (t, 2H)
LNH_3	0.89 (t, 3H); 1.91 (m, 2H); 4.54 (s, 2H)

1-Nitropropane (**2**) has an aqueous pK_a of 9 and a pK_a of 17.2 in DMSO, which suggests that there are significant solvation differences of the nitro group by protic and dipolar aprotic solvents. 1-Nitropropane (**2**) is not ionised in liquid ammonia, or in DMSO, based on ^{1}H NMR data (**Table 1.11**). Previous studies on the pK_a measurement of nitroalkanes by NMR in liquid ammonia showed that the ionisation of nitromethane and nitroethane are very dependent on the initial concentration of the nitro compound and the temperature, for example, higher concentrations of nitromethane and lower temperature resulted in a greater degree of deprotonation, e.g., 0.39M nitromethane at -10 ^{o}C is deprotonated by only 2% in liquid ammonia, the authors rationalised these observations in terms of ion aggregation.[185] In our study, the concentration of **2** is 0.1M and the experiment is carried out at 25 ^{o}C, and no ionisation is found at all. It is perhaps worth noting that phenols of aqueous pK_a of 9 are also not ionised in liquid ammonia, as described previously in this chapter.

Malonate diethyl ester (3)



3

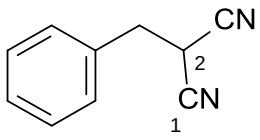
Malonate diethyl ester (**3**) has an aqueous pK_a of 13.3 and a pK_a of 15.9 in DMSO, but, perhaps surprisingly, it is not ionised in liquid ammonia (**Table 1.12**). A broad single peak of

the protons on the central carbon of **3** with a chemical shift similar to that in DMSO-d_6 is observed in liquid ammonia, probably due to a fast exchange of these protons with solvent In liquid ammonia, most of **3** exists in its 1,3-diketone form and there is no evidence of any of the enol form.

Table 1.12 ^{1}H NMR of malonate diethyl ester (**3**) in various solvents at 25 ^{o}C (Appendix C: **Figure N12**)

solvent	**^{1}H NMR shift (ppm)**
$CDCl_3$	1.29 (t, 6H); 3.36 (s, 2H); 4.21 (q, 4H) (J=7.3)
DMSO-d_6	1.20 (t, 6H); 3.47 (s, 2H); 4.11 (q, 4H) (J=8.4)
LNH_3	1.17 (t, 6H); 3.46 (bs, 2H); 4.11 (q, 4H) (J=5.7)

Benzylmalonodinitrile (4)



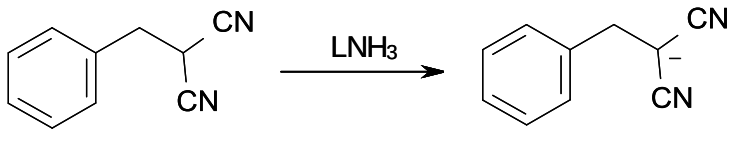
4

Table 1.13 ^{1}H NMR of benzylmalonodinitrile (**4**) in various solvents at 25 ^{o}C (Appendix C: **Figure N13**)

solvent	**^{1}H NMR shift (ppm)**
$CDCl_3$	3.28 (d, 2H); 3.92 (m, 1H); 7.32-7.39 (m, 5H)
DMSO-d_6	3.38 (d, 2H); 5.15 (t, 1H); 7.36-7.46 (m, 5H)
LNH_3	3.31 (s,2H); 7.34-7.54 (m, 5H)

Table 1.14 ^{13}C NMR of benzylmalonodinitrile (**4**) in various solvents at 25 ^{o}C (Appendix C: **Figure N14**)

solvent	**^{13}C NMR shift (ppm)**
$CDCl_3$	24.9; 36.7; 112.1; 128.8; 129.1; 129.3; 132.9
DMSO-d_6	24.8; 35.0; 114.6; 128.4; 129.3; 129.8; 135.2
LNH_3	11.5; 35.0; 125.0; 128.1; 134.0; 137.7; 145.1

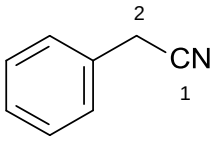


4 **4a**

Scheme 1.4

The ^{1}H NMR spectrum of benzylmalonodinitrile (**4**) in liquid ammonia does not show a proton attached to the methine carbon and ^{13}C also supports this by showing, compared with $CDCl_3$, a downfield shift of the cyano groups and an upfield shift of the central carbon as expected from an increased negative charge density on this carbon. (**Tables 1.13** and **1.14**) Ionisation of **4** in liquid ammonia is further supported by DEPT 135 spectrum (Appendix C: **Figure N15**) which show no coupling between the methine carbon and its attached proton in neutral (**4**). The large downfield shift of the cyano groups (145.1 ppm), although perhaps surprising, is in agreement with that reported for the cyano group of the lithium salt of benzyl cyanide anion in THF which has a carbon shift of 144.3 ppm.[186]

Benzyl cyanide (5)



5

Benzyl cyanide (**5**) has an aqueous pK_a of 22 and a pK_a of 21.9 in DMSO and, as expected, is not ionised in liquid ammonia, based on the comparison of ^{1}H NMR and ^{13}C NMR data in different solvents **(Tables 1.15 and 1.16)**.

Table 1.15 ^{1}H NMR of benzyl cyanide (**5**) in various solvents at 25 ^{o}C (Appendix C: **Figures N16-N18**)

solvent	**^{1}H NMR shift (ppm)**
$CDCl_3$	3.75 (s, 2H); 7.34-7.38 (m, 5H)
DMSO-d_6	4.02 (s, 2H); 7.32-7.43 (m, 5H)
LNH_3[a]	4.06 (s,2H); 7.30-7.40 (m, 5H)

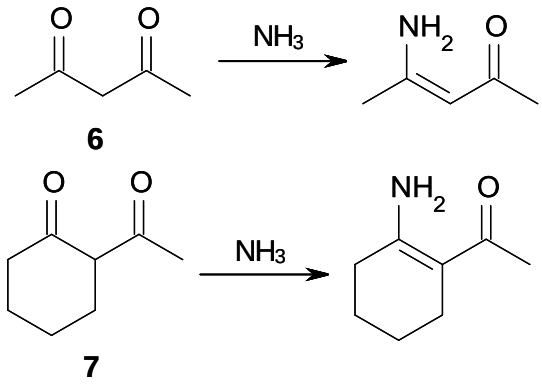
[a] Proton relaxation time prolonged to 10s

Table 1.16 ^{13}C NMR of benzyl cyanide (**5**) in various solvents at 25 ^{o}C (Appendix C: **Figure N19**)

solvent	**^{13}C NMR shift (ppm)**
$CDCl_3$	142.1; 129.1; 127.9; 127.8; 117.8; 23.5
DMSO-d_6	131.7; 129.3; 128.8; 128.1; 119.6; 23.0
LNH_3	131.5; 129.1; 128.0; 127.7; 119.4; 22.8

It is worth noting that the relaxation time of the methylene protons of **5** are extraordinarily fast compared with the aromatic protons[187] and, consequently, it takes 10s relaxation time to obtain the expected integration ratio between aromatic protons and methylene protons in liquid ammonia (Appendix C: **Figures N16-N18**). This is not seen in other solvents. The reason for this phenomenon in liquid ammonia is not clear, but it is likely due to the specific solute-solvent interactions of liquid ammonia solutions.[188]

Acetylacetone (6) and 2-acetocyclohexanone (7)

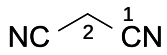


Scheme 1.5

Acetylacetone (**6**) and 2-acetocyclohexanone (**7**) have an aqueous pK_a of 8.95 and 10.1, respectively, and a pK_a of 13.3 and 14.1 in DMSO, respectively. In liquid ammonia, acetylacetone and 2-acetocyclohexanone react rapidly with ammonia to give corresponding enamines (**Scheme 1.5**), confirmed by GC-MS. Also equal molar of **6** and **7** react with benzyl chloride give the corresponding mono-substituted products together with the solvolysis products in the absence of strong bases, which suggest that both **6** and **7** are ionised in liquid

ammonia at room temperature (**Scheme 3.11**, **Section 3.4**). Due to the instability of **6** and **7** in liquid ammonia at room temperature, NMR investigation is not possible.

Malonodinitrile (8)



8

Malonodinitrile**,** MDN**,** (**8**) has an aqueous pK_a of 11.2 and a pK_a of 11.1 in DMSO. MDN (**8**) appears to behave very unusually in liquid ammonia, its ^{1}H NMR spectrum at 25 ^{o}C shows no protons attached to the central methylene carbon (Appendix C: **Figure N20**), which is in stark contrast to those observed in other solvents (**Table 1.17**), and suggesting that both protons have been removed to form a carbon dianion. The lack of a proton signal is not due to H-D exchange with the deuteriated dimethyl sulfoxide used to 'lock' the spectrometer as the same result is observed with d_8 toluene or d_6 benzene as a lock. A similar spectrum is also seen when one equivalent of acetonitrile is added using its three methyl hydrogens as an internal standard, apparently indicating that there is less than 2% MDN with hydrogen still attached. It is also not due to any rapid exchange mechanism leading to a very broad signal that is not observable because there are also no H signals associated with the methylene carbon of MDN in the ^{1}H NMR spectrum at -40 ^{o}C (Appendix C: **Figure N22**).

Table 1.17 ^{1}H NMR of malonodinitrile (**6**) in various solvents at 25 ^{o}C

solvent	**^{1}H NMR shift (ppm)**
$CDCl_3$	3.62 (s,2H)
D_2O[a]	4.79 (s,HOD)
HMPT[b]	5.34, s; 3.86, s (ratio=4:1)
DMSO-d_6	4.42, s; 3.37, s (ratio=4:1)
LNH_3[c]	not observed

[a] Fast proton exchange between **8** and D_2O generates the HOD signal at 4.79, all protons of **8** are replaced by deuterium, which is confirmed by GC-MS analysis. [b] With benzene-d_6 as deuterium lock, ^{1}H NMR of HMPT: δ_H ($CDCl_3$, ppm): 2.65 (d, 18H), J = 9.2 Hz; HMPT: δ_H (D_2O, ppm): 2.58 (d, 18H), J = 9.5Hz.

Ionisation of MDN would transfer the protons to ammonia to form ammonium ions but the addition of ammonium chloride does not affect the ^{1}H NMR spectrum (Appendix C: **Figures N21** to **N24**).

Table 1.18 ^{13}C NMR and DEPT 135 of malonodinitrile (**8**) in various solvents at 25 ^{o}C

solvent	**^{13}C NMR shift (ppm)**	**DEPT 135**
$CDCl_3$	8.77; 109.4	8.77(CH_2)
D_2O	-2.94; 8.44; 111.4	not observed
HMPT[a]	7.08; 112.5	7.08(CH_2); 112.51(CH)[b]
DMSO-d_6	8.79; 112.1	8.79(CH_2); 112.39(CH)[c]
LNH_3[d]	-3.12; 131.5	not observed

[a] With benzene-d_6 as deuterium lock, ^{13}C NMR of HMPT: δ_C ($CDCl_3$, ppm): 36.81; 36.83; HMPT: δ_C (D_2O, ppm): 35.93; 35.97. [b] CH peak is weak, the peak intensity ratio between the CH_2 and CH carbon is 32:1. [c] CH peak is also weak, the peak intensity ratio between the CH_2 and CH carbon is 12:1. [d] ^{13}C NMR is recorded with DMSO-d_6 or benzene-d_6 as deuterium lock.

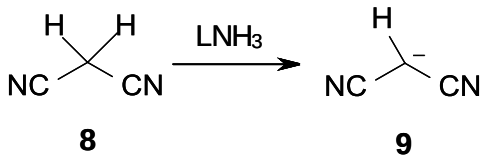
The ^{13}C NMR spectrum of MDN in liquid ammonia at 25 ^{o}C shows a very high field carbon signal at -3.12ppm (**Table 1.18,** Appendix C: **Figure N21**), consistent with the formation of a negatively charged carbon,[189] which can be compared with the methylene carbon signal of MDN in dimethyl sulfoxide which occurs at 8.8ppm. There are only two quaternary carbons as expected for the MDN carbon dianion, $(CN)_2C^{2-}$ and the DEPT 135 spectrum of malonodinitrile (**8**) in liquid ammonia shows no carbons attached to H. Interestingly, the ^{13}C NMR spectrum shows the cyano carbons shifted downfield in liquid ammonia to 131ppm compared with 112.1ppm in the neutral MDN in dimethyl sulfoxide.

All of these observations are not due to a chemical reaction of MDN. If MDN is left in liquid ammonia for two days at room temperature, followed by evaporation of the ammonia, acid neutralisation and extraction yields unreacted MDN, indicating that MDN is stable in liquid ammonia.

Malonodinitrile (**8**) undergoes fast H-D exchange in D_2O to give the mono- and then the di-deuterated compound, as shown from ^{1}H NMR and ^{13}C NMR spectra in D_2O (**Table 1.17**). MDN is not significantly ionised in water as shown by ^{13}C NMR spectra (**Table 1.18**), which

is consistent with its low acidity in water (aqueous pK_a = 11.2) however, the very small negative carbon signal (-2.94 ppm) is probably due to the partial formation of the monoanion. Although the evidence appears to support the formation of a stable carbon dianion formed by the removal of two hydrogens from a single methylene in MDN, it seems difficult to believe. The removal of one proton from MDN in water to form the carbon monoanion is associated with pK_a of 11.2, so the ability of liquid ammonia to increase the acidity of MDN to such an extent that it forms the dianion is unexpected. For example, although the effect of the solvent on the acidity of carbon acids is well known the pK_a of dimedone is 5.3 in water but is increased to11.2 in dimethyl sulfoxide. We can compare the data for MDN with that for a monoalkylated MDN, benzyl malonodinitrile, (**4**), which contains only one ionisable hydrogen and in DMSO (**4**) is unionised but in liquid ammonia it loses a proton to form the carbon monoanion. There is no proton signal associated with the CH in the ^{1}H NMR spectrum of (**4**) in liquid ammonia and the ^{13}C NMR spectrum shows this carbon to have moved upfield in liquid ammonia to 11.5ppm from 24.8ppm for neutral (**4**) in dimethyl sulfoxide (**Table 1.14**) which is consistent with the addition of a negative charge. The DEPT spectrum of (**4**) in liquid ammonia shows that the methine carbon CH is no longer attached to H whereas the other carbons show their expected environment. As with MDN, the cyano carbons of benzyl malonodinitrile in liquid ammonia shift downfield to 145ppm compared with 114ppm in the neutral compound in dimethyl sulfoxide.

There are also some reactions of MDN in liquid ammonia that are consistent with, but not proof of, the formation of a carbon dianion. MDN reacts with one equivalent of benzyl chloride $C_6H_5CH_2Cl$ in liquid ammonia to form the dialkylated product $(C_6H_5CH_2)_2C(CN)_2$ and with 1,2-dibromoethane ($BrCH_2CH_2Br$) to form the cyclic product 1,1-dicyanocyclopropane in excellent yields.



8 **9**

Scheme 1.6

It still does not seem clear that MDN actually forms a carbon dianion in liquid ammonia or simply forms a monoanion with unusual NMR properties. Consequently we decided to make the mono-anion (**9**) independently (**Scheme 1.6**) and compare its NMR spectra with those in other typical dipolar aprotic solvents, such as DMSO and HMPT.

The negative ^{13}C NMR chemical shift of the central carbon in MDN (-3.12 ppm) certainly is indicative that it does not exist in its neutral undissociated form in liquid ammonia. There is also a significant cyano carbon downfield shift of MDN in liquid ammonia compared with those in DMSO and HMPT (**Tables 1.17** and **1.18**). However, the ^{1}H NMR data for the monoanion **9** in other dipolar aprotic solvents also shows apparently the absence of any hydrogens (**Table 1.19**), similar to that seen in liquid ammonia. The ^{13}C NMR spectrum of the MDN monoanion in HMPT shows an upfield shift to 2.6ppm for the central carbon from 7.1ppm in neutral MDN, but not as much as the -3.12ppm seen in liquid ammonia (**Tables 1.18 and 1.20**), which, as already stated, is significantly further upfield compared with that (11.5ppm) of benzylmalonodinitrile anion (**4a**) in liquid ammonia (**Table 1.14**). It does appear therefore that the carbon shift of MDN in liquid ammonia is unusually low, but this could still be due to a poorly solvated monoanion with consequently a relatively larger negative charge density on the central carbon in liquid ammonia compared with other solvents.

Table 1.19 ^{1}H NMR of malononitrile monoanion (**9**) in various solvents at 25 ^{o}C

solvent	**^{1}H NMR shift (ppm)**
D_2O[a]	4.78 (s,HOD)
HMPT[b]	not observed
DMSO-d_6[c]	not observed
LNH_3[d]	not observed

[a] 40% wt NaOD was used to generate the monoanion (**9**), the molar ratio between **8** and NaOD was 1:1. [b] NaH was added into **8** in HMPT solution, the molar ratio between NaH and **8** is 1:1, benezene-d_6 as deuterium lock, benzene or biphenyl is also added as internal reference. It is worth noting that ^{1}H NMR spectrum of NaH with HMPT blank shows a broad single peak at 3.86 ppm, and chemical shift of protons of HMPT move upfield. ^{1}H NMR of HMPT with NaH: δ_H (HMPT, ppm): 2.46 (d, 18H), J = 8.4 Hz. [c] A broad single peak with chemical shift of 3.40-3.50 ppm is observed for DMSO-d_6 blank with NaH. [d] 2 eq. of $NaNH_2$ to **8** is added into the ammonia solution, with benzene-d_6 as deuterium lock (Appendix C: **Figure N25**).

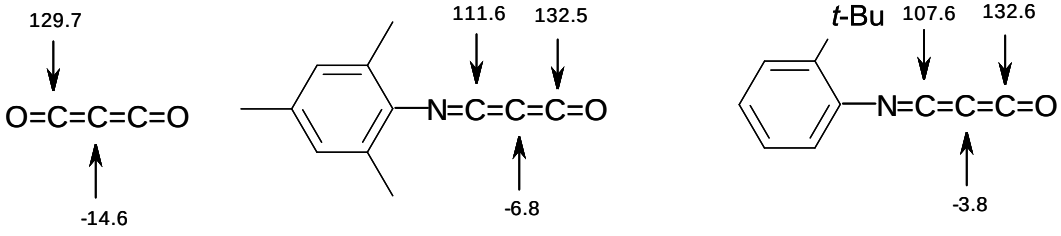
The carbon chemical shifts of MDN with 2 equivalents of NaH_2 in liquid ammonia are similar to those without the added base which does not distinguish between mono- and di-anion formation in both cases (Appendix C: **Figures N24** and **N25**).

Table 1.20 ^{13}C NMR of malonodinitrile monoanion (**9**) in various solvents at 25 ^{o}C[a]

solvent	^{13}C NMR shift (ppm)	DEPT 135
D_2O[b]	-1.37; 117.7; 124.2; 126.6; 165.1	not observed
HMPT[c]	2.56; 122.75	not observed
DMSO-d_6	not observed	not observed
LNH_3[d]	-3.27; 131.37	not observed

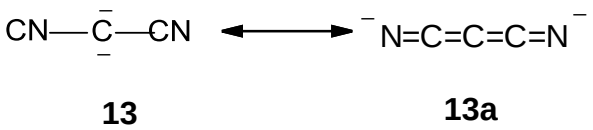
[a] Small amount of $Cr(acac)_3$, is added in order to shorten the spin-lattice relaxation times (T_1) of quaternary carbon nuclei.[190] [b] ^{13}C NMR of **8** in a molar ratio of 1:2 with NaOD in D_2O: -1.58; 117.9; 124.2; 126.5; 134.2; 170.1. [c] NaH is added into **8** in HMPT solution, the molar ratio between NaH and **8** is 1:1, benezene-d_6 as deuterium lock, benzene or biphenyl is also added as internal reference. ^{13}C NMR of HMPT with NaH: δ_C (HMPT, ppm): 36.13; 36.46. [d] 2 eq. of $NaNH_2$ to **8** is added into the ammonia solution, with benzene-d_6 as deuterium lock (Appendix C: **Figure N26**).

Very highfield carbon shifts are seen for carbon dianions or quasi-dianons in other solvents, for example, carbon suboxide (**10**) has a very negative carbon shift of -14.6 in $CDCl_3$ at -40 ^{o}C,[191] while iminopropadienones **11** and **12** have shifts, respectively, of -6.8 and -3.8 ppm in $CDCl_3$ at room temperature.[192]



10 **11** **12**

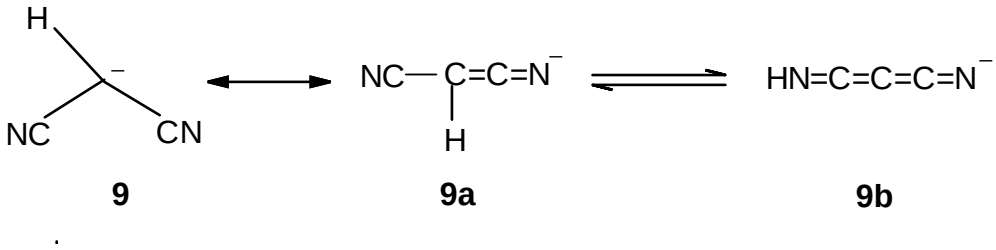
If MDN does exist as its dianion (**13**) in liquid ammonia it must be stabilised by delocalisation of the charges formally on the central carbon to give **13a**, in which the two negative charges are separated to reduce electrostatic repulsion (**Scheme 1.7**). Such delocalisation would result structures not too dissimilar from the allene type derivatives **10, 11** and **12**.



Scheme 1.7

In conclusion, it does not seem possible at present for NMR studies to unambiguously rule out the formation of the malonodinitrile dianion in liquid ammonia. However, it is clear that at least the monoanion is formed spontaneously from MDN in liquid ammonia, but the NMR studies of the monoanion in other aprotic polar solvents do seem to indicate that what we observe is more likely to be due to the unusual NMR properties of the monoanion rather than due to the formation of the malonodinitrile dianion.

The structure of monoanion **9** in liquid ammonia is itself of interest, because of the potential equilibrium between the delocalised anion and its tautomer **9a** (**Scheme 1.8**). In principle, structure **9a** should show C-H coupling which should be determined by DEPT 135, while **9b** has an imine motif with a characteristic NH but it could potentially rapidly exchange its proton with ammonia solvent so that no proton would be seen in ^{1}H NMR**.** To test the latter, the ^{1}H NMR of benzophenone imine in liquid ammonia shows a distinct sharp single peak for the the imine proton (Appendix C: **Figure N27**),[193] indicating slow exchange. This indicates that the malonodinitrile monoanion does not exist as its tautomer **9b,** because there is no signal observed in its ^{1}H NMR spectrum.

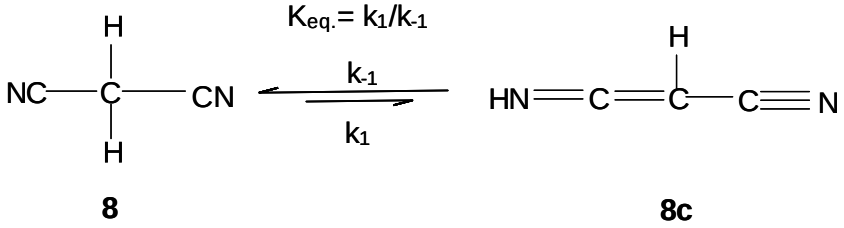


Scheme 1.8

Richard and Gao[194] investigated deprotonation rate of several cyanoalkanes in D_2O, and proposed that the significant resonance stabilisation of α-cyano carbanions is attributed to the differential solvation of cyanoalkanes and cyanocarbanions. The theoretical calculation of the

free energy change for the highly unfavorable tautomerisation of acetonitrile to ketenimine in water is computed as high as ΔG_T = 30.7 kcal/mol. Based on the experimental and calculation results, they also concluded that the large instability of the ketenimine cumulative double bond favours the valence bond resonance form of the α-cyanocarbanion in which there is a formal carbon-nitrogen triple bond and the negative charge is localised at the α-carbon. This may explain why there is such a highfield signal for MDN anion in liquid ammonia – there is a large negative charge density on the central carbon.

Another interesting observation is that there are two singlet peaks in the ^{1}H NMR spectrum of MDN **8** in DMSO-d_6 ($\delta_{H,DMSO}$ = 4.42 and 3.37ppm) and HMPT ($\delta_{H,HMPT}$ = 5.34 and 3.86ppm), the ratio between these two peaks is 4:1 in both solvents (**Table 1.17**). The ^{13}C NMR of MDN in HMPT shows the central carbon with a chemical shift at 112 ppm being a methylene CH_2 structure, whereas that at 7 ppm has a CH structure (**Table 1.17**) as shown by DEPT 135 spectrum. This can be explained by the tautomerisation of **8** and **8c** in those solvents as described in **Scheme 1.9** with an equilibrium constant, $K_{eq.}$, for the tautomerisation in these solvents of 0.25 at 25 ^{o}C, corresponding to a ΔG^o_{298K} = 3.4 kJ mol^{-1}. These observations suggest that perhaps the difference calculated by Richard for the tautomerisation of acetonitrile to ketenimine is overestimated (*vide supra*).[194]



Scheme 1.9

In summary, due to the basic properties of liquid ammonia, the ionisation of some carbon acids occurs spontaneously to form the corresponding anions. It appears that carbon acids with a pK_a in DMSO of <15 are ionised in liquid ammonia (**Table 1.21)** but there is not a simple correlation with their aqueous pK_a. An obvious anomaly is nitropropane, which is also shown by its deviation from a reasonably linear plot of the pK_a of carbon acids in water and DMSO (**Figure 3.10**) which will be discussed in the following section. Liquid ammonia

appears to behave like a typical dipolar aprotic solvents in its effects on ionisation and solvation of organic acids.

Table 1.21 The ionisation of carbon acids in liquid ammonia at 25 ^{o}C by NMR compared with pK_a values in water and DMSO

carbon acid	**pK_a (aq.)[a]**	**pK_a (DMSO)[b]**	**ionisation in LNH_3**
malononitrile	11.2	11.1	Yes
dimedone	5.25	11.2	Yes
HCN	9.21	12.9	Yes
acetylacetone	9.0	13.3	Yes
2-acetylcyclohexanone	10.1	14.1	Yes
diethyl malonate	12.9[c]	16.4[c]	No
1-nitropropane	9.0	17.2	No
benzyl cyanide	21.9[d]	21.9	No

[a] Aqueous pK_a is from reference 10c except otherwise noted. [b] pK_a in DMSO is from reference 195 except otherwise noted. [c] reference 196. [d] pK_a in DMSO.

2. Solvolysis in liquid ammonia Page

2. Solvolysis in liquid ammonia

Solvolysis and hence stability of organic compounds in liquid ammonia needs to be studied first before synthetic work and kinetic measurement of nucleophilic substitution reactions are undertaken. Due to the strong electron donating character of ammonia and its constant high concentration (36M/25 ^{o}C), when used as a solvent, ammonia can compete with nucleophiles to react with substrates in nucleophilic substitution reactions in liquid ammonia, The rates of these processes are especially important for the accurate determination of the rates of those reactions in which weak nucleophiles are involved.

From a synthetic point of view, solvolysis in liquid ammonia also can be very useful for the synthesis of amines, amides and imines, etc. and kinetic and product analysis enables the evaluation of rate and selectivity of these amination reactions. Strictly speaking, solvolysis in liquid ammonia is a 'special' case of nucleophilic substitution in which the nucleophile is ammonia which may have an effective constant concentration if it is in vast excess of the substrate concentration.

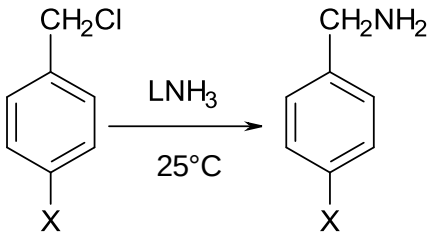
For solvolysis in liquid ammonia, the solvent, in addition to its role as a nucleophile, could act as a general base in an S_N3 type process,[197] and influence the mechanism of substitution by its effects on the stability of any intermediate and on its solvation of the leaving group. These solvent effects are also present for substitutions by other nucleophiles, especially by solvation of the nucleophile and leaving group in determining the extent of 'push and pull.'

2.1 Solvolysis of alkyl halides

Previous investigations of the solvolysis of organic compounds in liquid ammonia have been described earlier (**Introduction 3.3**). In order to determine the solvent effect on the transition state of the aliphatic nucleophilic substitution reactions and how the solvent may modify substituent effects, we investigated the rates of solvolysis of substituted benzyl chlorides in liquid ammonia.

The solvolysis of substituted benzyl chlorides in liquid ammonia give the corresponding benzylamines (**Scheme 2.1**) and the rates of appearance of the product and the disappearance of the reactant, followed by GC analysis, change exponentially with time. The derived pseudo

first order rate constants show little or no dependence of on the substituent (**Table 2.1**). This is very different from hydrolysis in water where the hydrolysis rates increase by about 7 orders of magnitude on going from 4-nitrobenzyl chloride to 4-methoxybenzyl chloride (**Table 2.1**). The rates of solvolysis in liquid ammonia are generally faster than those in water, but the difference decreases with electron-donating substituents, so that 4-methoxybenzyl chloride is more reactive in water than in liquid ammonia.



Scheme 2.1

Table 2.1 Pseudo first order rate constants (k_0) for the solvolysis of substituted benzyl chlorides in LNH_3 and water at 25 ^oC

substrate	$\mathbf{k_{0,\ LNH3}(s^{-1})}$	$\mathbf{k_{0,\ water}(s^{-1})}$
4-methylbenzyl chloride	7.85×10^{-4}	[a] 2.91×10^{-4}
benzyl chloride	8.89×10^{-4}	[a] 1.33×10^{-5}
4-chlorobenzyl chloride	9.81×10^{-4}	[a] 7.56×10^{-6}
4-carbomethoxybenzyl chloride	11.0×10^{-4}	N.A.
4-cyanobenzyl chloride	13.3×10^{-4}	N.A.
4-nitrobenzyl chloride	15.3×10^{-4}	[a] 3.38×10^{-7}
3-methoxybenzyl chloride	7.82×10^{-4}	N. A.
4-methoxybenzyl chloride	19.1×10^{-4}	3.70 [b]
α-methyl benzyl chloride	6.71×10^{-6}	0.48 [c]
α-methyl 4-methoxybenzyl chloride	9.68×10^{-4}	1.55 [d]

[a] The solvolysis rates were extrapolated data from ref. 198. [b] ref. 199. [c] ref. 34c. [d] ref. 200, the data is for 80% (v/v) ethanol in water.

There is no clear consensus on the mechanism of hydrolysis of benzyl halides in water and aqueous binary solvents, although that for 4-methoxybenzyl halides is described as an S_N1 mechanism with the intermediate formation of a carbocation,[201] and that for the 4-nitro derivative is claimed to be S_N2.[202] The rate of solvolysis in liquid ammonia is retarded dramatically when one of methylene hydrogen of benzyl chloride in the α-position is replaced by a methyl group, α-methyl benzyl chloride is solvolysed about 130 times *slower* than benzyl chloride. This is strong evidence for solvolysis occurring by an S_N2 mechanism due to a more sterically hindered transition state. It is also worth noting that the solvolysis rate of *t*-butyl chloride in liquid ammonia at 25 ^oC is very slow, the half life of the reaction was reported as long as 146 days,[203] which is in stark contrast with that for the hydrolysis and is indicative of a bimolecular process in liquid ammonia. Furthermore, α-methyl 4-methoxybenzyl chloride, which undergoes solvolysis by the unimolecular mechanism in protic solvents,[204] is solvolysed nearly at the same rate as benzyl chloride in liquid ammonia, but about 1600 and 400 times slower than in 80% (v/v) ethanol/water and 100% methanol at 25 ^oC, respectively.[200] This indicates that, even with activated benzyl chloride derivatives, the solvolysis of these compounds in liquid ammonia proceeds through a concerted bimolecular mechanism. The activation parameters for the solvolysis of substituted benzyl halides in liquid ammonia are significantly different from those in water (**Table 2.2,** Appendix A: **Tables A14** to **A18**, **Figures A16** to **A20**).

Table 2.2 Activation parameters for the solvolysis of substituted benzyl chlorides in LNH_3 and water at 25 ^oC

	LNH_3		**Water [a]**	
substrate	**$\Delta H^{\ddagger}$ (kJ mol^{-1})**	**$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})**	**$\Delta H^{\ddagger}$ (kJ mol^{-1})**	**$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})**
benzyl chloride	39.9	-200	83.1	-38.0
4-chlorobenzyl chloride	40.2	-197	85.9	-37.2
4-nitrobenzyl chloride	37.8	-202	87.6	-50.1
4-methoxybenzyl chloride	41.3	-188	70.6	-5.10
α-methyl benzyl chloride	67.7	-147	71.0	-50.2

[a] Activation parameters for 4-substituted benzyl chlorides were extrapolated from refs.198, 199 and ref.205; the data for 4-methoxybenzyl chloride were for 20% (v/v) methanol in water; the data for α-methyl benzyl chloride were from ref.34c.

Very large negative entropies of activation ($\Delta S^{\ddagger}$) are observed for the solvolysis of all substituted benzyl chlorides in liquid ammonia, indicative of a restricted activated complex relative to the reactant and a bimolecular concerted S_N2 mechanism for all derivatives. Bimolecular nucleophilic substitution processes are usually characterised by large negative entropies of activation of -90 and -120 J K^{-1} mol^{-1} due to the loss of translational and rotational entropy of the reactants and the development of charge in the transition state leading to solvent restriction.[206] By contrast the $\Delta S^{\ddagger}$ for typical hydrolytic reactions which follow the S_N1 mechanism are often positive, e.g. the $\Delta S^{\ddagger}$ of the hydrolysis of *t*-butyl chloride[34f] is about 50 J K^{-1} mol^{-1}. The additional methyl group on the α-position of benzyl chloride increases $\Delta H^{\ddagger}$ of the reaction significantly in liquid ammonia (**Table 2.2**), as expected from a more sterically hindered reaction in a bimolecular process. This is distinctly different from the hydrolysis in water, where the additional methyl group causes a *decrease* in $\Delta H^{\ddagger}$, presumably due to the formation of a more stable carbocation.

The C-Cl bond of benzyl halide has a dipole moment of 1.85D in gas phase.[207] Compared with liquid ammonia, the C-Cl bond of benzyl chloride is presumably more polarised in water due to the latter's greater hydrogen bond donating ability and so the fission of the C-Cl bond may be expected to be easier in water than in liquid ammonia. Although liquid ammonia is generally described as a protic solvent,[1] like water, with good hydrogen bond donor (HBD) and acceptor (HBA) ability, there is very little evidence to support this assertion. It actually has a very limited HBD ability, not only in the gas phase but also in the condensed phase,[56] and anions are poorly solvated in liquid ammonia. Expulsion of the chloride anion is thus expected to be more difficult in liquid ammonia than in water and so the probability of a unimolecular mechanism is less with the necessity of more 'push' required from the incoming nucleophile. In addition, ammonia is a better nucleophile than water, all of which indicate a more likely bimolecular process in liquid ammonia. Finally, based on a comparison of the effect of solvents on the rates of reactions, and, contrary to commonly accepted views, it appears that liquid ammonia acts more like a dipolar aprotic solvent in nucleophilic substitution reactions.[208]

There is surprisingly little or no dependence of the rate of solvolysis of benzyl chlorides in liquid ammonia upon ring substituents, again in contrast to that in water (**Table 2.1**).

Consequently the Hammett plot for the solvolysis in liquid ammonia is very different from that in water (**Figure 2.1**), the ρ value for the reaction in liquid ammonia is zero, while that in water, although not ideally linear, shows ρ = -4.32. It is worth noting that the data for solvolysis in liquid ammonia is effectively zero whether σ_p^+ or σ_p is used. These different values suggest that for the solvolysis of benzyl chlorides in liquid ammonia there is little or no charge developed on the central carbon atom in the transition state with any charge developed due to partial fission of the bond to the leaving group being counterbalanced by an equal transfer of charge from the incoming nucleophile.

A typical S_N1 solvolysis reaction generally has a high sensitivity to the solvent polarity and the rate constants tend to be accelerated by increasing the ionising power of the solvent. However, whether salts increase or decrease the rate of a solvolysis reaction depends on the substrate structure. For example, addition of halide ions decreases the rate of hydrolysis for diphenylmethyl in water but not of *t*-butyl halides.[209]

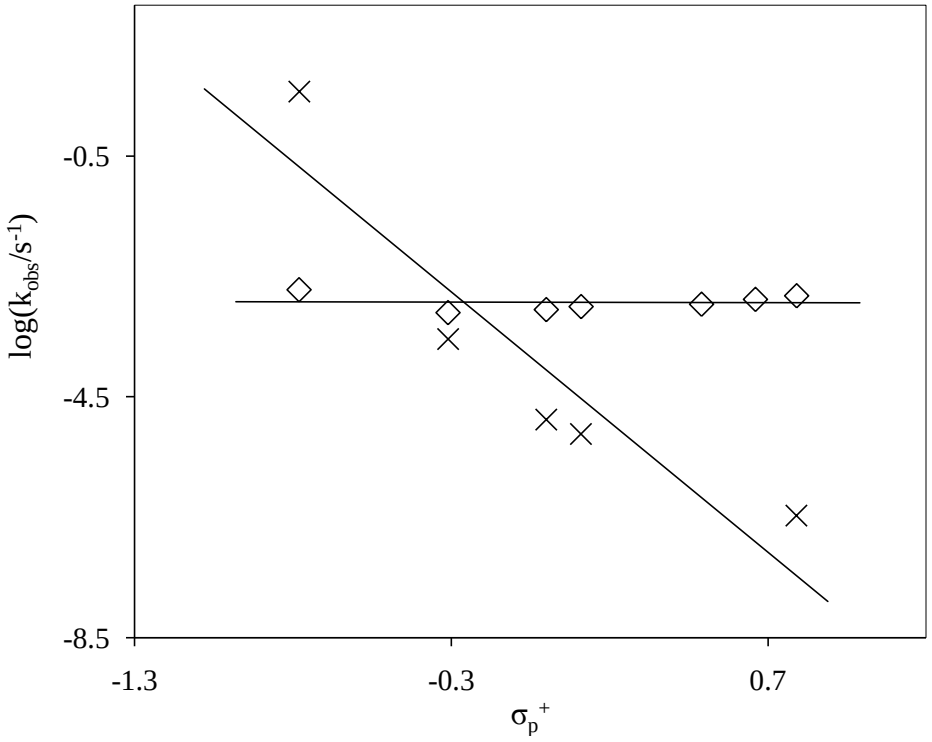


Figure 2.1 The Hammett plot for the solvolysis of 4-substituted benzyl chlorides in LNH_3 (◇) and water (×) at 25 °C.

Normally, the more stable the intermediate formed in an S_N1 process, the greater is the selectivity towards nucleophilicity of the nucleophile in the product determining step, but the similar is the sensitivity towards solvent polarity on the rate limiting step.[210] On the other hand, the salt effect normally has a positive effect on the rate of a S_N2 process when a neutral nucleophile attacks a neutral substrate,[211] due to the generation of charge in the transition state. Despite the difficulty of interpretation, salt effects on the rates of reaction have been used to distinguish between S_N1 and S_N2 processes.[212]

The pseudo first order rate constants for the rate of the solvolysis of 4-methoxybenzyl chloride in liquid ammonia increases linearly with increasing concentration of $KClO_4$ (**Table 2.3, Figure 2.1**), but the positive effect is not as marked as that for a typical S_N1 reaction, for which the rate often increases exponentially.[213] The solvolysis rate of 4-methoxybenzyl chloride is also increased both by adding NH_4Cl and $KClO_4$ in liquid ammonia (**Table 2.4**, **Figure 2.1**), but not significantly more than that with potassium perchlorate. Even though chloride ion is not a particularly good hydrogen bond acceptor, it may have been anticipated that ammonium ions may facilitate chloride ion expulsion but its effect is simply that of a simple salt effect. In addition, the solvolysis rate is also accelerated the same amount by adding NaCl or ammonium chloride which excludes the possibility of specific aid from the ammonium cation (**Table 2.4**). The smaller salt effect on the rate of solvolysis of 4-methoxybenzyl chloride in liquid ammonia compared with observed for typical S_N1 reactions in aqueous or aqueous binary organic solvents is also indicative of a bimolecular S_N2 process.

Table 2.3 Solvolysis rates of 4-methoxybenzyl chloride in presence of $KClO_4$ in LNH_3 at 25 ^oC

concentration of $KClO_4$(M)	0	0.5	1.0	1.5
solvolysis rate, k_0 ($10^3 s^{-1}$)	1.91	2.69	3.94	4.70

Table 2.4 Solvolysis rates of 4-methoxybenzyl chloride in presence of NH_4Cl and NaCl[a] in LNH_3 at 25 ^oC

concentration of NH_4Cl (M)	0	0.2	0.5	0.8	1.0
solvolysis rate,k_0 ($10^3 s^{-1}$)	1.98	2.54	3.37	3.91	4.66

[a] Solvolysis rate of 4-methoxybenzyl chloride in liquid ammonia at 25 ^oC in presence of 0.2M NaCl is 2.54×10^{-3} s^{-1}, identical to that for NH_4Cl, however, the poor solubility of NaCl in liquid ammonia at 25 ^oC (3.02g/100g)[44] prevents the kinetic measurement at higher NaCl concentration.

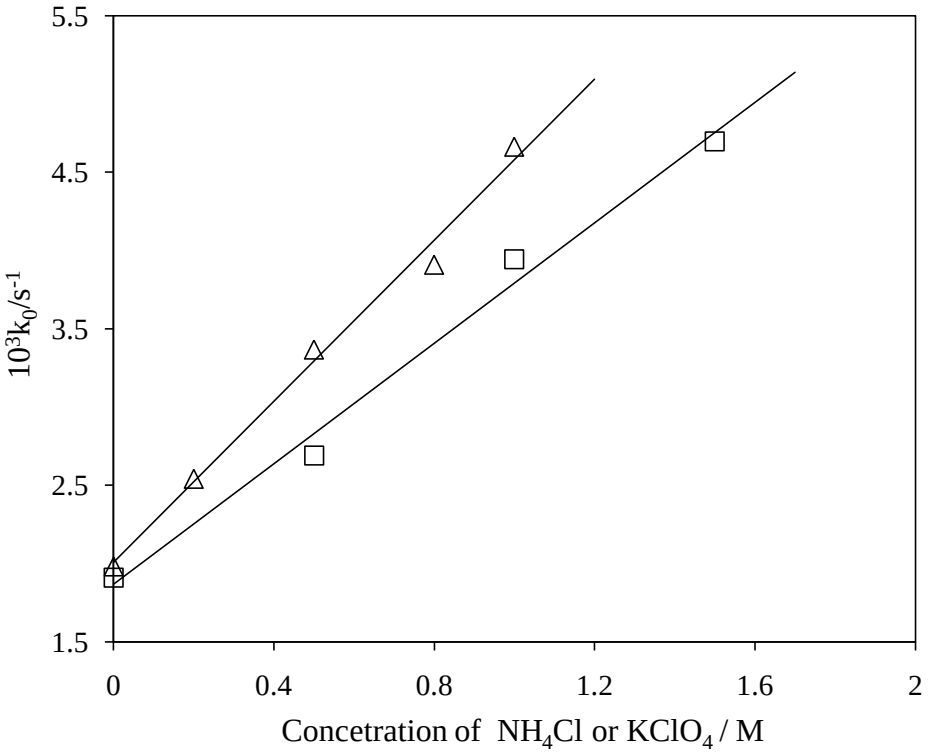
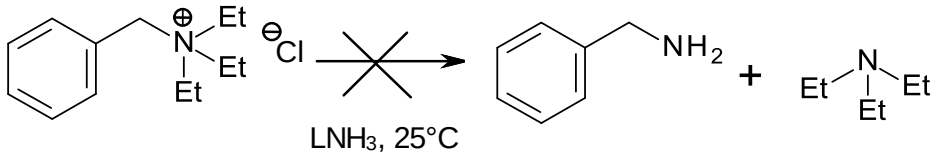


Figure 2.2 Changes in the solvolysis rate constants of 4-methoxybenzyl chloride with the addition of various salts in LNH_3 at 25 ^oC: (Δ) $KClO_4$; (□) NH_4Cl.

Due to the poorer solvation of the leaving group the chloride anion, in the solvolysis of benzyl chlorides in liquid ammonia, compared with that in water, the unimolecular S_N1 mechanism is unfavourable. The expulsion of the leaving group chloride ion is facilitated by increasing its solubility in liquid ammonia by increasing solvent ionising power, similar to the effect of increasing ionic strength on increasing the ionisation constants for phenols, described in the previous section.

Unlike the ammonium ion (NH_4^+), quaternary ammonium cations (R_4N^+) are permanently charged, independent of the pH of the solution. The quaternary ammonium group can exert strong electron withdrawing and field effect as a substituent, as shown by its large positive Hammett sigma constant derived from its effect on the ionisation of benzoic acids.[214] It is also a good leaving group in elimination[215] and nucleophilic substitution[216] reactions. However, despite all of this, there is no solvolysis of benzyltriethyl ammmonium chloride observed in liquid ammonia at 25 ^oC for days (**Scheme 2.2**), and there is also no elimination product

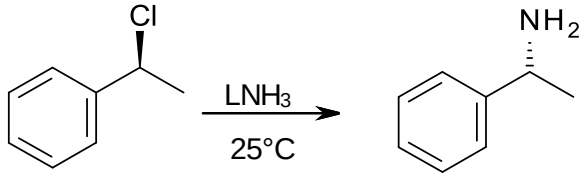
detected. This is probably due to the bulky triethyl ammonium group prevents the attack from ammonia molecule on either the benzylic or the ethyl methylene.



Scheme 2.2

The stereochemical consequences of aliphatic nucleophilic substitutions are classic criteria for mechanisms. Based on a racemised product, Ingold claimed that the solvolysis of α-methyl benzyl chloride in liquid ammonia at room temperature occurs completely through a unimolecular path.[217] However, in our hands the synthesis of enantiomerically pure α-methyl benzyl chloride proved to be difficult; α-methyl benzyl alcohol racemises during the chlorination process and also during the silica gel purification step.[217,218] The best result we achieved was only about 40% ee chloride and enantiomeric synthesis via tosylation, mesylation, phosphorylation of α-methyl benzyl alcohol all proved to be unsuccessful. α-Methylbenzyl acetate proved to be very inert towards nucleophilic attack by ammonia and no reaction was observed after 2 hours at 45 ^{o}C in liquid ammonia, and the lack of formation of acetamide is also consistent with our observation[219] that alkyl esters solvolyse slowly in liquid ammonia (*vide infra*).

Complete inversion of configuration of 40% ee S-α-methyl benzyl chloride was observed during the solvolysis to give 40% ee R-enriched α-methyl benzylamine (**Scheme 2.3**) with almost 100% yield after the reaction reached completion and no elimination product was found. This is another strong indication that the solvolysis of primary and secondary aliphatic halides in liquid ammonia follows an S_N2 mechanism.



Scheme 2.3

It is of interest to determine the degree of inversion not only in liquid ammonia but also in aqueous liquid ammonia solutions to see if any adventitious water would compromise the use of liquid ammonia as a solvent for large scale enantiomeric synthesis. However, there is little indication that significant racemisation occurs with increasing water content. The solvolysis of 41% ee S-α-methyl benzyl chloride gives a barely detectable reduction in the ee of R-α-methyl benzylamine in 10%, 20% and 30% water-ammonia solution (**Table 2.5)**. The increasing water content could facilitate the expulsion of chloride due to better solvation from water and the rate of solvolysis does increase exponentially with the increasing of water content the half life decreases from 29 hours in pure liquid ammonia to 3.7 hours in 10% water, however, even

Table 2.5 Solvolysis of enantiomerically rich S-α-methyl benzyl chloride in aqueous ammonia at 25 ^{o}C

H_2O volume fraction	**0% H_2O**	**10% H_2O**	**20% H_2O**	**30% H_2O**
ee% of reactant chloride(S)	37.8	40.8	40.8	40.8
ee% of product amine(R)	37.8	36.6	36.5	35.9

Table 2.6 The rate and product analysis for the solvolysis of α-methyl benzyl chloride in aqueous ammonia at 25 ^{o}C.

H_2O volume fraction	**0% H_2O**	**10% H_2O**	**20% H_2O**	**30% H_2O**
rate/s^{-1}	6.71×10^{-6}	1.93×10^{-5}	5.2×10^{-5}	1.40×10^{-4}
molar ratio (amine/alcohol)	——	110 :1	42:1	12:1
$k_{rel.}$	1	2.9	7.7	21

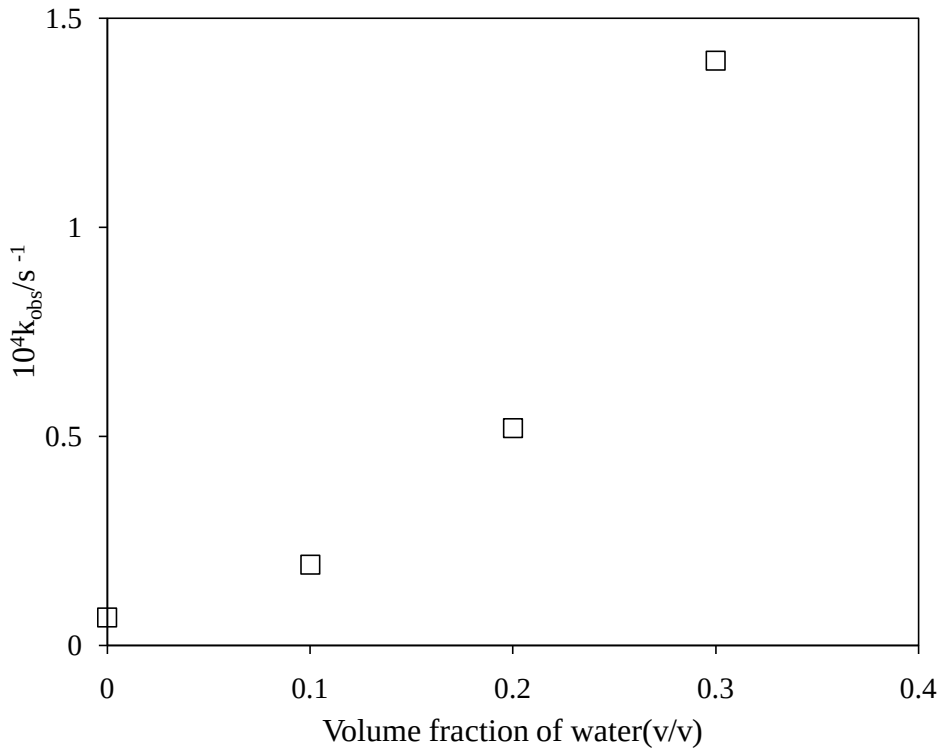
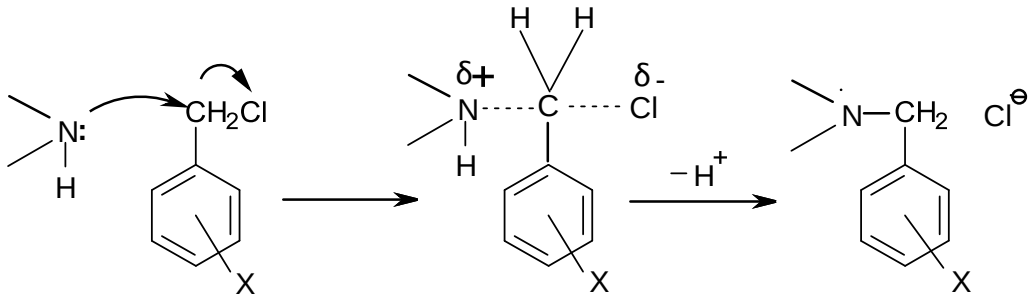


Figure 2.3 The increase in the solvolysis rate of α-methyl benzyl chloride with increasing volume fraction of water in water-ammonia solution at 25 ^{o}C.

in 10% water-ammonia there is little or no competing hydrolysis, with less than 1% of alcohol produced (**Table 2.6**). The rate of solvolysis of α-methyl benzyl chloride dramatically increases with increasing content of water in liquid ammonia (**Figure 2.3**), as is generally observed in aqueous binary organic solvents,[34c,220] presumably the driving force coming from the differences in solvation of the leaving chloride anion, as shown by the large positive Gibbs transfer energy of chloride anion from water to ammonia or DMSO.[221]



Scheme 2.4

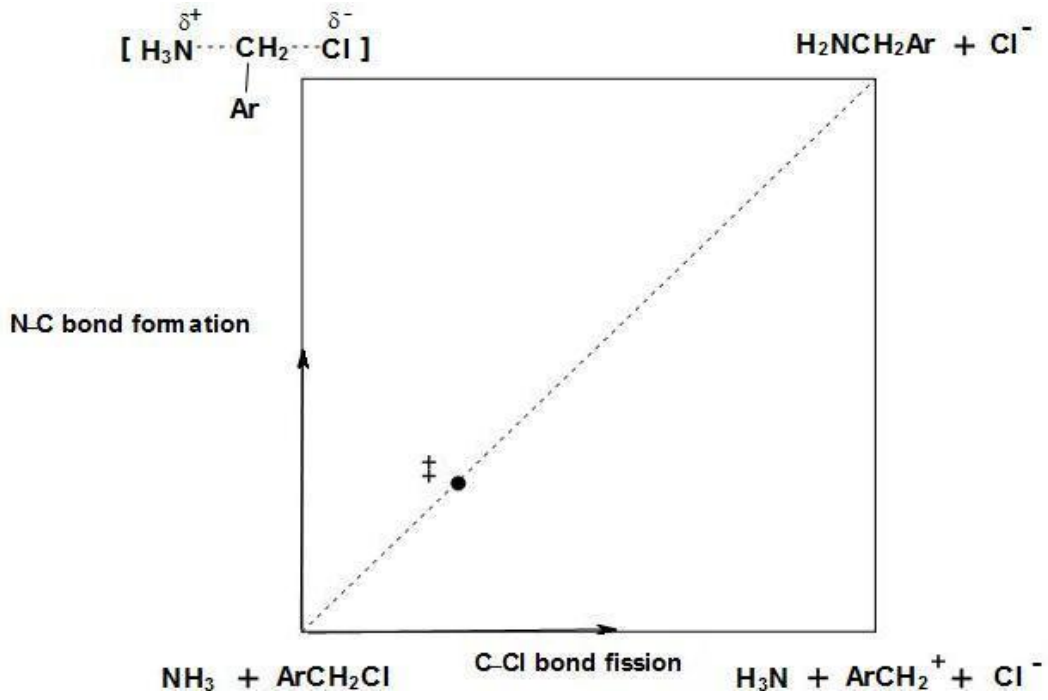


Figure 2.4 Jencks-More O'Ferrall reaction coordinate-energy diagram for the solvolysis of benzyl chloride derivatives in liquid ammonia at 25 ^{o}C

In summary, the solvolysis of alkyl halides in liquid ammonia is a concerted bimolecular process which follows a distinct S_N2 mechanism, as indicated by the substituent effects, activation parameters, salt effects and stereochemistry for the solvolysis of benzyl halides. The solvolysis of alkyl halides proceeds through a symmetrical 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 initial state (**Schemes 2.4** and **Figure 2.4**).

2.2 Solvolysis of aromatic compounds

Aryl halides and aromatic heterocyclic halides undergo solvolysis in liquid ammonia to give the corresponding aromatic amines. The rates of these reactions were determined by monitoring the exponential appearance of product and disappearance of reactant using GC or HPLC normalised area as a function of time to give the first order rate constants for solvolysis which are dependent on the nature of the leaving group and aromatic substituents and show the expected trends (**Table 2.7**).

As expected, the rates of solvolysis of aryl halides in liquid ammonia are slower than those for aliphatic benzyl halides[222] but the reactivity of halobenzenes can be dramatically activated through the introduction of electron-withdrawing groups (**Table 2.7**). In liquid ammonia, there

Table 2.7 Solvolysis rate constants of some aromatic compounds in liquid ammonia

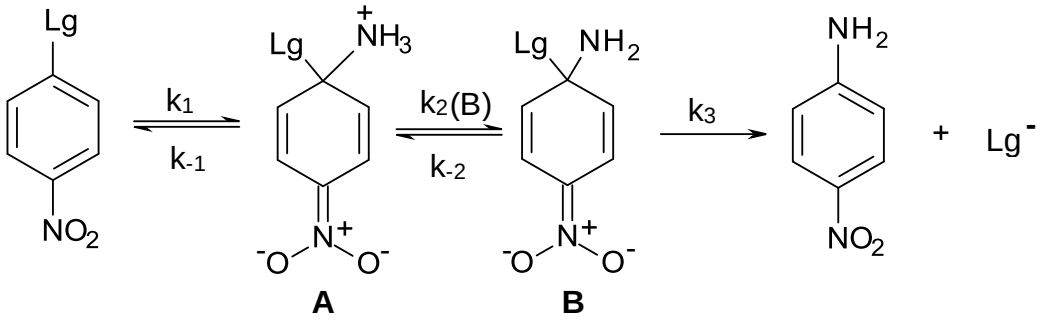
Substrate	**Temp (^oC)**	**$10^6k_0(s^{-1})$**	**$t_{1/2}$**
2-NFB	25	2.15×10^2	54mins
3-nitrofluorobenzene [a]	100	no reaction	——
4-NFB	20	7.86	24.4hrs
2,4-DFNB	25	6.72×10^3	1.7mins
2,4-dinitrofluorobenzene	25	$>1.4\times10^5$	<5s
4-nitrochlorobenzene	25	no reaction	——
2,4-dinitrochlorobenzene	25	6.18×10^3	1.9mins
3-nitroiodobenzene [b]	25	no reaction	——
2-NAB	20	5.81	33.1 hrs
4-NAB	25	5.11	37.7hrs
2,4-dinitroazidobenzene	25	$>1.4\times10^5$	<5s
2-chloropyrimidine	20	14.2	13.3hrs
2-chlorobenzthiazole	20	5.33	36.1hrs
2-fluoropyridine [a]	25	no reaction	——

[a] Stable for days at 100 ^{o}C, no reaction observed. [b] Stable for days at 25 ^{o}C.

is no reaction of unsubstituted halobenzenes and 3-nitrohalobenzenes at ambient temperature, but as expected, the 2- and 4-nitro activated derivatives and the substituted aryl fluorides are much more reactive.[223] The introduction of additional fluoro or nitro groups increases the solvolysis rates by more than 4 orders of magnitude. The solvolysis rate of 4-NAB, in the absence of salts, are similar to those for 4-NFB, but that for 2-NFB is nearly two orders of magnitude greater than that for 2-NAB.

Given the demonstration that nitro substituted aromatic compounds without a leaving group reversibly form Meisenheimer complexes in liquid ammonia (**Scheme 1.1**), 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 2.5**). The first formed intermediate (**A**) will have a charged ammonium ion but product formation probably requires deprotonation to form the anionic intermediate (**B**) before the leaving group can be expelled, especially as liquid ammonia is a poor solvent for anions. We have shown that aminium ions in liquid ammonia are invariably deprotonated by the vast excess of basic solvent and so exist in their free base form (chapter 1). It is therefore likely that the zwitterionic intermediate (**A**) is rapidly converted to the thermodynamically more stable anionic intermediate (**B**) by proton transfer to the solvent (k_2 step in **Scheme 2.5** where B = NH_3). In fact the intermediate (**B**) may be formed directly from the reactants by general base catalysis by solvent ammonia. The rate-limiting step for solvolysis is therefore likely to be the breakdown of the intermediate (**B**), step k_3 (**Scheme 2.5**) which is also compatible with the observations for other aromatic nucleophilic substitutions in liquid ammonia (*vide infra*).



Scheme 2.5

The solvolysis rates of 4-NFB and 2-NFB show relatively small salt effects (**Figures 2.5** and **2.6**), however, it worth noting that 2M salt increases the rate for the 4-isomer nearly 3-fold but by only 28% for the 2- isomer (Appendix A: **Table A19**).

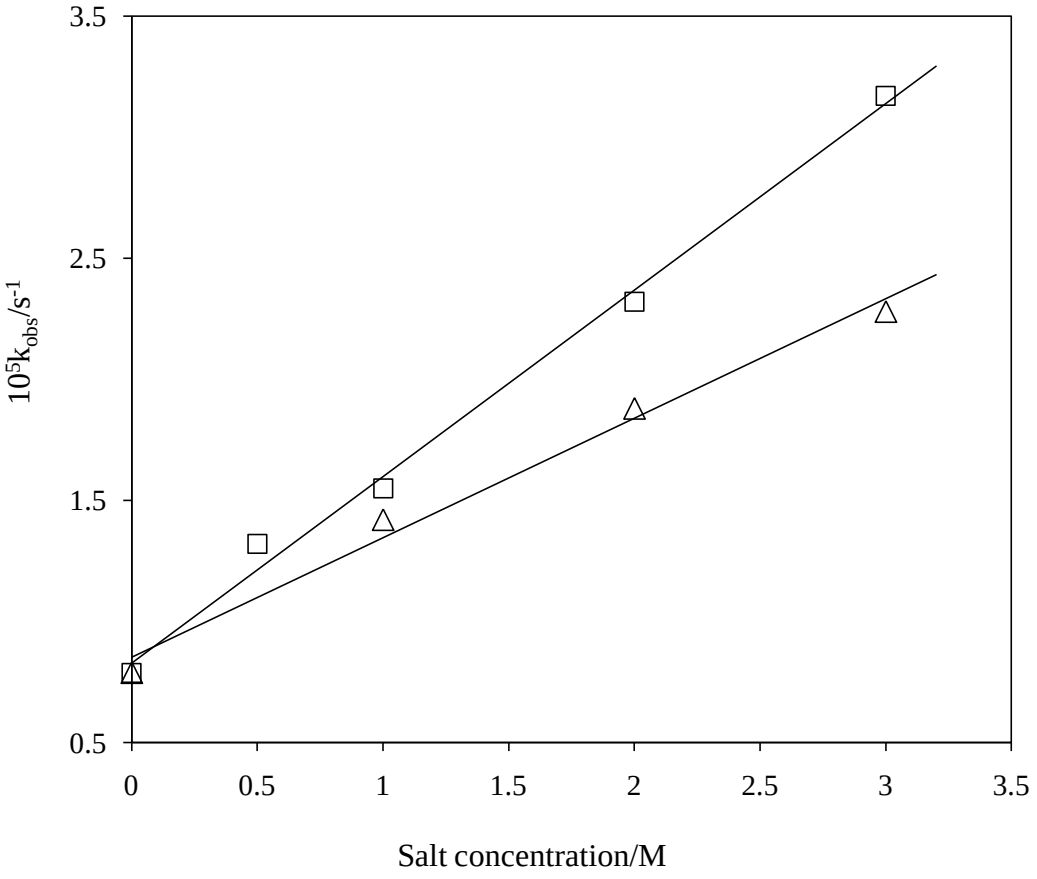


Figure 2.5 The first order rate constants for the solvolysis of 4-NFB as a function of added salt concentration in LNH_3 at 25 ^oC. (Δ) NH_4Cl; (□) $NaNO_3$

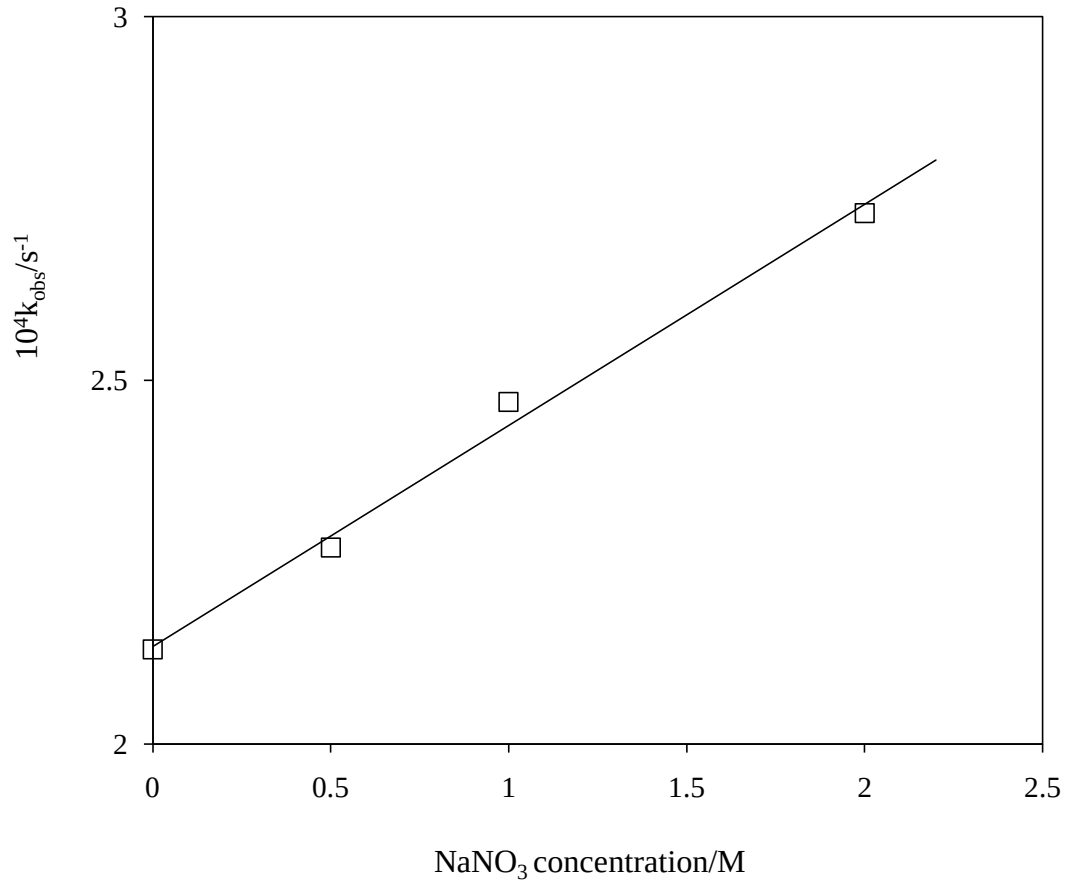
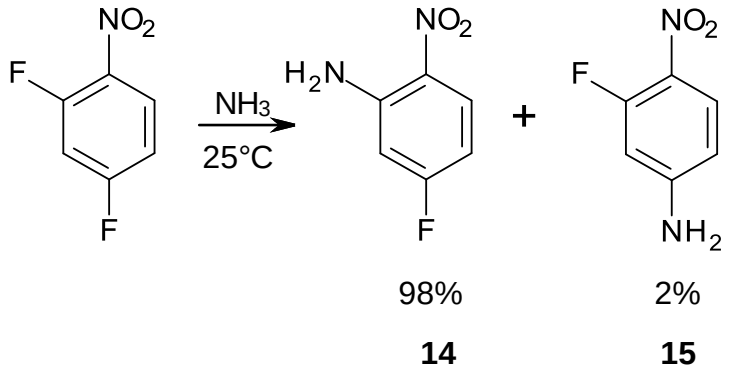


Figure 2.6 The first order rate constants for the solvolysis of 2-NFB as a function of added salt concentration in LNH_3 at 25 ^oC

The solvolysis rate of 4-nitroazidobenzene (4-NAB), in the absence of salts, is similar to that for 4-NFB, but that for 2-NFB is nearly two orders of magnitude greater than that for 2-NAB (**Table 2.7**). As well as a significant difference in salt effects, 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 for 2-NFB, but not 2-NAB, is also seen in the solvolysis of the more reactive di-substituted 2,4-DFNB which gives almost exclusively the *σ*-substituted derivative (**14**) as product in liquid ammonia at 25 ^oC (**Scheme 2.6)**. The product ratio of ortho to para isomers is compatible with the rate differences observed between 2-NFB and 4-NFB (**Table 2.7**). Interestingly, the product analysis of the solvolysis of 2,4-DFNB in liquid ammonia shows that the solvolysis product ratio between **14** and **15** increases with,

although not very pronounced, the decreasing of the reaction temperature (**Table 2.8**, Appendix C: **Figures N28-N29**).



Scheme 2.6

Table 2.8 Product analysis (^{19}F NMR) for the solvolysis of 2,4-DFNB in liquid ammonia under various temperature

temperature(K)	**molar ratio 12/13**
288.2	52:1
295.2	49:1
308.2	43:1

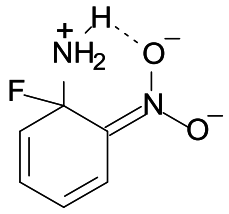
Preferential substitution ortho to the nitro group is sometimes observed in the reactions of halonitrobenzenes with neutral nucleophile, and even with sterically hindered nucleophiles.[224] Bunnett indicated that a halogen atom ortho to a nitro group could lead to the rotation of the nitro group out of benzene plane which weakens the conjugation due to the secondary steric effect, thus the reduced ratio between ortho and para would be expected.[225] On the contrary, Miller stated that although the nitro group ortho to the halogen atom is not coplanar to the ring in the initial state, it can be so in the transition state, so the reduction in activating power due to absence of coplanarity has little or no importance in determining the para and ortho ratios.[226]

The reason for the higher reactivity of ortho over para position for nitrofluorobenzenes in nucleophilic substitution is unlikely to be attributable to the steric effect of fluorine, given the

Van Der Waals radius of fluorine is relatively small (1.47 A).[227] It is therefore likely that the enhanced reactivity of 2-NFB over 4-NFB is due to a transition state effect. In support of this, entropy of activation for the ortho-isomer is less negative than that for the para-isomer (**Table 2.9**, Appendix A: **Tables A21** to **A23** and **Figures A21** to **A23**). Although this is compatible with some interaction between the ortho substituents such as the formation of an intramolecular hydrogen bond within the activated complex to stabilise the intermediate (**16**),[228] it would not explain why this favourable interaction cannot occur with 2-NAB. The generation of negative charge on the nitro group oxygens in the σ-adduct formed from 4-NFB requires solvation and restriction of solvent molecules giving rise to a slightly more negative entropy of activation.

Table 2.9 The rates and activation parameters of the solvolysis of 2-NFB, 4-NFB and 2,4-DFNB in LNH_3 at 25 ^oC

substrate	$10^6 k_{obs}$ / s^{-1}	$k_{rel.}$	$\Delta G^{\ddagger}$ / kJ $mole^{-1}$	$\Delta H^{\ddagger}$ / kJ $mole^{-1}$	$\Delta S^{\ddagger}$ / J $K^{-1}mole^{-1}$
4-NFB	7.86	1	101.1	53.0	-161.3
2-NFB	215	27.1	94.1	51.3	-143.4
2,4-DFNB	6717	852	87.7	40.0	-151.6

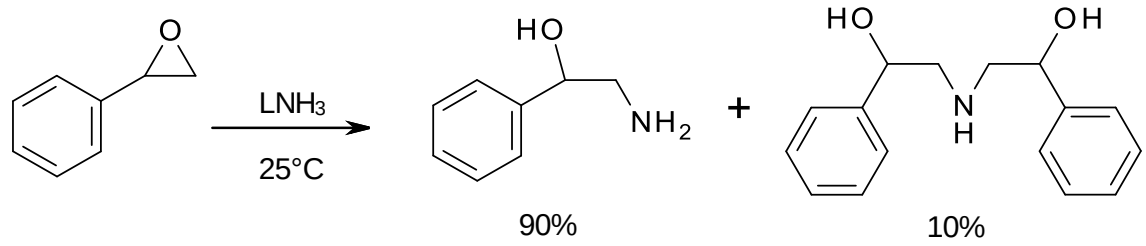


16

The additional fluorine in 2,4-DFNB compared with 2-NFB increases the solvolysis rate by about 30-fold presumably due to the inductive effect of fluorine which normally shows an additive effect on the reactivity of the polyfluorobenzenes.[229] Introduction of a second nitro group causes the solvolysis of 2,4-DNFB in liquid ammonia to be too fast to measure with our present equipment. The solvolysis of 4-nitrochlorobenzene does not occur at room temperature, unless under forcing conditions,[230] while the solvolysis of 2,4-

dinitrochlorobenzene completes within minutes, but much slower than that for 2,4-DNFB (**Table 2.7**)

2.3 Solvolysis of epoxides, esters and sulfonyl chloride



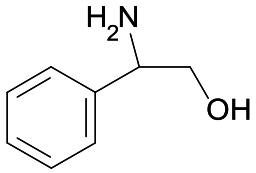
Scheme 2.7

Table 2.10 Pseudo first order rate constants (k_0) for the solvolysis of epoxides, esters and ketones in LNH_3 at 25 ^oC

substrate	$\mathbf{k_{0,\ LNH3}(s^{-1})}$	$\mathbf{t_{1/2}}$
styrene oxide	3.06×10^{-6}	62.9hrs
styrene oxide/1M NH_4Cl	6.89×10^{-6}	27.9hrs
phenyl acetate	>0.14	<5s
4-nitrophenyl acetate	>0.14	<5s
4-nitrophenyl pivolate	>0.14	<5s
phenyl benzoate	7.70×10^{-3}	1.5mins
methyl-4-nitrobenzoate	1.44×10^{-5}	13.4hrs
ethyl-4-nitrobenzoate	5.29×10^{-6}	36.4hrs
methyl-3-hydroxybenzoate	no reaction	——
triphenylphosphate	3.5×10^{-6}	54.4hrs
triethylphosphate	no reaction	——
benzenesulfonyl chloride	>0.14	<5s

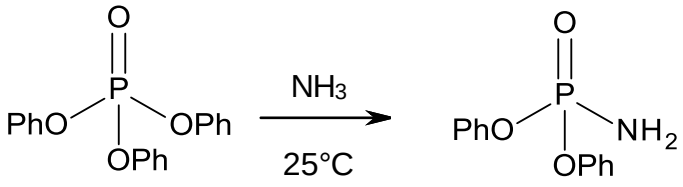
The solvolysis of styrene oxide is slow in liquid ammonia at 25 ^oC (**Table 2.10**), but smoothly to give the corresponding β-hydroxyamine as the major product, together with a small amount of bis-β-hydroxyamine as the minor product (**Scheme 2.7**). No oxygen-benzylic carbon bond

fission of styrene oxide is found by GC or HPLC analysis, which would lead to the formation of **17**. This is in stark contrast with the hydrolysis of styrene oxide in water at 25 ^{o}C. Although the rate of hydrolysis ($4.18\times10^{-6}s^{-1}$) is similar to that in liquid ammonia, the diol product is mainly formed by the attacking of the benzylic carbon from water molecule.[231] The solvolysis rate for styrene oxide in liquid ammonia does not significantly accelerated by added NH_4Cl, which is also in stark contrast with that for acid catalysed hydrolysis process of styrene oxide (**Table 2.10**).[231]Obviously, the hydrolysis of styrene oxide involves a process that the O-C bond dissociation ahead of N-C bond formation (D_N+A_N), on the contrary, the solvolysis in liquid ammonia probably follows a concerted mechanism (A_ND_N). It worth noting that, with 1M NH_4Cl as Lewis acid catalyst for the solvolysis of styrene oxide in liquid ammonia, the major products are bi- and tri-β-hydroxyamine.



17

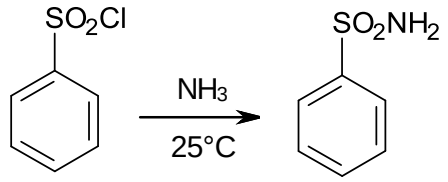
In liquid ammonia, esters with aryl groups solvolyse much faster than those with alkyl groups as leaving group (**Table 2.10**). The solvolysis of esters gives the corresponding amide and alcohol or phenol, and follows a classical addition-elimination mechanism (A_ND_E) in liquid ammonia. The solvolysis of triphenyl phosphate is slow and gives only mono-substituted amide (**18**) in liquid ammonia (**Scheme 2.8**), surprisingly, the less bulky triethyl phosphate fails to react with ammonia at 25 ^{o}C.



18

Scheme 2.8

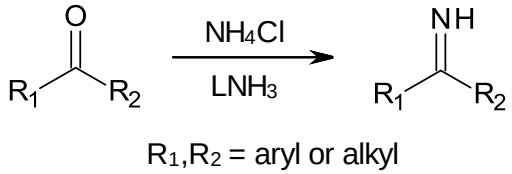
The rate for the solvolysis of benzenesulfonyl chloride in liquid ammonia is so fast that the accurate measurement is beyond our current experimental condition (**Scheme 2.9**). Interestingly, the solvolysis rate of benzenesulfonyl chloride in liquid ammonia is much faster than the hydrolysis rate at 25 ^{o}C,[232] although the leaving chloride anion is better solvated by water than liquid ammonia.



Scheme 2.9

2.4 Solvolysis of ketones with ammonium salt as catalyst

In the absence of ammonium salts or other Lewis acids, aromatic ketones, such as acetophenone and benzophenone, are very stable in liquid ammonia at room temperature or even higher. However, they can be smoothly converted into the corresponding ketimines in the presence of ammonium salts at room temperature with good to excellent yields in liquid ammonia (**Scheme 2.10** and **Table 2.11**).



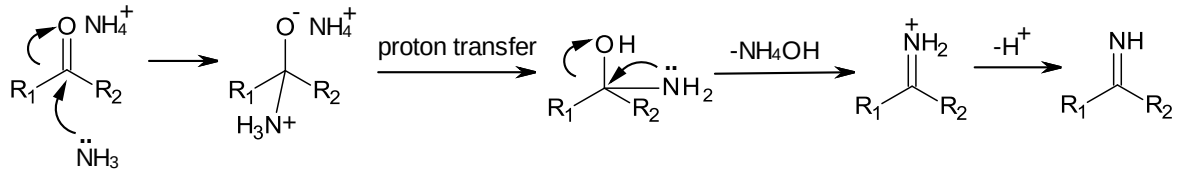
Scheme 2.10

Table 2.11 Ketimine yields for the solvolysis of ketones in the presence of various concentration of NH_4Cl in liquid ammonia at 25 ^{o}C[a]

	ketimine yield [b]		
ketone	**0.1M NH_4Cl**	**0.5M NH_4Cl**	**1M NH_4Cl**
acetophenone	95.2%	97.4%	98.5%
benzophenone	82.2%	86.9%	92.7%

[a] Reaction condition: 0.1M ketones with ammonium salt in 10ml liquid ammonia for 12hours. [b] GC yield.

The yield of the solvolysis of ketone is dependent on the concentration of NH_4Cl added, but reaction temperature is much lower and the yields are higher than previously reported.[233] Catalytic ammonium salts may have two functions in the solvolysis process, firstly it acts as a Lewis acid to activate the carbonyl group of ketones, which facilitates the attack from ammonia molecule; secondly it also can remove the resulting water from the system, thus significantly change the equilibrium towards the formation of ketimine (**Scheme 2.11**).



Scheme 2.11

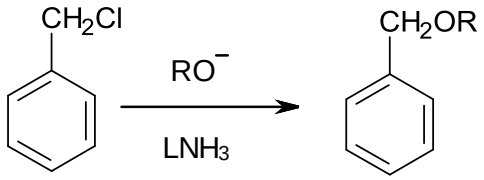
The solvolysis of ketones also can be efficiently catalysed by other Lewis acids in liquid ammonia, such as TiO_2, and gives excellent yields in a high temperature flow system using liquid ammonia as eluent.[234] These ketimines are very useful intermediates for the synthesis of primary amines though reduction in liquid ammonia.

3. Aliphatic nucleophilic substitution reactions in liquid ammonia Page

3 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). It is well known that the nature of the solvent used for these reactions can influence the mechanism adopted and the transition state structure with, for example, a gradation of transition states between the S_N1 and S_N2 extremes with varying degrees of participation by the solvent.[235] However, some theoretical calculations indicate that changes in solvent should not lead to significant changes in transition state structure.[29] An additional complication, particularly in solvents of low polarity, is the possible intervention of ion pairs. There are many examples of reactions of various nucleophiles with benzyl derivatives that show a mixed rate law compatible with the occurrence of simultaneous S_N1 and S_N2 mechanisms. There have also been attempts to predict when the change from one mechanism to the other occurs by variation in the structure of the reactants or solvent.

3.1 Nucleophilic substitution with oxygen-nucleophiles



Scheme 3.1

Generally, in nucleophilic substitution reactions, oxygen-nucleophiles act as hard bases having a small polarisability.[236] In protic solvents, these hard nucleophiles and oxygen anions are highly solvated to solvent molecules through hydrogen bonding, therefore the nucleophilicity of oxygen-nucleophiles are greatly decreased as bond formation to oxygen will require at least partial desolvation. On the contrary, due to the poor solvation of anions in dipolar aprotic solvents, the nucleophilicity of these oxygen-nucleophiles are generally greater than in protic solvents.[237] Aliphatic nucleophilic substitution reactions between anionic oxygen-nucleophiles and a neutral substrate are generally regarded as charge dispersion processes, and so the rates of these reactions should have a little or no sensitivity to the change of solvents according to

the Hughes-Ingold rules, However, the specific solvation of nucleophiles and nucleofuges could be crucial for the kinetics and mechanisms of these reactions.

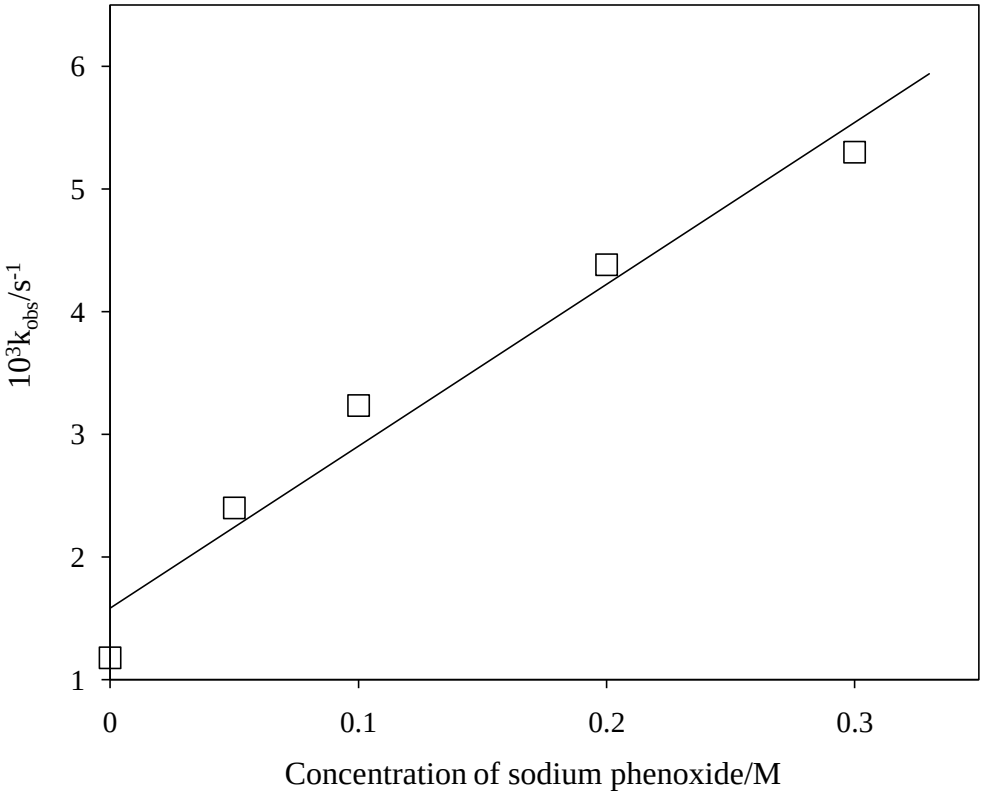


Figure 3.1 The dependence of the pseudo first rate constant on the concentration of sodium phenoxide for the reaction of benzyl chloride with phenoxide anion in LNH_3 (I = 0.3 M, $KClO_4$) at 25 ^oC

A variety of anionic oxygen-nucleophiles react with benzyl chloride in liquid ammonia to give the corresponding substitution products (**Scheme 3.1**), although solvolysis is sometimes competitive with these reactions and a mixture of products is obtained. The kinetics of nucleophilic substitution was determined under pseudo first order conditions with excess of nucleophile over substrate concentration. A typical plot of the rate constants against the concentration of the nucleophile shows an intercept corresponding to the rate constant for solvolysis under constant ionic strength (**Figure 3.1**, Appendix A: **Table A24**). The slope of these plots gives the corresponding second order rate constants for alkoxide ions reacting with benzyl chloride in liquid ammonia. This first order dependence of the pseudo first order

constants on the concentration of the nucleophile supports the conclusion from solvolysis kinetic data 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 benzylalkoxide ion with benzyl chloride in liquid ammonia compared with that in methanol (**Table 3.1**). The second order rate constants for the nucleophilic substitution of benzyl chloride by phenoxide ion are similar in liquid ammonia and DMF, a typical dipolar aprotic solvent, and are about 5000 times greater than that in methanol (**Table 3.2**).

Table 3.1 The second order rate constants of the reactions between alkoxides and benzyl chloride in different solvents at 25 ^oC

nucleophile	**temp/^{o}C**	**solvent**	**k_2/$M^{-1}s^{-1}$**	**$k_{rel.}$**	**reference**
BnONa/BnOH[a]	25	LNH_3	0.456	12500	this work
MeONa/MeOH[a]	25	LNH_3	0.201	5500	this work
MeONa	25	MeOH	3.61×10^{-5}	1	238
MeOLi	25	MeOH	2.41×10^{-5}	0.68	239

[a] The solubility of sodium alkoxides in liquid ammonia at room temperature is very poor. The rate for methoxide and benzylalkoxide with benzyl chloride was measured by adding 2.5 equivalents of the corresponding alcohol (the total alcohol volume added is less than 3.5%v/v) in order to give a homogeneous solution. There is no reaction between the alcohols and benzyl chloride in liquid ammonia at 25 ^oC.

Table 3.2 The second order rate constants of the reactions between phenoxide and benzyl chloride in different solvent

nucleophile	**temp/^{o}C**	**solvent**	**k_2/$M^{-1}s^{-1}$**	**$k_{rel.}$**	**reference**
PhONa	20	MeOH	8.02×10^{-6}	1	240
PhONa	25	LNH_3	2.01×10^{-2}	2500	this work
PhONa	20	DMF	4.15×10^{-2}	5100	240

These rates increase on going from protic to dipolar aprotic solvents 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.[241] This is also shown by the large positive Gibbs transfer energies of anions from protic solvents to non-polar and dipolar aprotic solvents.[57] On

the other hand, some dipolar aprotic solvents strongly favour the solvation of cations due to the availability of electron donation from a solvent molecule's lone pair, which can lead to the destruction ion pairs and thus an increased nucleophilicity of the counter-anion. One of main reasons for dipolar aprotic solvents favouring bimolecular concerted over a unimolecular mechanisms lies in their poor solvation of the leaving anion.

There is a small decrease in the second order rate constant of the reaction of benzyl chloride with phenoxide ion with increasing ionic strength by adding non-nucleophilic inorganic salts, e.g., $NaNO_3$, $KClO_4$. This is in line with the Hughes-Ingold rules,[211] that the increasing polarity of the medium will cause a small decrease of rate if the transition state involves charge dispersion between nucleophile, substrate and leaving group. Similarly, increasing ionic strength in liquid ammonia decreases the pK_a of the phenol leading to a weaker nucleophilic phenoxide ion.

The second order rate constants for substituted phenoxide ions reacting with benzyl chloride in liquid ammonia vary significantly with substituents (**Table 3.3**). 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.[242] The Brønsted plot for the rate constants in liquid ammonia using the aqueous pK_a of the phenol shows a very good linear free energy relationship (**Figure 3.2a**) with a $\beta_{nuc} = 0.66$.

Table 3.3 The second order rate constants of the reactions between 4-substituted phenoxide and alkoxide ions with benzyl chloride in LNH_3 at 25 ^oC

phenoxide/alkoxide ion	**pK_a (aq.) [a]**	**pK_a (LNH_3)**	**$10^2 k_{2,LNH3}$ ($M^{-1}s^{-1}$)**
4-cyanophenoxide	7.95	2.71	0.077
4-carbomethoxyphenoxide	8.47	4.04	0.273
4-chlorophenoxide	9.20	4.69	0.95
phenoxide	9.99	6.02	2.01
4-methoxyphenoxide	10.27	6.62	3.97
4-^{t}butylphenoxide	10.31	6.67	3.19

[a] Corresponding aqueous pK_a of phenols and alcohols are from ref.243.

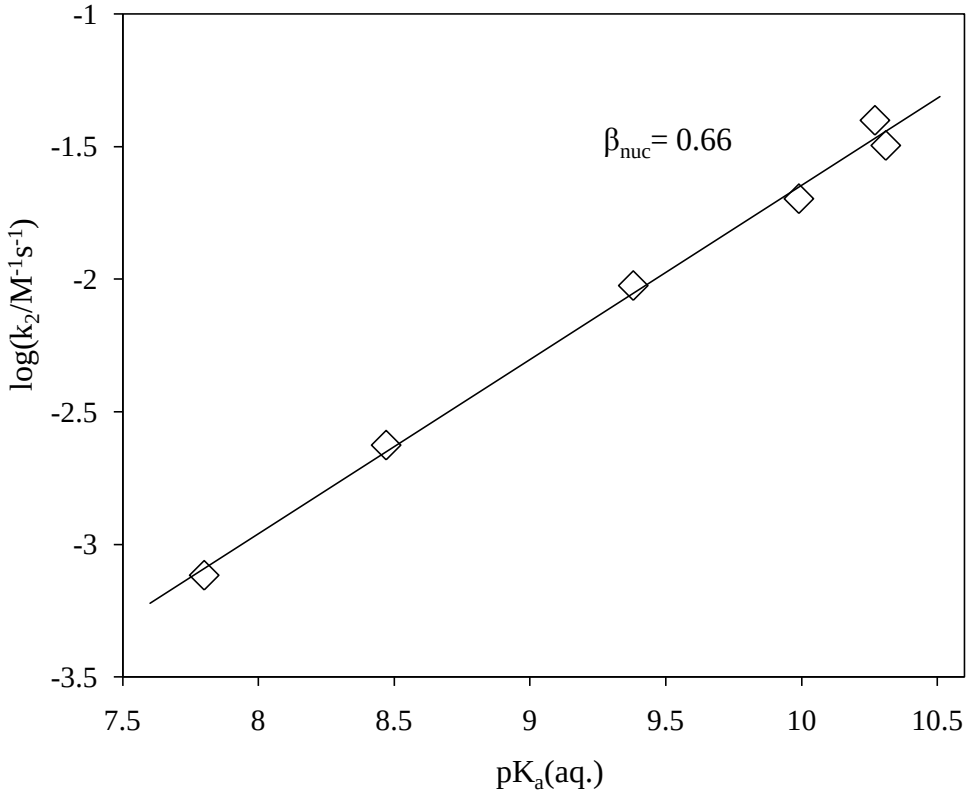


Figure 3.2a The Brønsted plot for the reaction of para substituted phenoxides with benzyl chloride in LNH_3 at 25 ^oC using the aqueous pK_a of the phenols

As shown in chapter 1, there is a linear relationship between the ionisation of substituted phenols in liquid ammonia and those in water, the slope of a plot of the pK_a of the former against the corresponding aqueous pK_a is 1.68 (**Figure 1.5**). Hence a more meaningful Brønsted β_{nuc} for the substituted phenoxides reacting with benzyl chloride in LNH_3 is 0.40 (**Figure 3.2b**). The latter value indicates the transfer of some negative charge from the attacking phenoxide anion to the benzyl group and the leaving chloride ion and partial bond formation between the phenoxide oxygen and the benzylic carbon in the transition state. The β_{nuc} of the analogous reaction in methanol is 0.28,[244] suggesting an earlier type of transition state with a smaller fraction of charge transferred from oxygen to carbon in this solvent. The solvation ability of a solvent is not only a function of its dielectric constant and dipole moment, but also of 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 from the ammonia lone pair, thus decreasing ion-pair formation.

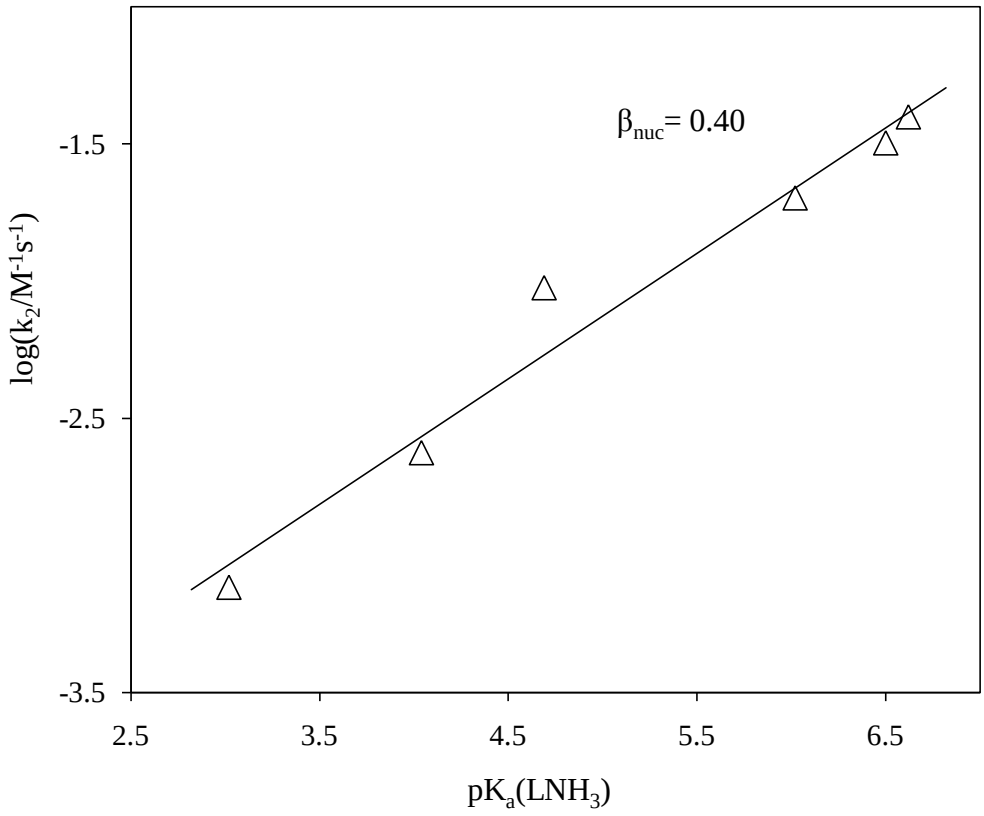


Figure 3.2b The Brønsted plot for the reaction of para substituted phenoxides with benzyl chloride in LNH_3 at 25 ^oC using the pK_a of the phenols in liquid ammonia

In order to obtain a more detailed picture of the transition state structure the rates of phenoxide ion reacting with substituted benzyl chloride were measured. A plot of the second order rate constants for this reaction against the Hammett constant for the substituent (**Figure 3.3**, Appendix A: **Table A25**) is linear apart from the typical deviation for 4-methoxybenzyl chloride.[245] The latter is not due to a change in mechanism from S_N2 to S_N1 as the kinetics are still clearly first order in phenoxide ion (**Figure 3.4**, Appendix A: **Table A26**). The most likely explanations 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[245a] 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.[245b,c] Further investigation shows that 3-methoxy derivative behaves normally, as expected, and fits the linear relationship well.[246] The ρ value of 1.11 for the reaction of phenoxide ion with 4-substituted benzyl chlorides, excluding the 4-methoxy derivative (**Figure 3.3**), suggests that appreciable charge has been transferred from phenoxide oxygen to benzylic carbon in the transition state and which is more than that lost to the departing chloride ion. The ρ value of 1.11 contrasts markedly with that of zero for the solvolysis reaction (**Figure 2.1**). 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.

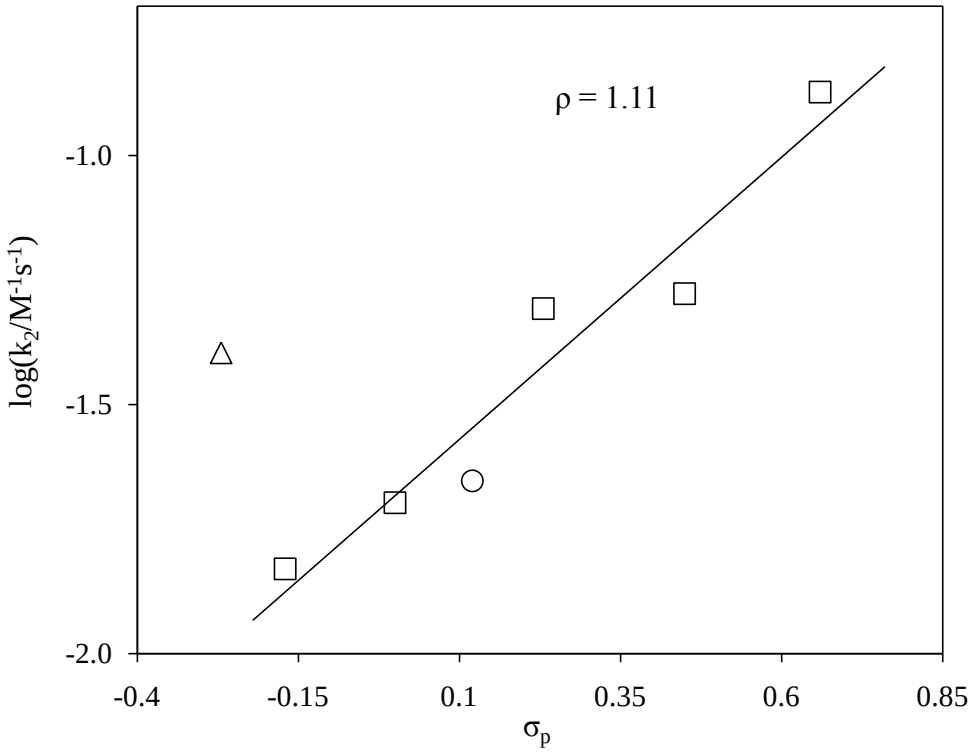


Figure 3.3 The Hammett plot for the reaction between 4-substituted benzyl chloride with phenoxide anion in LNH_3 at 25 ^oC, triangle (△) shows the positive deviation of 4-methoxybenzyl chloride, while round circle (○) shows 3-methoxybenzyl chloride fits the linear relationship.

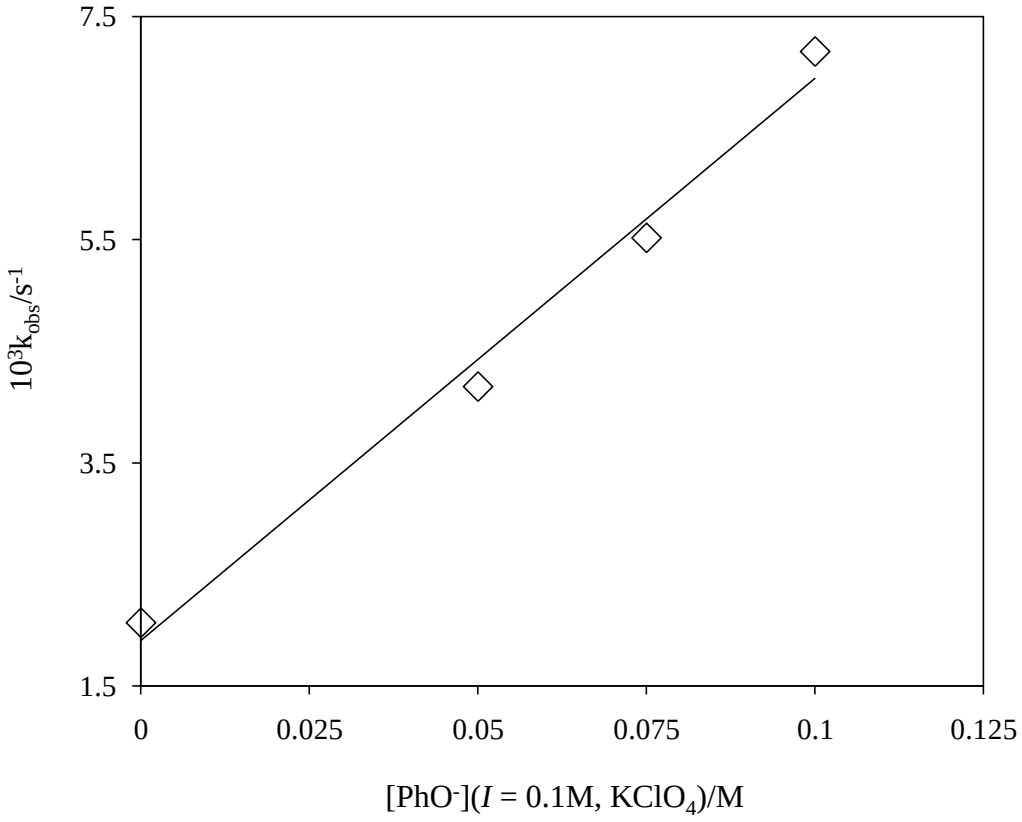
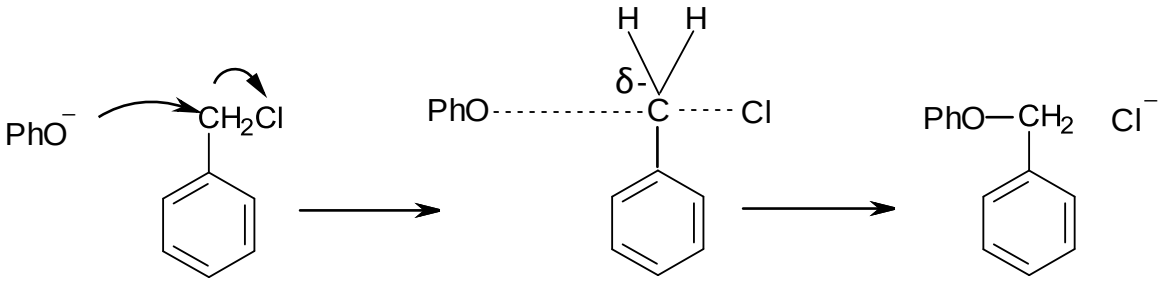


Figure 3.4 The dependence of the pseudo first order rate constant on the concentration of sodium phenoxide for the reaction of 4-methoxybenzyl chloride with phenoxide anion in LNH_3 (I = 0.1 M, $KClO_4$) at 25 ^oC



Scheme 3.2

The Hammett and Brønsted plots indicate that most of the negative charge is distributed between the attacking phenoxide oxygen and the benzylic methylene and aromatic ring with little transferred to the leaving chloride anion, therefore, there is relatively little C-Cl bond

fission in the transition state (**Scheme 3.2**). The changes in transition state structure can be envisaged on a Jencks-More O'Ferrall reaction coordinate-energy diagram (**Figure 3.5**) with separate axes for O-C and C-Cl bond formation and cleavage, respectively.

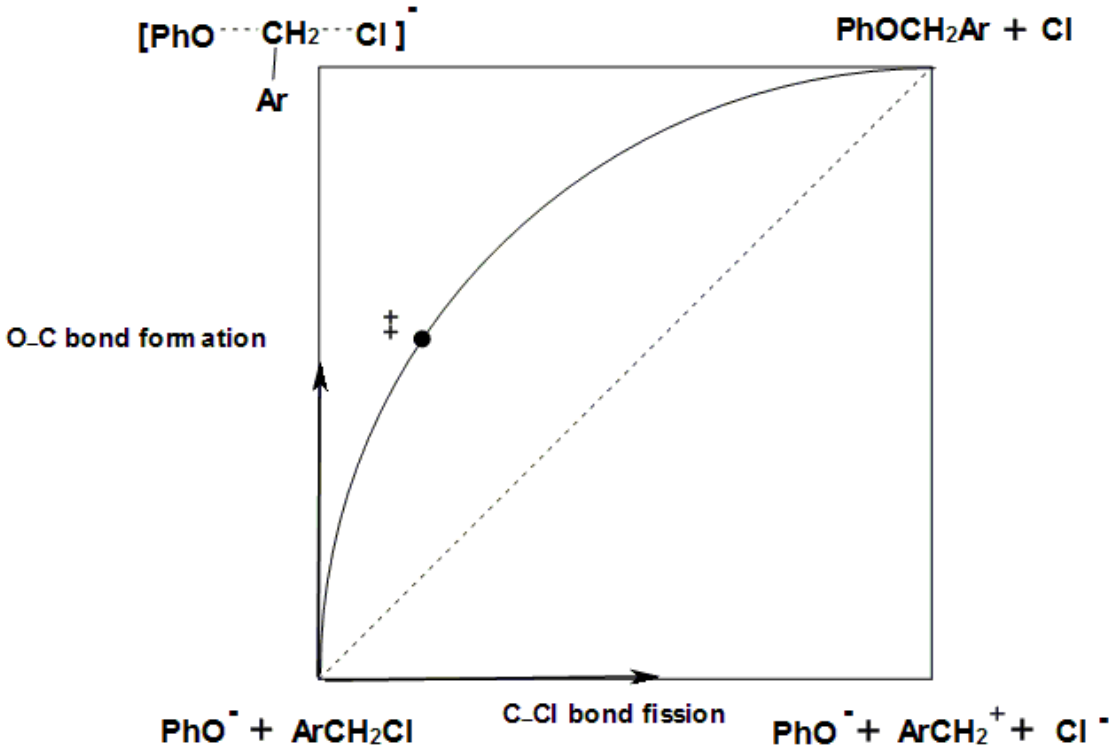
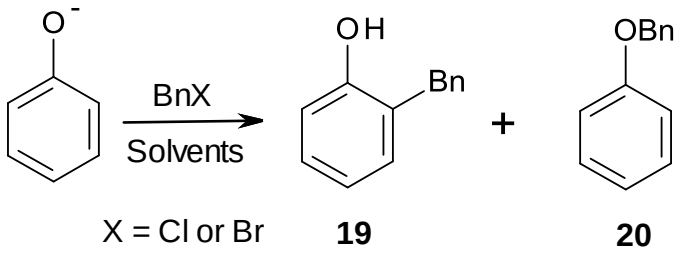


Figure 3.5 Jencks-More O'Ferrall reaction diagram for the reaction between phenoxide anion and benzyl chlorides in LNH_3 at 25 ^oC

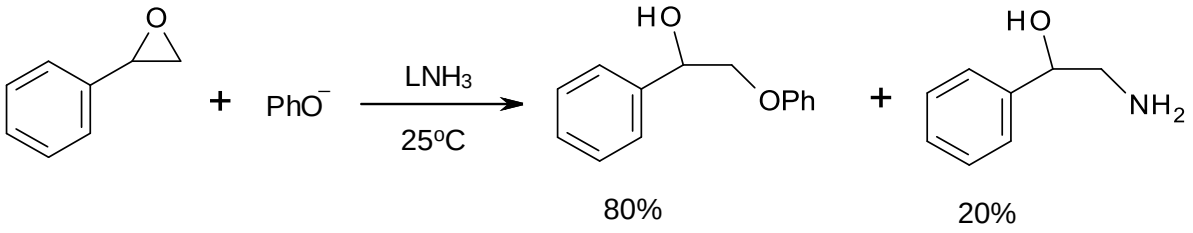
Phenoxide ion is a well known ambident nucleophile[247] and it can undergo both C- and O-alkylation (**Scheme 3.3**) and which reaction dominates depends very much on the medium. Under homogeneous conditions in liquid ammonia, with 0.3M sodium phenoxide and 0.1M



Scheme 3.3

benzyl chloride there is less than 0.5% solvolysis product and no C-alkylated product (**19**) formed, giving a selectivity for O-alkylation (**20**) of almost 100% within half an hour. In diethyl ether as solvent, under heterogeneous conditions, the reaction between benzyl bromide and phenoxide ion, after 3 days at 35 ^{o}C, the major product (75%) is the C-alkylated one.[247] 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.

The nucleophilic substitution reaction between 0.01M styrene oxide and 0.1M phenoxide in liquid ammonia is slow ($t_{1/2} \approx 35$ hours) but faster than that for the solvolysis and gives **21** as the major product (**Scheme 3.4**).

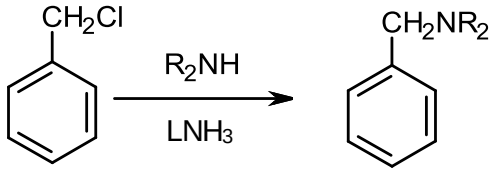


21

Scheme 3.4

3.2 Nucleophilic substitution with nitrogen-nucleophiles

The background solvolysis reaction in liquid ammonia obviously involves nucleophilic attack by a nitrogen nucleophile, but benzyl chloride also reacts with secondary amines in liquid ammonia to give predominantly the substituted product (**Scheme 3.5**). The pseudo first order



Scheme 3.5

rate constants for the aminolysis of benzyl chloride and the reactions of benzyl chloride with nitrogen anionic nucleophiles were obtained by the general sampling method and measuring the formation of the product and the disappearance of the reactant by GC analysis (**Table 3.4**). The reaction between benzyl chloride and neutral amines may give neutral or charged products depending on the pK_a of the product relative to the ammonia solvent; although, as was shown in chapter 1, all amines exist in their free base form in liquid ammonia. The reaction between two neutral reactants will have a transition state structure in which the overall charge is neutral, but charge is created on the N-nucleophile during the formation of the activated complex, assuming no general base catalysis by the solvent. The differences in solvation of the reactant amines by aprotic and dipolar aprotic solvents is not as marked as for anions and the rate differences between protic and dipolar aprotic solvents is not so pronounced as that seen for anionic oxygen nucleophiles.

There is a first order dependence of the pseudo first order rate constant on the concentration of the amine for the aminolysis of benzyl chloride by morpholine (**Figure 3.6**, Appendix A: **Table A27**), which again confirms that these reactions follow a bimolecular S_N2 type mechanism. The rate constant for hydrazine was obtained by adding 1M hydrazine dihydrochloride to liquid ammonia to generate the free base and so to correct for the effect of 2M NH_4Cl produced from 1M $N_2H_6Cl_2$, the rate of solvolysis of benzyl chloride with was measured in the presence of 2M NH_4Cl ($k_{obs} = 3.42 \times 10^{-3} s^{-1}$) and so the derived second order rate constant (**Table 3.4**) is that for ionic strength 2.0M. There is no reaction of neutral imidazole or triazole with benzyl chloride in liquid ammonia, but there is with their anionic salts, indicating that these anions remain deprotonated in liquid ammonia.

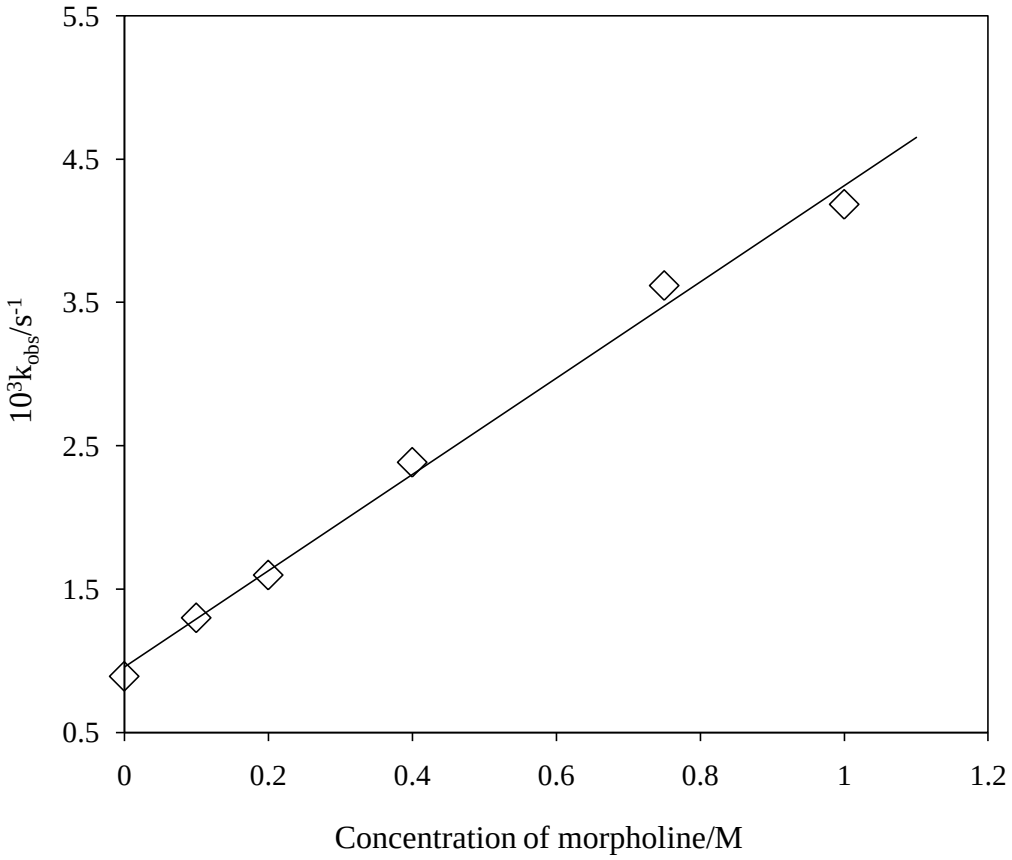


Figure 3.6 The dependence of the pseudo first order rate constant on the concentration of morpholine for the reaction of benzyl chloride with morpholine in LNH_3 at 25 ^oC

The second order rate constants for the aminolysis of benzyl chloride with various amines (**Table 3.4**) generate a reasonable Brønsted plot using the aqueous pK_a of the amine to give a β_{nuc} of 0.21 (**Figure 3.7**). This plot includes both neutral and negatively charged amines and yet both types give a reasonable single plot. Given the work described earlier which showed that all amines exist in their free base unprotonated form in liquid ammonia it is not possible to evaluate a Brønsted plot using the pK_a of the aminium ions in this solvent. Nonetheless, the apparent value of 0.21 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.

Table 3.4 The second order rate constants for the aminolysis of benzyl chloride with various N-nucleophiles in LNH_3 at 25 ^oC

nucleophile	**pK_a (aq.) [a]**	**$10^2k_2(M^{-1}s^{-1})$**
pyrrolidine	11.4	2.67
piperidine	10.4	1.70
morpholine	8.5	0.324
sodium azide	4.7	0.773
sodium triazolate	10.3	0.942
sodium benzotriazolate	8.37	0.261
sodium imidazolate	14.5	5.56
hydrazine[b]	8.1	0.514

[a] Corresponding aqueous pK_a of amines are from and ref. 248. [b] 1M hydrazine dihydrogen chloride was used.

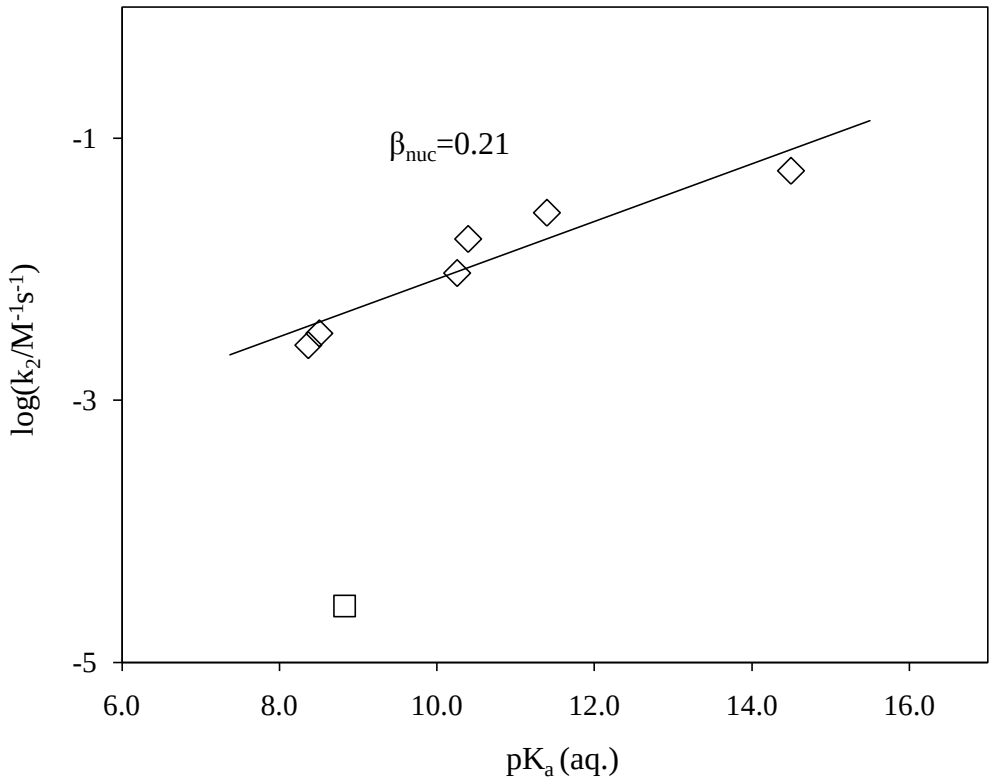
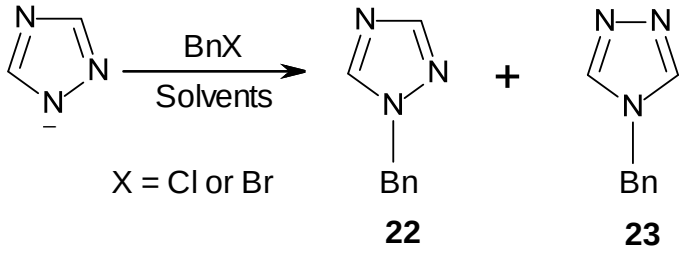


Figure 3.7 The Brønsted plot for the substitution of benzyl chloride by various amines in LNH_3 at 25 °C, ammonia (□) is negatively deviated from the line, but the positive deviation of azide anion is not shown.

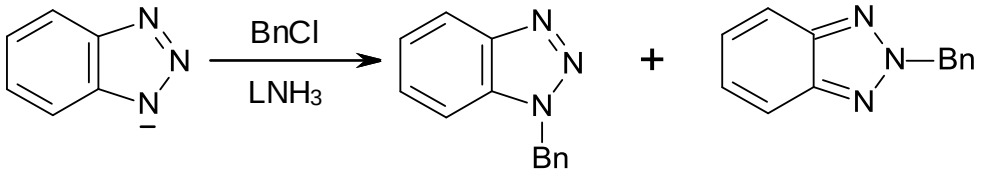
The second order rate constant for ammonia shows a large negative deviation from the Brønsted plot explaining why aminolysis by amines is easily observed in liquid ammonia. This could result from the formation, in the transition state, of only one possible hydrogen bond donor on the attacking nucleophile from secondary amines compared with three from ammonia, resulting in either a considerable energetic cost in terms of solvent reorganisation or a lack of hydrogen bond stabilisation/solvation, making ammonia less reactive. The rate constant for azide ion reacting with benzyl chloride in liquid ammonia shows a positive deviation of about 15 fold from the Brønsted plot (**Figure 3.7** and **Table 3.4**). It is not known if there is a similar deviation in the plot of the pK_a of aminium ions in liquid ammonia against their corresponding values in water and so it is not known if this deviation is a consequence of a higher basicity than 'expected' of azide ion in liquid ammonia or an enhanced reactivity. The other anionic nitrogen nucleophiles studied may be subject to more steric hindrance compared to azide ion. The rate constant for azide ion reacting with benzyl chloride in liquid ammonia is only about 150-fold[241a] greater than that in methanol and this relatively modest rate difference is in stark contrast to the 2500-fold rate enhancement for phenoxide anion reacting with benzyl chloride in liquid ammonia compared with that in methanol. Presumably, the difference in solvation energies of azide anion in liquid ammonia and methanol is relatively smaller than that of phenoxide ion.



Scheme 3.6

1,2,4-Triazolate and benzotriazolate anions are widely used in agriculture and pharmaceutical industries[249] and, as they are ambident nucleophiles,[250] the regioselectivity of their nucleophilic reactions is important of interest. In liquid ammonia, within a few hours, the major product of equimolar reaction between benzyl chloride and sodium triazolate is 1-benzyl-1,2,4-triazole (**22**) rather than 4-benzyl-1,2,4-triazole (**23**) in a ratio of 12 : 1 (**Scheme 3.6**). Previous studies of this reaction in other solvents, often under heterogeneous conditions, also preferentially

gives 1-substituted triazole products, but with much lower selectivity and longer reaction times.[251]



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Scheme 3.7

Also 1-benzyl-1,2,3-benzotriazole (**24**) is the main product of the reaction of 0.1M benzotriazolate and benzyl chloride in liquid ammonia at 25 ^{o}C (**Scheme 3.7**), however, the background solvolysis reaction strongly competes with that of benzotriazolate anion. The rate of reaction between hydrazine and benzyl chloride with 2M NH_4Cl does not show a pronounced α-effect, in common with its general reactivity for nucleophilic attack at sp^3 carbon centres.[252]

In order to see if the difference in the susceptibility of the rate of nucleophilic substitution to the substituent in substituted benzyl chlorides for solvolysis (Hammett ρ = 0) and with phenoxide-ion (ρ = 1.11) is a function of the basicity, charge or nature of the attacking nucleophilic element (O vs N), the rate constants for the reaction of piperidine and triazolate with 4-substituted benzyl chloride were determined. A Hammett plot of the second order rate constants (**Figure 3.8**, Appendix A: **Tables A28** and **A29**) shows that the reaction with the neutral amine piperidine is insensitive to the para-substitutent in benzyl chloride, similar to that seen for solvolysis. By contrast, 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. Interestingly, the rate constant for triazolate anion shows the typical deviation for 4-methoxybenzyl chloride, similar to that seen with phenoxide ion.

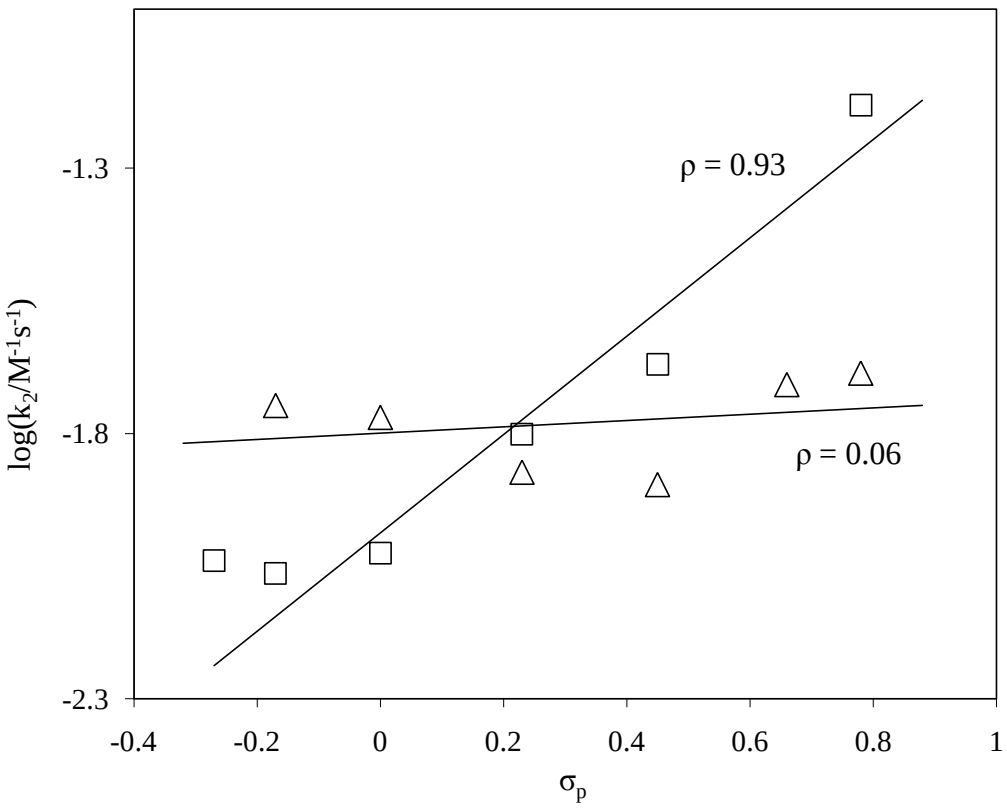
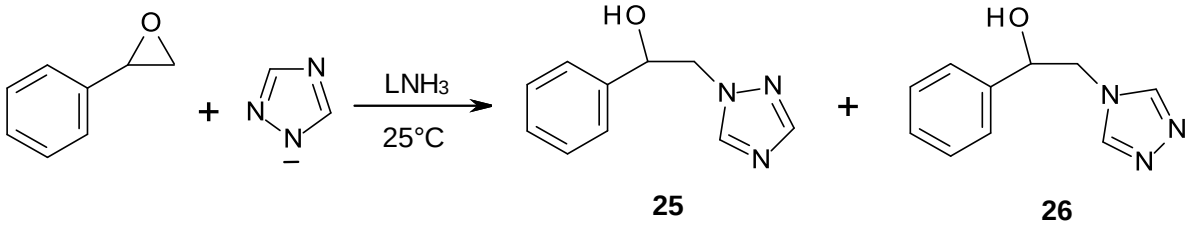


Figure 3.8 The Hammett plot for the reaction of 4-substituted benzyl chloride with piperidine (△) and triazolate anion (□) in LNH_3 at 25 ^oC.

There is no nucleophilic reaction observed between 0.1M aniline and 0.01M benzyl chloride in liquid ammonia at 25 ^oC, except for the solvolysis reaction product benzylamine, and the rate of the solvolysis is not significantly changed by the added aniline. The predicted second order rate constant determined by extrapolation of the Brønsted plot for amines (**Figure 3.7**) for an aminium ion of pK_a 4.6 (i.e. that corresponding to anilinium ion) is 5.50×10^{-4} $M^{-1}s^{-1}$, so 0.1M aniline would be predicted to have a pseudo first order rate constant of 5.50×10^{-5} s^{-1}compared with 8.89×10^{-4} s^{-1} for the solvolysis.

High regioselectivity for the reaction between 0.1M 1,2,4-triazolate anion and 0.01M styrene oxide is found in liquid ammonia (**Scheme 3.8**). The reaction was complete after 85 hours at room temperature, and the total yield of the reaction is 95% according to GC and HPLC analysis. The ratio between **25** and **26** is 30:1, which is much higher than those previously reported in conventionally used solvents.[253]



Total yield 95%, **25**:**26** = 30 : 1

Scheme 3.8

3.3 Nucleophilic substitution with sulfur-nucleophiles

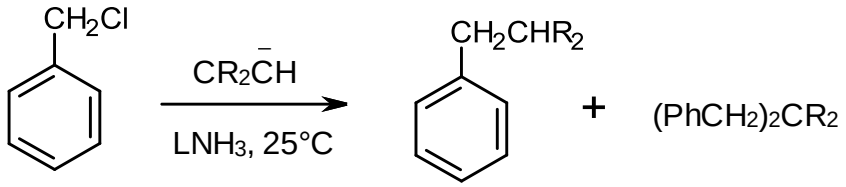
Thiophenoxide is a good nucleophile in many reactions with electrophilic centres largely due to the 'softness' of the sulfur anion.[254] The rate for the reaction between thiophenoxide and benzyl chloride in liquid ammonia is again much faster than that in typical protic solvents under the same conditions (**Table 3.5**).

Table 3.5 Second order rate constants for reaction of thiophenoxide with benzyl chloride in various solvents

nucleophile	**temp/^{o}C**	**solvent**	**$10^2k_2/M^{-1}s^{-1}$**	**reference**
PhSNa	25	MeOH	2.42	239
$PhSNH_4$[a]	20	LNH_3	3.15×10^3	this work
PhSNa	25	DMSO	$\sim10^8$	255

[a] Thiophenol (aqueous $pK_a = 6.5$) is fully ionised in liquid ammonia, see ref. 256 for details.

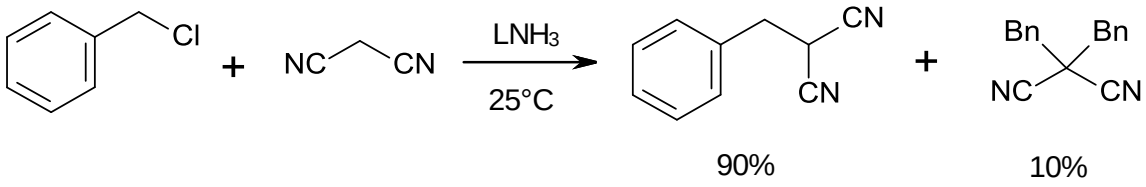
3.4 Nucleophilic substitution with carbon-nucleophiles



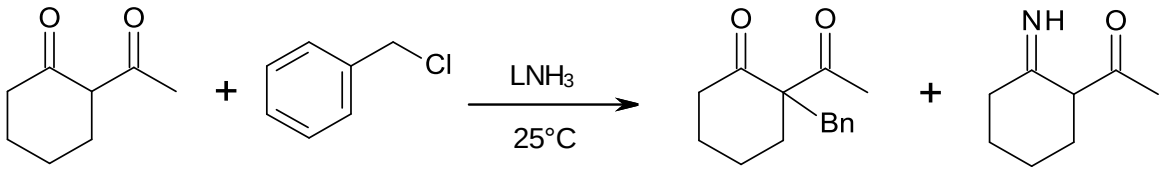
Scheme 3.9

The nucleophilic substitution reactions of benzyl chloride by carbanions in liquid ammonia are complicated by self-ionisation, dibenzylisation and instability of these carbon nucleophiles (**Scheme 3.9**). For examples, as shown earlier by NMR studies, carbon acids with a pK_a (DMSO) < 15, such as malonodinitrile, and 2-acetylhexanone, will be deprotonated in liquid

ammonia at room temperature, hence the nucleophilic substitution reactions between these carbon acids and benzyl chloride can occur without the aid of strong bases in liquid ammonia as is often required in other solvents. The reaction between 0.2M malonodinitrile and 0.01M benzyl chloride gives both mono-benzylated and dibenzylated products, but with the former dominant (**Scheme 3.10**), and with 0.5M malonodinitrile as nucleophile, less than 1% dibenzylated product is formed. The reaction between 0.2M 2-acetylhexanone with 0.01M benzyl chloride in liquid ammonia at 25 ^{o}C forms the corresponding mono-benzylated product, and also a small amount of 2-iminocyclohexyl ethanone, which is due to the solvolysis of the 1,3-diketone in liquid ammonia (**Scheme 3.11**).



Scheme 3.10



Scheme 3.11

Malonate diethyl ester and benzyl cyanide remain in their neutral forms and are stable in liquid ammonia at room temperature, however, their anionic conjugate bases can be generated in situ by using sodium amide in liquid ammonia and these carbanions react readily with benzyl chloride to give only mono-benzylated products.

The second order rate constants for cyanide ion reacting with benzyl chloride in various solvents are given in **Table 3.6** which shows that its reactivity is similar to that in DMF. The second order rate constants for carbanions reacting with benzyl chloride in liquid ammonia are given in **Table 3.7**. The rates of reactions which involve different types of carbanions as nucleophiles are often found to be poorly correlated with the corresponding pK_a of their

conjugate acids in various solvents.[196,257] Some specific factors for a certian types of carbanion, such as solvent reorganisation and rehybridisation of nitroalkanes carbanions,[258] cyano carbon acids,[194,259] must be considered in order to rationalise the abnormal reactivities of these carbanions in nucleophilic substitution reactions.

Table 3.6 Second order rate constants for reaction of carbanions with benzyl chloride in various solvents

nucleophile	**temp/^{o}C**	**solvent**	**$10^3k_2/M^{-1}s^{-1}$**	**reference**
NaCN	25	LNH_3	2.18	this work
Et_4NCN	30	DMF/water=95:5	3.20	260
Et_4NCN	30	DMF/water=80:20	0.57	260
KCN	30	DMF/water=95:5	5.3	260
KCN	25	[bmim][PF6]	0.022	261

Table 3.7 Second order rate constants for various carbanions reacting with benzyl chloride in liquid ammonia at 25 ^{o}C and their corresponding pK_a in water and DMSO

carbon acid	**pK_a(aq)**	**pK_a(DMSO)**	**$10^3k_2(M^{-1}s^{-1})$**
malonodinitrile[a]	11.2	11.1	8.88
HCN	9.21	12.9	2.18
2-acetylhexanone[b]	10.1	14.1	6.44
diethyl malonate[c]	12.9	16.4	2.27
acetophenone[d]	19.1	19.8	256
benzyl cyanide[d]	21.9[e]	21.9	1400

[a] 0.5M malonitrile and 0.01M benzyl chloride. [b] 0.2M 2-acetylhexanone and 0.01M benzyl chloride. [c] Sodium malonate anion was generated in situ by reacting diethyl malonate(1.25eq.) with $NaNH_2$ (1eq.) in liquid ammonia until all the solid ($NaNH_2$) disappeared. The reaction was studied under the pseudo first order conditions. The product was confirmed by GC-MS. The tests showed that without adding $NaNH_2$ diethyl malonate does not react with benzyl chloride and diethyl malonate is stable in liquid ammonia at 25 ^{o}C for days.[d] 0.15M carbon acids and 0.1M $NaNH_2$, then 0.01M benzyl chloride injected into the reaction vessel. The excess carbon acids do not react with benzyl chloride. [e] pK_a in DMSO, no aqueous pK_a data available.

The Brønsted plot for the reactions between various common carbanions and benzyl chloride in liquid ammonia at 25 ^{o}C gives an apparent β_{nuc} = 0.30, using pK_a of their corresponding carbon acids in DMSO. However, the exact pK_a of these carbon acids in liquid ammonia are

unknown (**Table 3.7** and **Figure 3.9**). The positive deviation of malonodinitrile anion from the correlation line is observed in other systems,[262] and reason for this is probably due to the negative charge mainly resting on the central carbon as charge delocalisation is accompanied by an unfavourable structure,[194,196] thus makes malonodinitrile a better nucleophile compared with strongly delocalised carbanions.

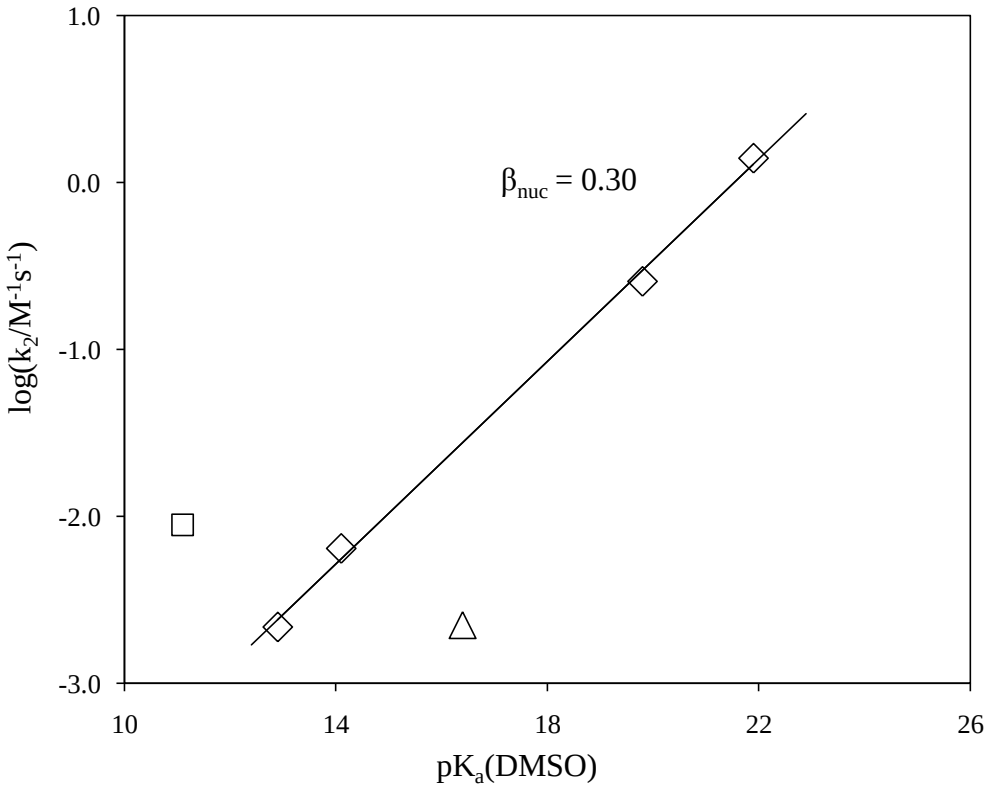


Figure 3.9 Brønsted plot for the reactions of some carbanions with benzyl chloride in liquid ammonia at 25 ^{o}C using the pK_a of their conjugate acids in DMSO. (□) Shows malonodinitrile positively deviated from the line, and (△) shows malonate diethyl ester negatively deviated from the line.

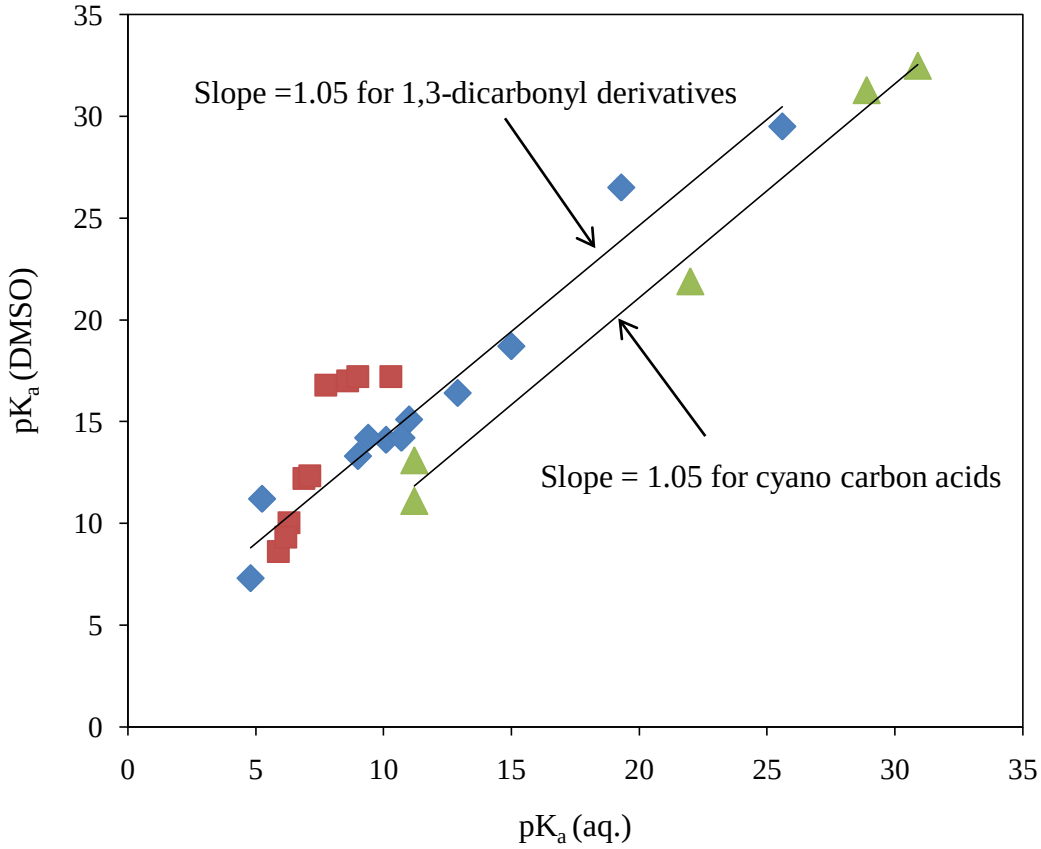


Figure 3.10 pK_a of carbon acid in DMSO against its aqueous pK_a. (■) nitroalkanes; (◆) 1,3-dicarbonyl derivatives; (▲) cyano carbon acids.

Interestingly, the aqueous pK_a of some common used carbon acids, except for nitroalkanes, correlate well with their corresponding pK_a in DMSO, and has a slope of 1.05 (**Figure 3.10**, for details, see: Appendix A: **Table A31**). This is very different from the similar plots seen previously for phenols (**Figure 1.5**), and this slope of 1.05 indicates that the pK_a of carbon acids are insensitive to the solvation effects of dipolar aprotic and protic solvents. Presumably this is due to the majority of the stabilisation coming from the delocalised carbanion structures which do not require substantial stabilisation from the solvent. The small $\beta_{nuc} = 0.30$ observed in the Brønsted plot, for carbanions reacting as nucleophiles in liquid ammonia, using their corresponding pK_a of carbon acids in DMSO, therefore becomes more meaningful, even without the knowledge of the pK_a of these carbon acids in liquid ammonia. Thus, similar to that seen for nitrogen anionic nucleophiles, the reactions between carbanions and benzyl

chloride occur with a transition state in which only a small amount of charge is removed from the carbanion to the benzylic carbon and leaving group and transferred in liquid ammonia.

In order to see if there is much charge development on the benzylic carbon in the transition state, the rates of nucleophilic substitution of malonate diethyl ester carbanion with substituted benzyl chlorides were determined. The Hammett plot the second order rate constants for the reaction of malonate diethyl ester carbanion with 4-substituted benzyl chlorides in liquid ammonia at 25 ^{o}C (**Figure 3.11**) is scattered, but an apparent $\rho = 0.87$ is obtained excluding 4-methyl and 4-methoxy benzyl chlorides. This ρ value, is smaller compared to those observed for the reaction of substituted benzyl chlorides reacting with phenoxide anion ($\rho = 1.11$) and nitrogen anionic nucleophiles ($\rho = 0.93$).

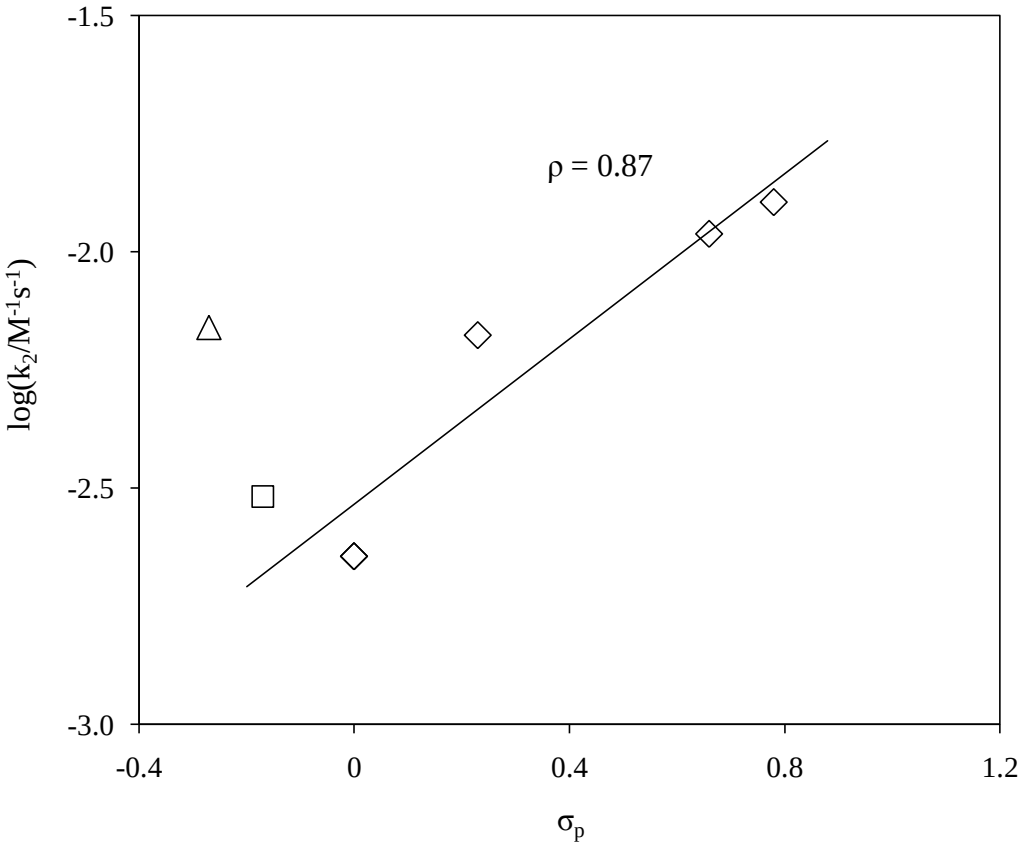


Figure 3.11 Hammett plot for the reaction of malonate diethyl ester carbanion with 4-substituted benzyl chlorides in liquid ammonia at 25 ^{o}C. (△) 4-methoxy benzyl chloride and (□) 4-methyl benzyl chloride show positive deviations from the line.

Interestingly, both 4-methyl and 4-methoxy benzyl chloride derivatives show a positive deviation from the correlation. The Hammett plot could be seen as two parts, showing the 'V' shape (**Figure 3.11**, Appendix A: **Table A30**) often seen in other correlations.[245c] This is again probably not because of a change in the reaction mechanism from S_N2 to S_N1, as the reaction rates all show a first order dependence on the concentration of malonate carbanion. This behaviour probably reflects a single transition state structure but with the 4-methoxy substituent stabilising the transition state with a different balance of polar and resonance effects.

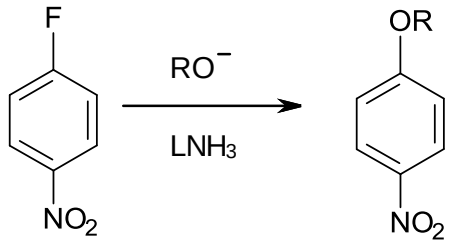
4. Aromatic nucleophilic substitution reactions in liquid ammonia Page

4. Aromatic nucleophilic substitution reactions

A significant proportion of reactions carried out by the pharmaceutical and agrochemical industries involve aromatic nucleophilic substitution reactions. The nature of the solvent used for these reactions influences both the kinetics and mechanisms of the process,[1] and when solvents are used in large quantities on an industrial scale, their efficiency, cost and environmental impact are major factors involved in their selection.

The rates of some S_NAr reactions are much faster in dipolar aprotic solvents than aprotic solvents largely due to the special solvation effects on these reactions. Generally speaking, due to the large dissociation energies for sp^2 C-X bond of aryl halides,[263] unsubstituted aryl halides are often inactive towards nucleophiles in aromatic substitution reactions, therefore electron withdrawing groups are often required for the activation of aryl ring. As described previously, 4-NFB solvolyses rather slowly but is active enough to react with various nucleophiles in liquid ammonia. For this reason, 4-NFB is chosen as a representative substrate to study the kinetics and mechanisms of S_NAr reactions in liquid ammonia.

4.1 Nucleophilic substitution with oxygen-nucleophiles



Scheme 4.1

Oxygen nucleophiles, such as alkoxide and phenoxide ions, react readily with 4-NFB in liquid ammonia to give the corresponding substitution product (**Scheme 4.1**). 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. With excess nucleophile, the rate of substitution shows pseudo first order kinetics and the associated rate constants show a first order dependence on the concentration of the anion and the derived

second order rate constants (**Table 4.1**, Appendix A: **Table A32**) were obtained from the slope of these plots (**Figure 4.1**).

The rates of reactions of 4-NFB with O-nucleophiles in liquid ammonia are are similar to those in DMSO and are 4-5 orders of magnitude faster than in methanol and. 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.

Table 4.1 The second order rate constants for the nucleophilic substitution of 4-NFB by oxygen anions in different solvents at 25 ^{o}C

O-nucleophile	**solvent**	**k_2/$M^{-1}s^{-1}$**	**$k_{rel.}$**	**reference**
MeO^-	LNH_3	>3.5[a]	>20,000	this work
MeO^-	DMSO-MeOH[b]	3.77×10^{-1}	2,106	264
MeO^-	MeOH	1.79×10^{-4}	1	265
PhO^-	LNH_3	0.0528	41,000	this work
PhO^-	DMSO[c]	0.52	400,000	266
PhO^-	MeOH	1.29×10^{-6}	1	28

[a] Rate is too fast to be measured accurately. [b] 80% (%v/v) DMSO-MeOH solution. [c] 20 ^{o}C

The second order rate constant for the reaction of phenoxide with 4-nitrochlorobenzene, 2.51×10^{-7} $M^{-1}s^{-1}$ at 25 ^{o}C, is 5 orders magnitude *smaller* than that of 4-NFB (**Table 4.1**), 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 2.5**) in which negative charge of an incoming nucleophile is spread into the aromatic ring and substituents through resonance, and so any stabilising influence of the solvent is expected to be less in the transition state than in the relatively localised reactant anion. Liquid ammonia, in common with dipolar aprotic solvents and unlike protic ones,[267,219] increases the rate of aromatic nucleophilic substitution by anions by several orders of magnitude primarily due to the less solvated but more reactive nucleophile.

There are some interesting differences in the activation parameters for oxygen anions reacting with 4-NFB in liquid ammonia compared with those in methanol. The lower free energies of activation in liquid ammonia appear as much lower enthalpies of activation which more than compensate for unfavourable large negative entropies of activation compared with those in the protic solvent methanol (**Table 4.2**, Appendix A: **Table A32**).

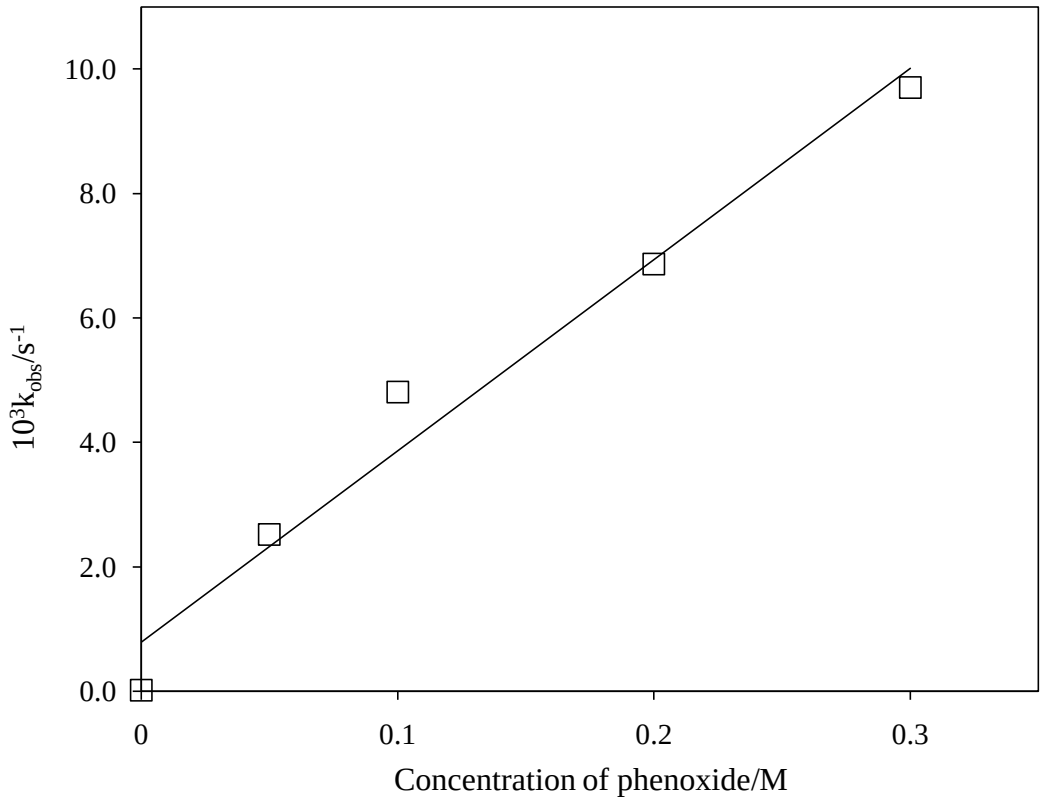


Figure 4.1 The dependence of the pseudo first order rate constants on the concentration of phenoxide ion for the reaction between 4-NFB and sodium phenoxide in LNH_3 at 25 ^oC (I = 0.3M, $KClO_4$).

Table 4.2 Activation parameters for the nucleophilic substitution of 4-NFB by oxygen anions in LNH_3 and methanol

nucleophile	**solvent**	**$\Delta H^{\ddagger}$ / kJ mol^{-1}**	**$\Delta S^{\ddagger}$ / J K^{-1} mol^{-1}**	**reference**
PhO^-	LNH_3	38.1	-141.3	this work
PhO^-	MeOH	102.9	-19.7	224d,e
MeO^-	MeOH	88.6	-27.6	224a,268

This suggests that the oxygen anions are strongly hydrogen-bonded to the solvent molecules in methanol so that the large negative entropy loss expected for the bimolecular process[269] is partially compensated by the release of solvent molecules on going from the initial reactant state to the transition state. By contrast, in liquid ammonia, the poor solvation of the oxygen anions leads to a smaller contribution to the entropy of activation from the solvent and consequently there is a large negative loss of entropy as a result of covalently linking two molecules together.[9] The good solvation of metal cations in liquid ammonia through electron donation from ammonia presumably also increases the nucleophilicity and reactivity of the counter anion in this solvent, which is reflected in the low enthalpy of activation compared with that in methanol.

A rigorous interpretation of linear free-energy relationships for reactions in liquid ammonia requires a knowledge of the effect of substituents on equilibria in this solvent. In chapter 1 the ionisation constants for substituted phenols in liquid ammonia and that these show a linear relationship with the corresponding values in water (**Figure 1.5**). The Brønsted plot for the reaction of 4-NFB with para-substituted phenoxides in liquid ammonia using the aqueous pK_a for the phenols gives an apparent β_{nuc} of 1.49, but a more meaningful β_{nuc} of 0.91 is obtained using the pK_a of the substituted phenols in liquid ammonia (**Figures 4.2a** and **4.2b**, Appendix A: **Table A34**). These values are much larger than those for the similar reaction of 4-NFB with phenoxides or thiophenoxides in protic solvents which are around 0.5.[270] The large value is indicative of significant, if not total, removal of the negative charge on the oxygen anion and complete bond formation in the transition state and therefore suggests that the decomposition of σ-complex is the rate limiting step. This is probably due to the difficulty of expelling and solvating the leaving fluoride anion from the Meisenheimer σ-intermediate (**Scheme 2.5**) in liquid ammonia.[271] As stated earlier, the second order rate constant for the reaction of phenoxide with 4-nitrochlorobenzene is 5 orders magnitude smaller than that of 4-NFB,[272] which probably reflects the less favourable formation of the σ-complex and expulsion of chloride ion.

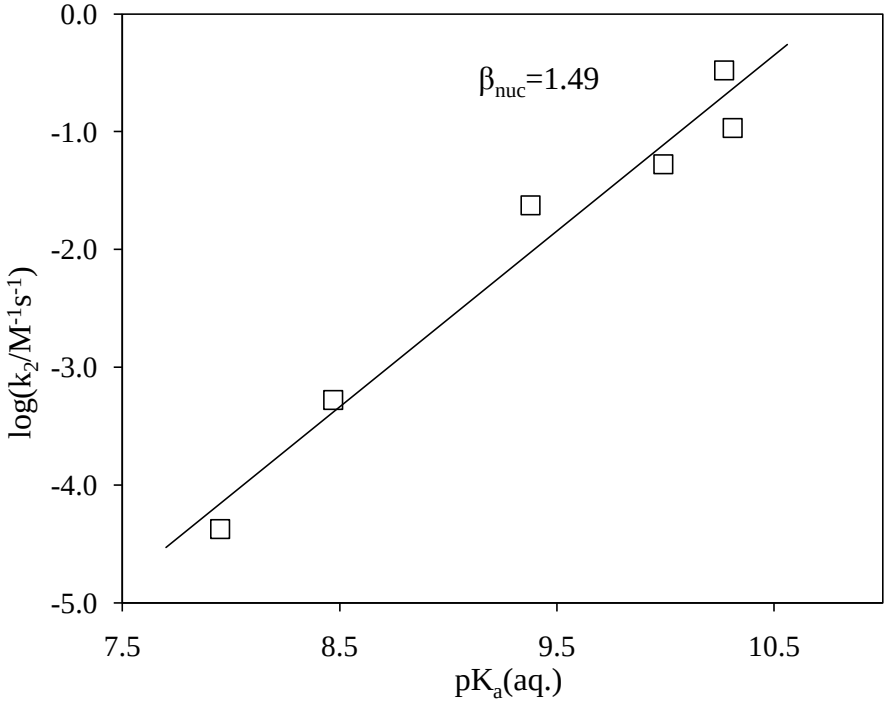


Figure 4.2a Brønsted type plot for the second order rate constants for the reaction between para-substituted phenoxides and 4-NFB in LNH_3 against the aqueous pK_a of the phenol

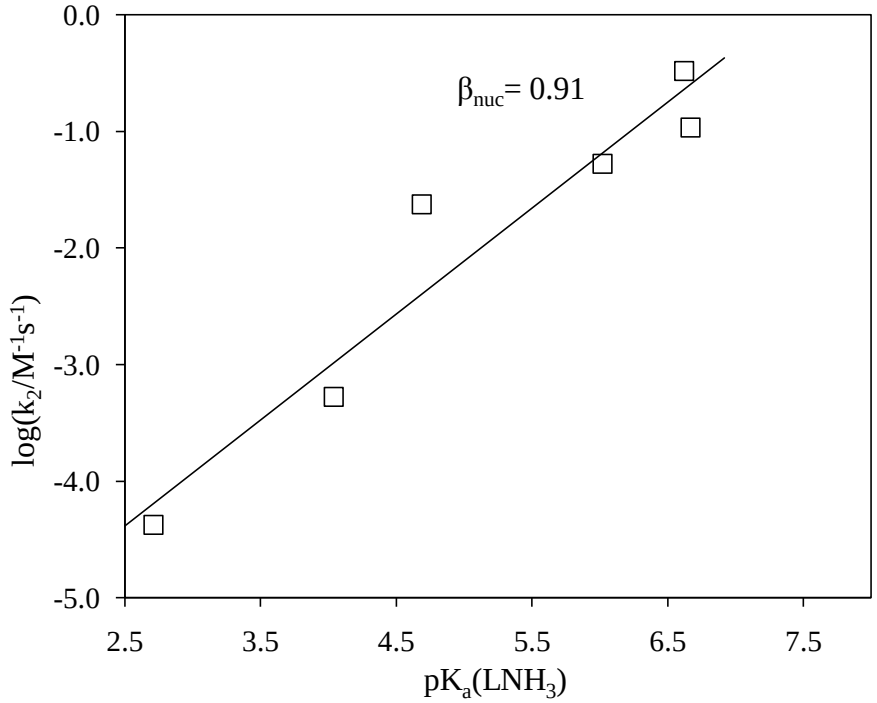


Figure 4.2b Brønsted type plot for the second order rate constants of the reaction between para-substituted phenoxides and 4-NFB in LNH_3 against the pK_a of the phenol in LNH_3

An alternative interpretation of the large Brønsted β_{nuc} for nucleophilic substitution of 4-NFB by phenoxide ion is a single electron transfer (SET) mechanism which would convert the phenoxide ion to a radical and the 4-NFB to an aromatic radical anion.[278]

As described earlier (chapter 2), the solvolysis rates of 4-NFB shows a relatively small salt effect with 2M salt increasing the rate by nearly 3-fold but, by contrast, the rate of substitution of 4-NFB by phenoxide ion shows a decrease in rate with increasing salt concentration (**Figure 4.3**). Presumably, this reflects a greater dispersion of the negative charge in the transition state.

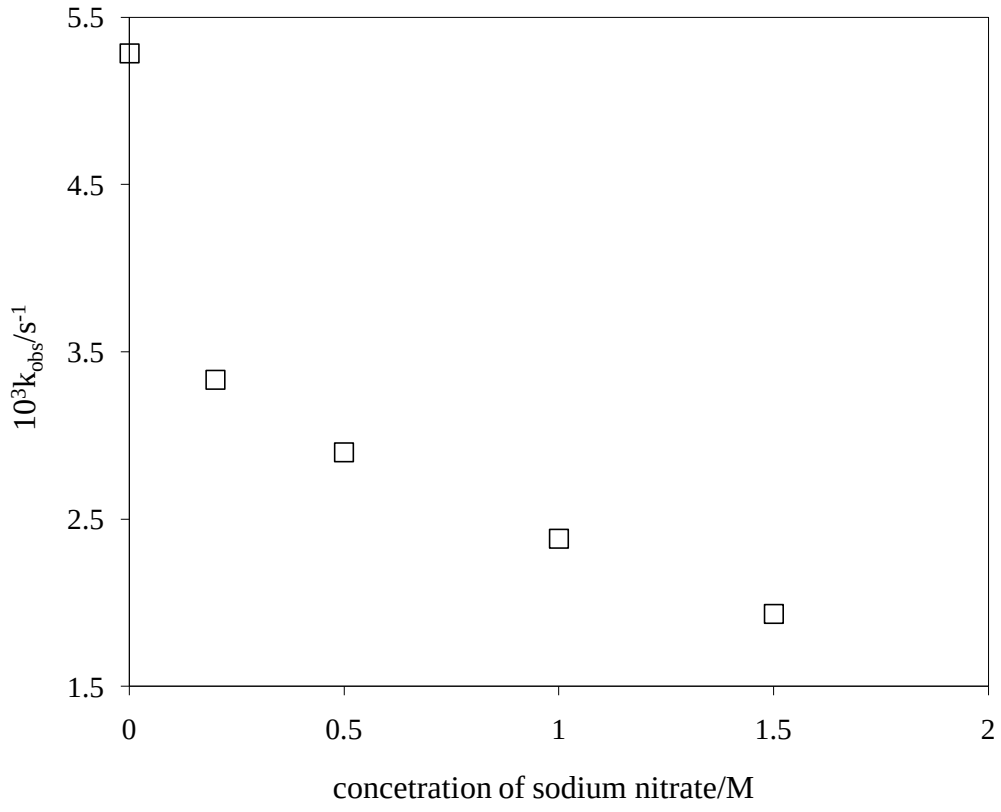
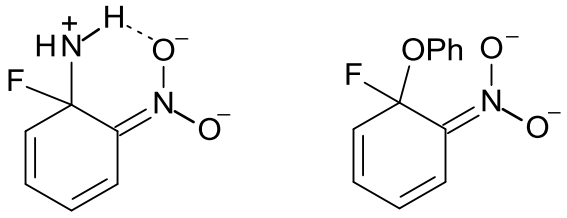


Figure 4.3 Dependence of the pseudo first order rate constant for the on the reaction of 4-NFB with phenoxide anion upon the concentration of added salt in LNH_3 at 25 ^oC

Interestingly, the rate of the reaction between 2-NFB and phenoxide anion is only less than 2 times faster than that for 4-NFB in liquid ammonia at 25 ^oC,[273] which is in stark contrast with the 30-fold rate difference in the solvolysis of NFBs in liquid ammonia. It was postulated that the difference in solvolysis rates was due to stabilisation of the Meisenheimer σ-intermediate

by intramolecular H-bonding between the ortho nitro group and the ammonium ion, but this is not possible with the reaction of 4-NFB and phenoxide (**27**). The small rate enhancement for



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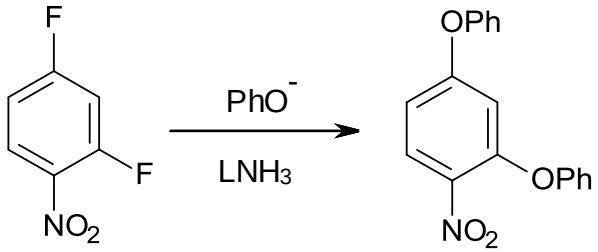
the reaction of 2-NFB with phenoxide anion in liquid ammonia, compared with that for 4-NFB as the substrate, is probably due to the net result of a stronger inductive and unfavourable steric effect of the neighbouring ortho nitro group.

The reaction between 0.01M 2,4-DFNB and 0.1M phenoxide gives exclusive di-substituted derivative (**28**) within minutes (**Scheme 4.2**), with less than 1% solvolysis product (**14**) observed.



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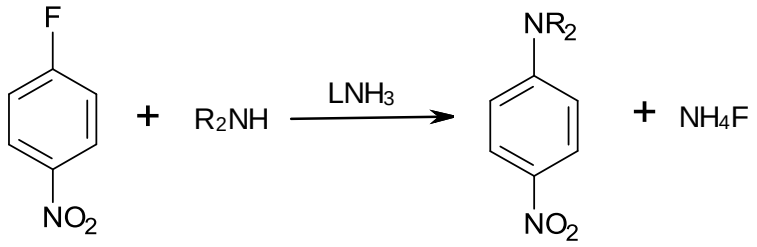
Scheme 4.2

4.2 Nucleophilic substitution with nitrogen nucleophiles

The kinetics and mechanisms of secondary amines reacting with activated aryl halides have been well studied.[274] The solvent effects on those reactions are often complicated by base catalysis and the extent of which depends on the reaction medium and substrate structure. Normally, general base catalysis occurs in non-polar aprotic solvents especially when proton removal is required from the attacking nucleophile before the leaving group is expelled,

although it may also occur coupled with the decomposition of the σ-complex.[275] However, in dipolar aprotic solvents the general base catalysis is generally not observed.[274e-g]



Scheme 4.3

Secondary amines react with 4-NFB in liquid ammonia to form the corresponding nitroaniline and ammonium fluoride (**Scheme 4.3**). The reaction progress was determined by monitoring the appearance of the product using GC analysis which followed an exponential change with time, from which the pseudo first order rate constants were calculated.

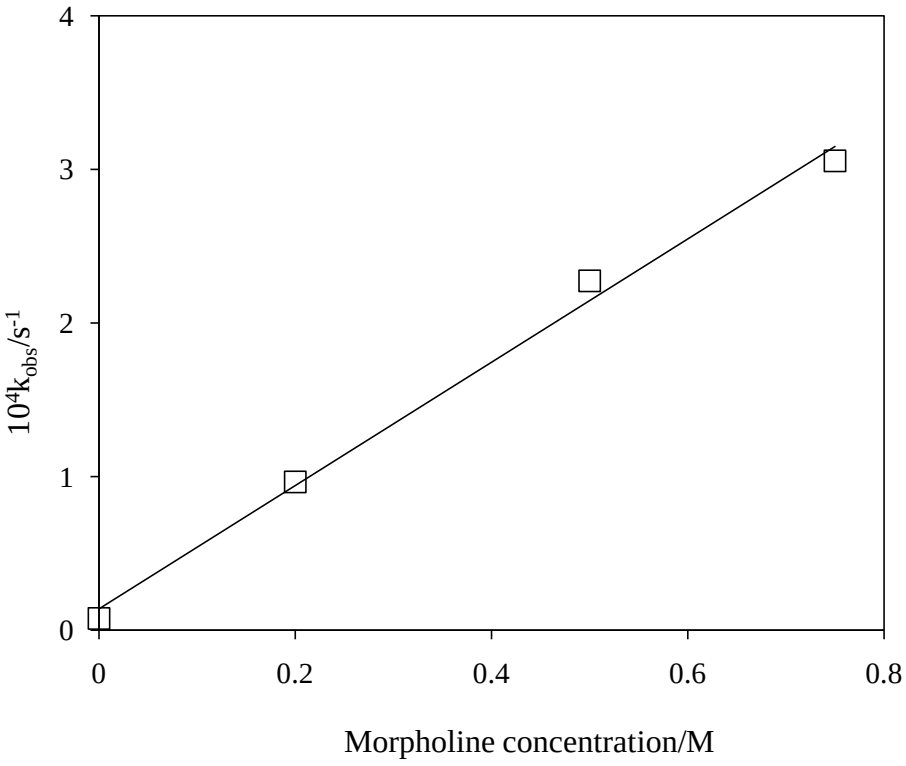


Figure 4.4 The dependence of the pseudo order rate constant for the reaction between 4-NFB and morpholine on the concentration of morpholine in LNH_3 at 25 ^oC.

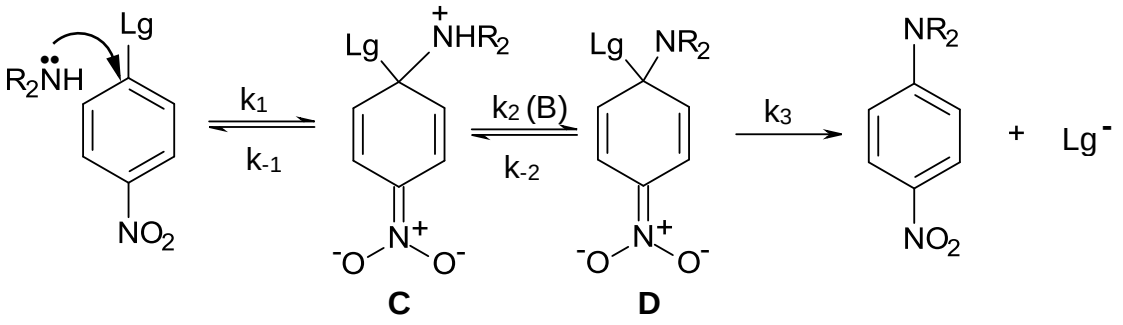
These observed pseudo first order rate constants increase linearly with increasing amine concentration (**Figure 4.4**, Appendix A: **Table A36**), indicating just a first order dependence on amine concentration and the absence of general base catalysis by a second molecule of amine. The corresponding second order rate constants for secondary amines and other nitrogen nucleophiles are shown in **Table 4.3**.

Table 4.3 The second order rate constants for the substitution of 4-NFB by nitrogen nucleophiles in LNH_3 at 25 ^oC

N-nucleophile	pK_a (aq.)	10^3k_2 ($M^{-1}s^{-1}$)
sodium azide	4.70	0.382[a]
morpholine	8.50	0.401
1,2,4-triazolate	10.3	0.560
piperidine	10.4	2.23
pyrrolidine	11.4	5.01
imidazolate	14.5	5.73

[a] Reaction conditions: 0.1M 4-NFB with 0.01M sodium azide.

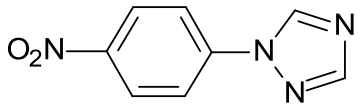
As discussed in the solvolysis section, aminium ions exist only in their free base unprotonated form in liquid ammonia i.e. the latter is more basic than amines. The anionic Meisenheimer σ-intermediate (**D**) (**Scheme 4.4**) therefore is thermodynamically more stable than its conjugate acid (**C**) in liquid ammonia and other amines are unlikely to be able to compete with solvent ammonia in converting (**C**) to (**D**) and so the absence of general base catalysis by amines is not surprising.



Scheme 4.4

There is no nucleophilic substitution of 4-NFB with aniline, with DABCO [(1,4-diazabicyclo(2.2.2)octane] and triethylamine in liquid ammonia and only the solvolysis

product, 4-nitroaniline, is formed. The rate of solvolysis is not significantly increased by these amines, again indicating no general base catalysis by these amines. The rates of reaction of sodium azide and piperidine with 4-NFB are similar to those in some typical dipolar aprotic solvents such as acetonitrile, DMSO, DMF (Appendix A: **Tables A37** and **A38**).[276] The reaction between 1,2,4-triazolate and 4-NFB in liquid ammonia gives only the 1-substituted product **29**.



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As already stated all amines exist in their free base unprotonated form in liquid ammonia and so it has not been possible to evaluate the pK_a of aminium ions in this solvent. Nonetheless, the second order rate constants (**Table 4.3**) do increase with increasing aqueous basicity of the amine, and there is actually a reasonable correlation between the second order rate constants for aminolysis of 4-NFB in liquid ammonia and aqueous pK_a values of the amines which generates an apparent Bronsted $\beta_{nuc} = 0.36$ (**Figure 4.5**).

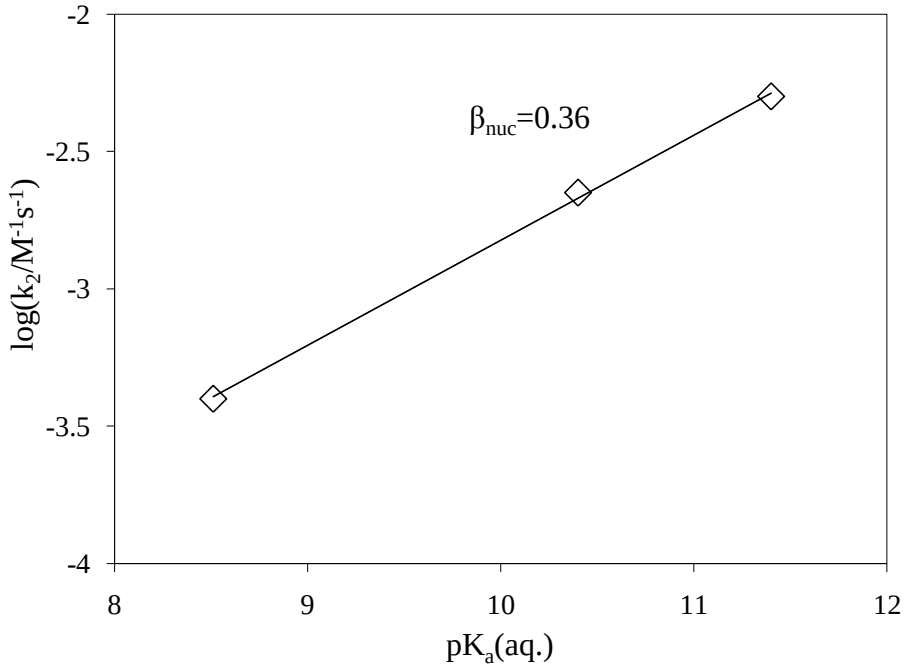
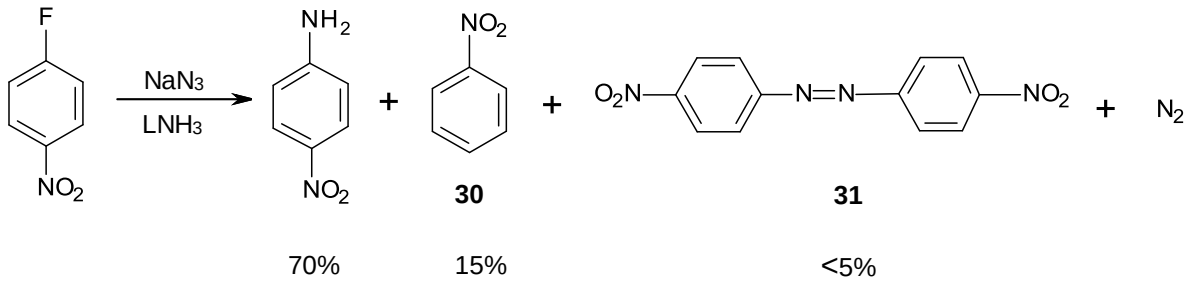


Figure 4.5 Brønsted type plot for the substitution of 4-NFB by nitrogen nucleophiles in LNH_3 using the corresponding aqueous pK_a of the aminium ion.

A plot of the pK_a values of aminium ions in acetonitrile against those in water is linear of slope = 1.0 [277] and so using the pK_a values in this aprotic solvent would generate the same Brønsted β_{nuc}. It seems reasonable to conclude that a similar or even smaller value of Brønsted β_{nuc} would be seen if the pK_a of aminium ions in liquid ammonia could be used. The small Brønsted β_{nuc} contrasts with the β_{nuc} of 0.91 observed with phenoxide anion which was obtained using pK_a values for phenols determined in ammonia. Without the knowledge of the relative pK_a in liquid ammonia it is not possible to interpret this value 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 (**D**), following the deprotonation of the aminium ion in the Meisenheimer intermediate (**C**) (**Scheme 4.4**). 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. This suggestion is further supported by the lack of reactivity of tertiary amines, discussed earlier, which may well be due to the lack of a removable proton. 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. The small Brønsted β_{nuc} value is incompatible with a SET mechanism in which an electron is transferred from the amine to the aromatic residue generating a positive charge on the amine to give a radical cation and a full positive charge on the amine nitrogen.[278]

In addition to the enhanced reactivity of azide-ion compared with its aqueous basicity (**Table 4.3**), there are some unusual observations with the reactions of this nucleophile with 4-NFB in liquid ammonia. The reaction between sodium azide and 4-NFB in other solvents affords, as expected, the corresponding 4-NAB. However, in liquid ammonia the reaction is very complicated giving no 4-NAB after the 4-NFB has completely reacted. The final reaction products are 4-nitroaniline, nitrobenzene (**30**), diazene (**31**) and nitrogen (**Scheme 4.5**). The molar ratio of **30** and **31** in the products is independent of whether the reaction vessel is covered in aluminium foil or not. In the absence of air, with control of ionic strength (I = 3M, $NaNO_3$) the rate of the disappearance of 4-NFB in liquid ammonia is proportional to the azide concentration at 25 ^oC (**Figure 4.6**, Appendix A: **Table A39**).



Scheme 4.5

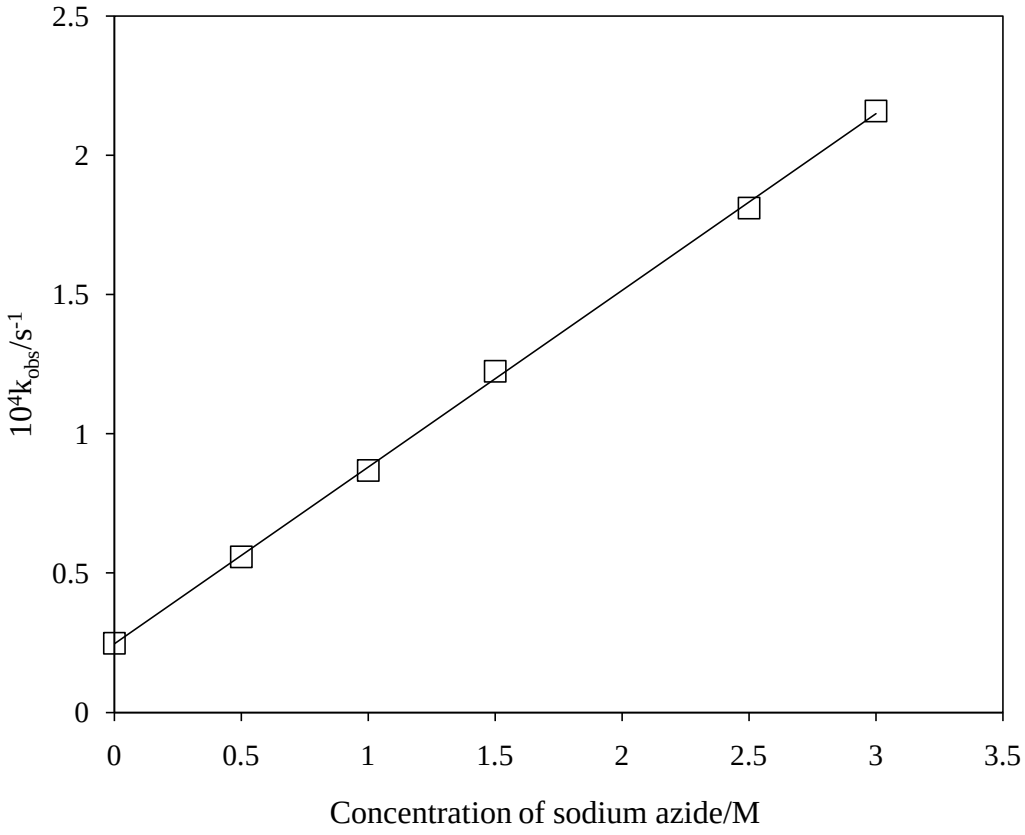


Figure 4.6 The dependence of the pseudo first order rate constant concentration for the reaction between 4-NFB and sodium azide on sodium azide in LNH_3 at 25 ^oC (I = 3M, $NaNO_3$).

A careful investigation, by GC and HPLC, of the reaction of azide ion with 4-NFB shows that 4-NAB is, in fact, a reactive intermediate and its concentration initially increases, reaches a maximum and then decreases (**Figure 4.7**).

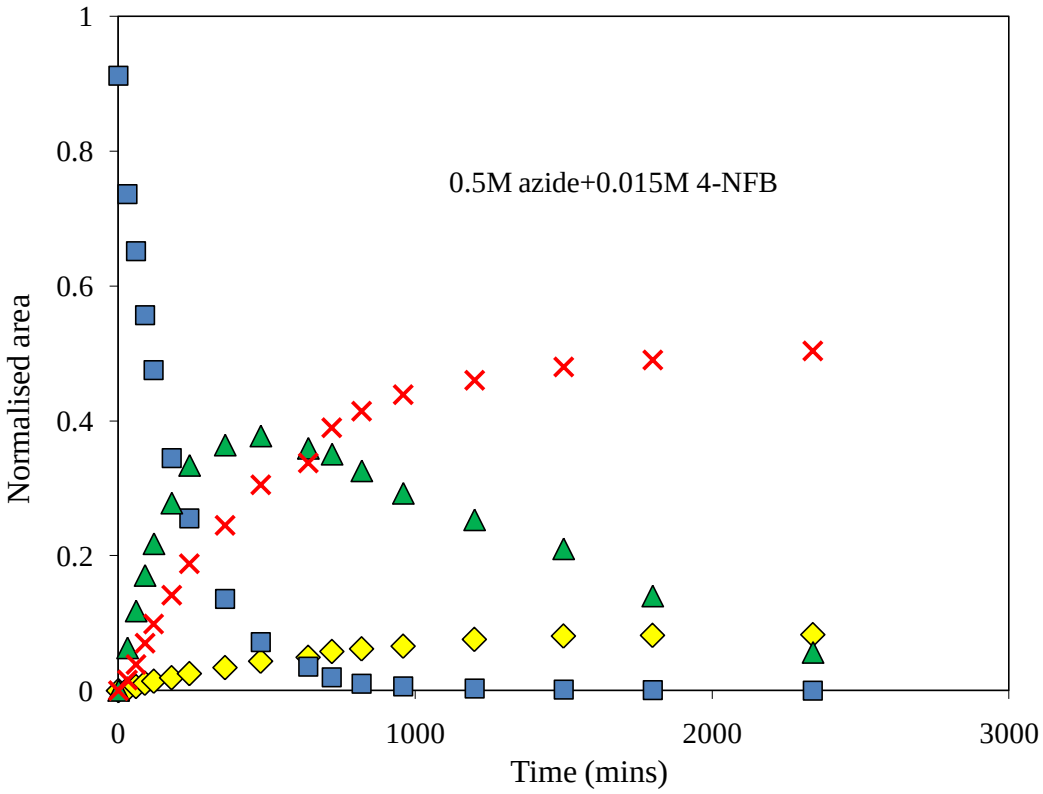


Figure 4.7 The reaction profile for 4-NFB reacting with sodium azide in LNH_3 at 25°C (■ : 4-NFB; x : 4-nitroaniline; ▲: 4-NAB; ◆ : nitrobenzene)

Consequently, we investigated, in separate experiments, the solvolysis of 4-NAB in liquid ammonia. In the absence of salts, 4-NAB has a half life of 38 hours and yields the same products as does 4-NFB with azide anion (**Scheme 4.5**). Furthermore, unlike the other aromatic substitution reactions, the rate of decomposition of 4-NAB in liquid ammonia is very dependent upon salt concentration. For example, it is 35 fold faster in the presence of 1.0 M perchlorate and the observed pseudo first order rate constant for the decomposition of 4-NAB is proportional to the concentration of potassium perchlorate (**Figure 4.8**, Appendix A: **Table A40**). The rate of decomposition of 4-NAB in liquid ammonia is independent of the nature of salt, whether sodium nitrate, sodium azide or potassium perchlorate. The nitrogen gas formed originates from 4-NAB and not from ammonia solvent as shown by using ^{15}N enriched liquid ammonia for the solvolysis of 4-NAB.[279]

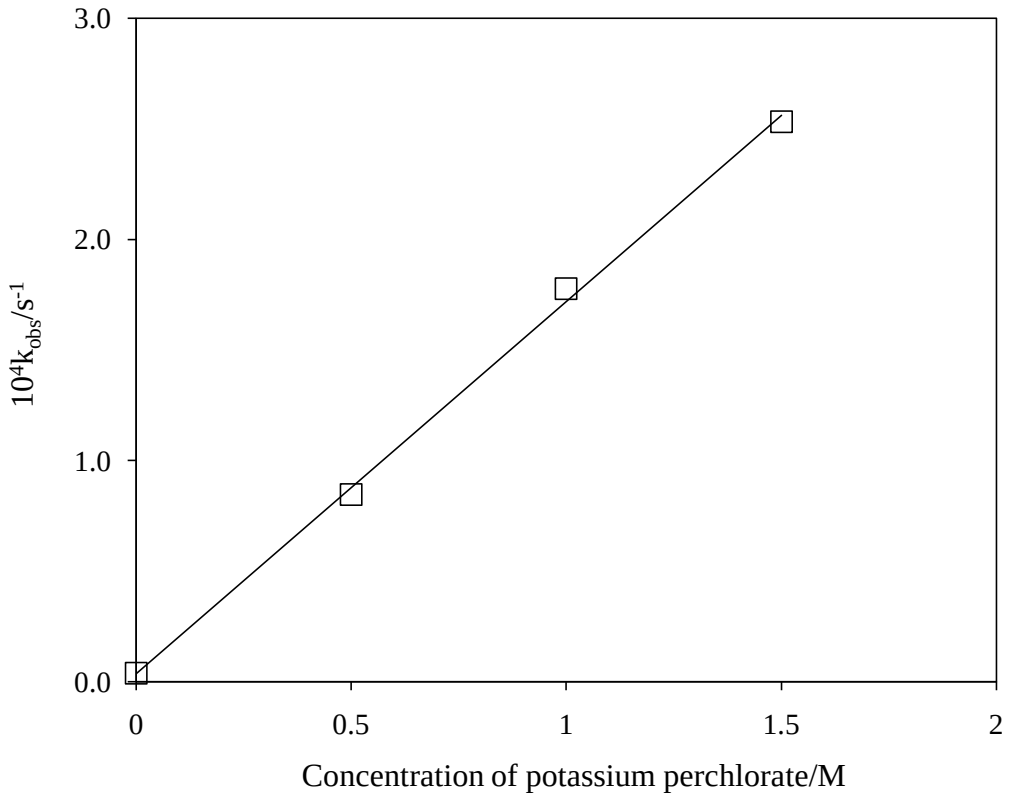
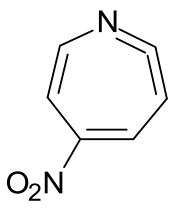


Figure 4.8 The dependence of the observed pseudo first order rate constant for the decomposition of 4-NAB in LNH_3 at 25 ^oC on potassium perchlorate concentration.

The unusual products, nitrobenzene (**30**) and diazene (**31**) formed from 4-NFB and azide ion (**Scheme 4.5**) could be explained by the formation of an intermediate nitrene which is trapped by ammonia to form 4-nitrophenyl hydrazine. Interestingly, the reaction of hydrazine with 4-NFB in liquid ammonia gives, after work-up with sodium hydroxide and extraction with dichloromethane, a mixture of nitrobenzene, 4-nitroaniline and aniline in a molar ratio of 12:5:1.[280] The formation of nitrobenzene and aniline in this reaction suggests that 4-nitrophenyl hydrazine could be an unstable intermediate formed in the reaction of 4-NFB with azide ion in liquid ammonia.

So a possible origin of nitrobenzene (**30**) and diazene (**31**) from the reaction of azide ion with 4-NFB in liquid ammonia is the decomposition by the loss of nitrogen of the initially formed azide, 4-NAB, to give 4-nitrophenyl nitrene which is trapped by ammonia to form 4-nitrophenyl hydrazine. The generation of the nitrene from 4-NAB by the release of nitrogen does occur under thermal and photolytic conditions and also electrochemically,[281] and singlet

aromatic nitrenes with electron-withdrawing groups are known to undergo insertion into the N-H bonds of amines to give the corresponding hydrazines.[282] The major product of 4-nitrophenyl nitrene trapped by diethylamine is 4-nitroaniline, with the minor product being 4-nitrophenyl hydrazine under photo irradiation, but no diazene (**31**) is found whether the reaction is under high or low power photo irradiation.[282a,b]



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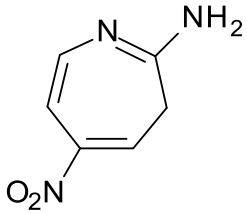

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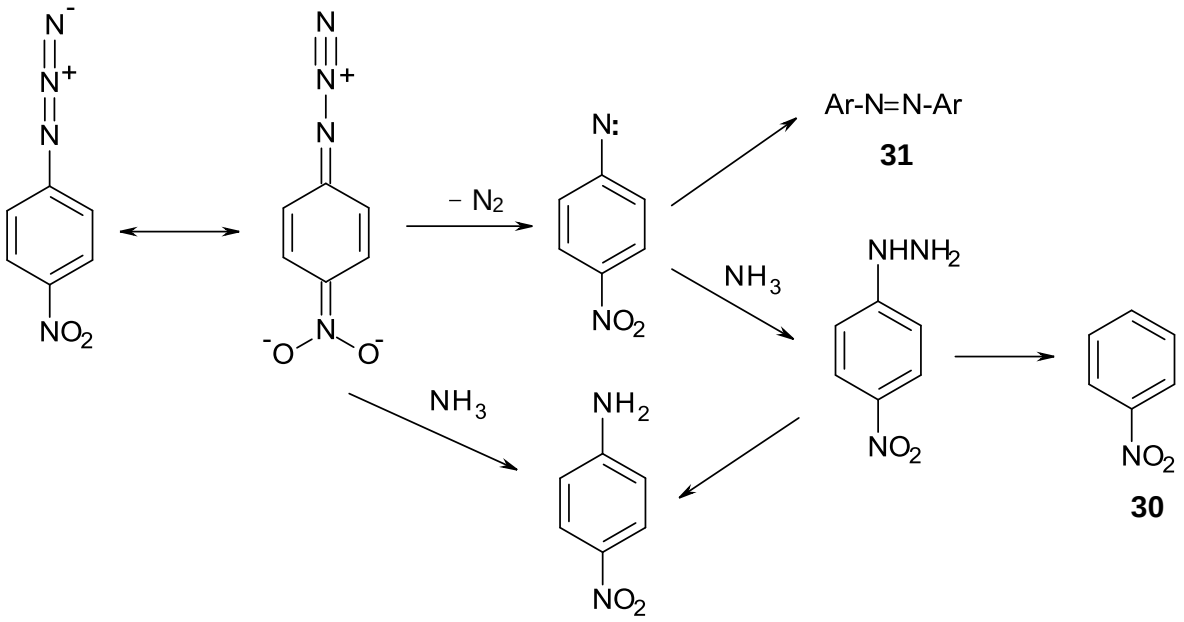
The formation of the diazene (**31**) is perhaps surprising given the expected low concentration and stability of the nitrene and its formation may require the triplet state 4-nitrophenyl nitrene.[282b] No possible ring enlargement products, such as 5-nitro-1,2-didehydroazepine (**32**) or its amination derivative (**33**) were found from the solvolysis of 4-NAB in liquid ammonia,

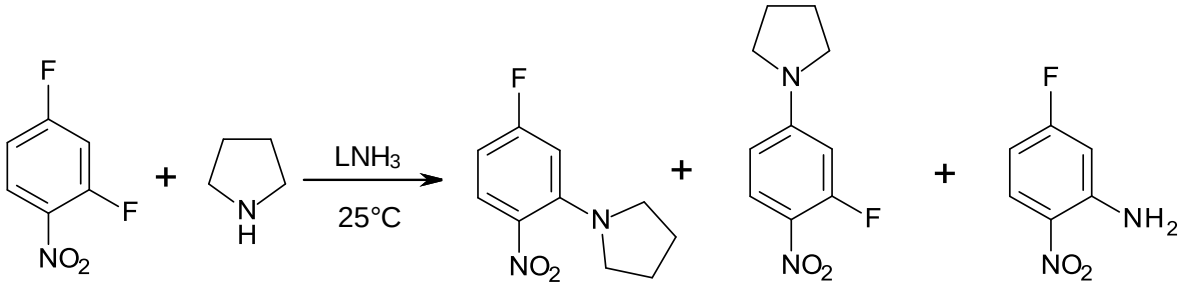


Scheme 4.6

and the molar ratio between 4-nitroaniline and nitrobenzene is about 5:1 in the product mixture. The diazene compound (**31**) is quite stable in liquid ammonia at room temperature. The possible routes for the decomposition of 4-NAB in liquid ammonia are therefore summarised as in **Scheme 4.6**.

The nitrene could undergo insertion into the N-H bond of solvent ammonia to form 4-nitrophenylhydrazine, which decomposes into nitrobenzene and a small amount of 4-nitroaniline. The nitrene could also dimerise to form the diazene (**31**). Some of the 4-nitroaniline formed may also come from the direct solvolysis of 4-NAB. Interestingly, the similar results were observed when 4-NAB was dissolved in DMSO together with excess of tetraethylammonium azide, followed by passing ammonia gas into the solution for several hours, however, no reaction was observed in methanol.

The reaction between equal molar of 2,4-difluoronitrobenzene (2,4-DFNB) and secondary amines in liquid ammonia at 25 ^{o}C forms ortho substituted derivative (**34**) as the predominant product, together with samll amount of para substituted derivate (**35**) and solvolysis product **14** (**Scheme 4.7**).

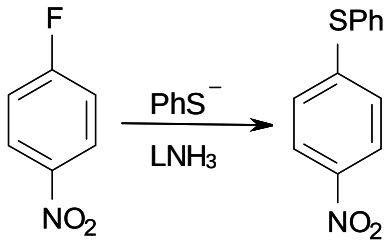


Scheme 4.7

4.3 Nucleophilic substitution with sulfur nucleophiles

4-NFB reacts rapidly with thiophenoxide anion in liquid ammonia to give 4,4'-dinitrodiphenyl disulfide and a trace amount of diphenyl thioether, probably due to the oxidation of thiophenoxide by air during the sample processing stage (**Scheme 4.8**). The second order rate

constant for the reaction between thiophenoxide and 4-NFB in liquid ammonia is significantly greater than that in methanol, and is similar to that in DMSO (**Table 4.4**).



Scheme 4.8

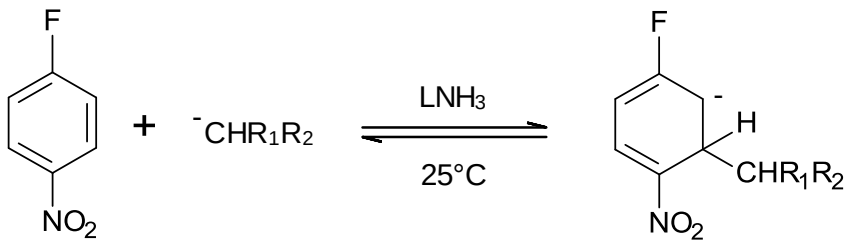
Table 4.4 The second order rate constants for the reaction of thiophenoxide ion with 4-NFB in various solvents at 25 ^{o}C

nucleophile	solvent	$k_2/M^{-1}s^{-1}$	$k_{rel.}$	reference
PhSNa	DMSO	10.4	5×10^{4}	283
$PhSNH_4$	LNH_3	3.1	1.5×10^{4}	this work
PhSNa	MeOH	2.1×10^{-4}	1	284

4.4 Nucleophilic substitution with carbon nucleophiles

To investigate aromatic nucleophilic substitution in liquid ammonia, the reactions of some typical carbanions, i.e., cyanide and diethyl malonate anions, with 4-NFB were studied at 25 ^{o}C. However, only the solvolysis product of 4-NFB is observed. Interestingly, orange or red colours are observed for the reactions of 4-NFB in liquid ammonia in the presence of these carbanions, but, upon the vapourisation of ammonia, followed by the general work up procedure, only 4-nitroaniline is found.

The colour may be due to the reversible formation of an anionic Meisenheimer σ-intermediate however, possibly carbanions do not attack the carbon 1 of 4-NFB attached to the fluoride atom, but they attack the α-position to the nitro group (**Scheme 4.9**).



Scheme 4.9

In summary, 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 the nucleophilic substitution reactions are sufficiently faster than the background solvolysis reaction so that useful synthetic procedures are possible in liquid ammonia. The rates of S_NAr reactions with neutral amines in liquid ammonia are slower than those for anionic O- and S-nucleophiles of similar aqueous basicity. Liquid ammonia can increase the regioselectivity of some reactions compared with more conventional solvents. These results indicate that liquid ammonia has potential as an easily recoverable solvent in many reactions usually carried out in dipolar aprotic solvents by the chemical industry.

5. Metal catalysed organic reactions in liquid ammonia Page

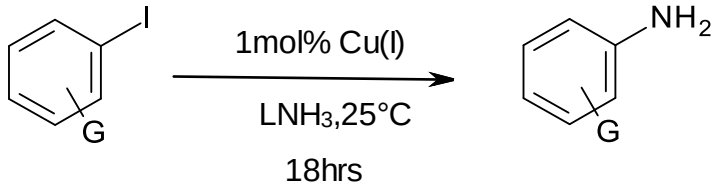
5.1 Copper (I) catalysed amination of aryl halides

Primary aromatic amines are widely used in the manufacture of pharmaceuticals, agrochemicals, dyes, polymers and thus are very important intermediates in the chemical industry.[285] In recent years, transition metal catalysed C-N bond formation has become a powerful and reliable method for the synthesis of a variety of aromatic amines under mild and convenient conditions.[286] However, these metal catalysed reactions are rarely carried out directly with ammonia in industry or for synthetic purpose due to: 1) the difficulty of forming the metal complexes without ammonia displacing the chelating ligands and thus causing the deactivation of the catalyst.[287] 2) the amination products, primary aromatic amines, could be more reactive than ammonia and potentially further react with starting aryl halides to form di- and triaryl amines in conventionally used solvents.[288] Despite the disadvantages mentioned above, the investigation of metal catalysed direct amination of aryl halides using ammonia itself rather than ammonia surrogates[286a,b,d, 289] has been investigated by several research groups.[290] Recent results have shown that, although using palladium or copper as metal catalyst with auxiliary chelating ligands for the amination of aryl halides with ammonia in conventional solvents are promising, there are still many problems associated with their application in industry. For example, the use of expensive palladium catalysts and toxic ligands; the unavoidable formation of di- and triaryl amines as by-products; the need to incorporate a deprotection step in the overall transformation for those reactions involving ammonia surrogates, which is not an atom economic process, and the relatively high loading of copper catalyst, etc. are all barriers yet to be overcome.

As reported elsewhere in this thesis, we have been trying to combine the unique solvent properties of liquid ammonia and the potential benefit of using ammonia as a direct nitrogen source, instead of using ammonia surrogates, to realise a number of amination reactions in liquid ammonia. Ideally this would be under catalytic conditions and would be applicable to a range of reactions such as the reductive amination of ketones, and the direct amination of aryl halides.

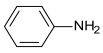
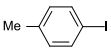
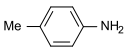
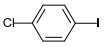
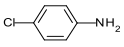
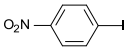
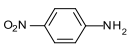
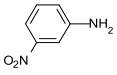
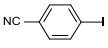
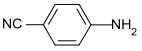
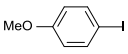
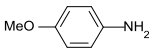
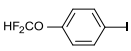
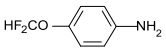
5.1.1 Copper (I) catalysed amination of aryl iodides

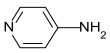
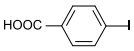
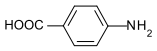
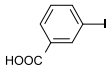
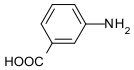
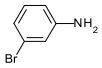
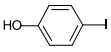
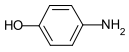
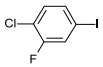
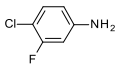
Aryl iodides are stable in liquid ammonia at room temperature for days, however, in the presence of a catalytic amount (1mol%) copper (I) iodide and 1mol% of ascorbic acid, iodobenzenes react with ammonia smoothly to give the corresponding anilines with excellent yields (**Scheme 5.1, Table 5.1**). No further coupling reactions between starting iodobenzenes and product anilines are found. Presumably, the product anilines are unable to compete with ammonia in forming the necessary complexes with copper ion due to the high effective concentration (35.5M at 25 ^{o}C) and good nucleophilic properties of liquid ammonia.



Scheme 5.1

Table 5.1 Amination of a variety of aryl iodides with copper (I) iodide (1mol%) and ascorbic acid (1mol%) in liquid ammonia at room temperature[a]

entry	substrate	product	Yield(%)[b]
1			97.3(95[c])
2			94.5
3			97.2
4			99.0
5			97.8(96[c])
6			98.0
7			90.5
8			97.6

entry	substrate	product	Yield(%)[b]
9			96.8 (94[c])
10			96.5
11			96.0
12			98.6
13			77.4 (93.6[e])
14			57.2
15			99.3
16			98.2

[a] General conditions except otherwise noted: 1mmol iodobenzenes, 1mol% CuI, 1eq. ascorbic acid to the catalyst and 1ml liquid ammonia at 25° C for 18 hours. [b] GC or HPLC yield unless otherwise noted. [c] Isolated yields. [e] 36 hours.

Upon optimisation of the reaction conditions, we were pleased to find that the copper (I) catalysed amination of iodobenzene in liquid ammonia at room temperature requires only 1 mol% copper catalyst, which is much lower than that generally reported.[291] Also the reaction does not require the presence of a strong base, such as *tert*-butoxide, which is widely used in similar reactions in other conventional solvents. Furthermore, the product separation is much easier with liquid ammonia as reaction medium, as the product can be simply collected by the evaporation of ammonia.

It appears that electron-withdrawing groups increase the yields of the amination of aryl iodides in liquid ammonia (**Table 5.1**, entries 4, 5, 6, 8 and 10), although given the high yields and fixed reaction time, this data is not a clear indicator of the effect of substituents. The reaction yields also seem to be independent of the position of the substituent to the iodo group, for example, 3-nitro and 4-nitroiodobenzne give similar yields under same reaction conditions

(**Table 5.1**, entries 4 and 5). Some heterocyclic iodides can also be converted to corresponding amines with excellent yields (**Table 5.1**, entries 9 and 15). Furthermore, under the present conditions, amination occurs preferentially with iodide as the leaving group compared with other aryl halides (**Table 5.1**, entries 3, 12 and 16). Lower yields are observed when the ring substituents of aryl iodides are hydroxyl (**Table 5.1,** entry 14) or amino group, although the latter gives an excellent yield after a prolonged reaction time (**Table 5.1,** entry 13). Currently, the palladium catalysed amination of aryl halides that contain free N-H or O-H bonds still remain problematic.[300b] To our knowledge, there has been no previous report on the metal catalysed amination of iodophenols, although Buchwald has reported a yield of 62% for the copper (I) catalysed (5mol%) amination of 4-iodoaniline by benzylamine in isopropanol, after 38 hours at 90 ^{o}C.[295a]

Table 5.2 Amination of iodobenzene with various copper salts as catalyst in liquid ammonia at 20 ^{o}C[a]

entry	**copper (I) salt**	**yields(%)[b]**
1	CuI (99.999%)	97.3
2	CuCl (99%)	97.3
3	Cu(OAc) (97%)	97.6
4	$Cu(CH_3CN)_4BF_4$ (97%)	98.5
entry	**copper (II) salt**	**yields(%)[b]**
5	$Cu(OAc)_2$ (98%)[c]	trace
6	$Cu(OAc)_2$ (98%)[d]	95.2
entry	**copper (0)**	**yields(%)[b]**
7	copper powder	88.4

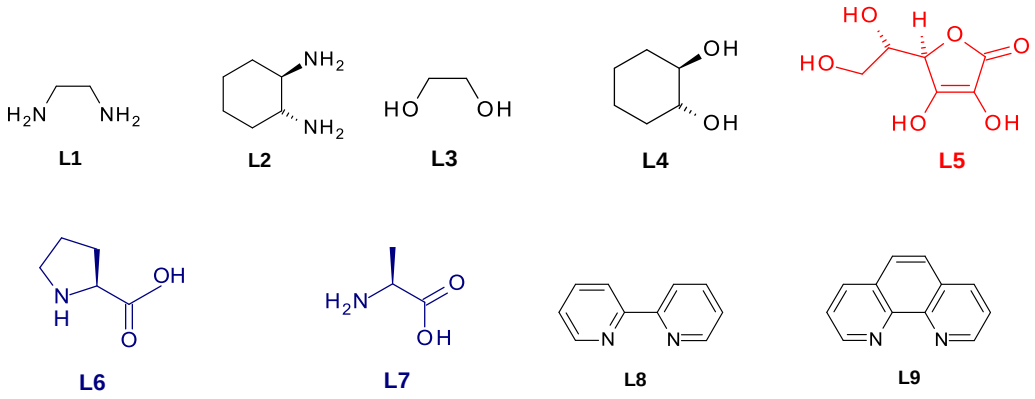
[a] Reaction conditions: 1mmol iodobenzene, 1 mol% copper catalyst, 1eq. ascorbic acid to the catalyst and 1ml liquid ammonia, 18 hours. [b] GC yields. [c] In the absence of ascorbic acid. [d] 2eq. Ascorbic acid to the catalyst.

Different copper (I) salts can be used to catalyse the amination of iodobenzene in liquid ammonia, and the yields of the reaction appear to be independent of the source of copper (I) (**Table 5.2**, entries 1 to 4). Copper (II) shows no catalytic activity in liquid ammonia, but can be active in the presence of 2 equivalents of ascorbic acid (**Table 5.2**, entries 5 and 6). Presumably, copper (II) is reduced to an active copper (I) species by the ascorbic acid.[292] The stability of Cu (I) relative to Cu(II) is very dependent on solvent and so, for example, Cu(I) is

more stable than Cu(II) in acetonitrile and the tetrahedral ion $[Cu(MeCN)_4]^+$ is well established (**Table 5.2** entry 4). Surprisingly, under the same conditions, copper (0) shows reasonable catalytic ability, even though the reaction conditions are apparently heterogeneous in liquid ammonia (**Table 5.2**, entry 7).

Normally,[293] copper catalysed C-N bond formations involve ancillary ligands, such as 1,2-diamines (**L1** and **L2**), [294] 1,2-diols (**L3-L5**), [290e,295] amino acids (**L6** and **L7**), [296] 2,2'-biprydine (**L8**)[297] or 1,10-phenanthroline (**L9**),[286c,298] which can effectively reduce the amount of copper (I) catalyst required, and achieve benign reaction conditions in some conventionally used solvents.

Consequently, we measured the kinetics of the copper (I) catalysed amination of iodobenzene in liquid ammonia at 25 ^oC, with and without some of these ancillary ligands (**L1-L9**) (**Table 5.3**). There is no nucleophilic displacement by any of the ligands (**L1** to **L9**) in the copper (I) catalysed reaction of iodobenzene in liquid ammonia at room temperature, also the addition of nucleophiles, such as morpholine and phenoxide ion, give no substitution products other than aniline. The reaction rates are significantly hampered by added amino acids (**L6** and **L7**) as ligands (**Table 5.3**, entries 8 and 9) which is very different from that observed in other conventional solvents, [296] while 1,2-diamines (**L1** and **L2**), 1,2-diols (**L3** and **L4**), bipyridine (**L8**) and phenanthroline (**L9**) slightly enhanced the reaction rate.



Only **L5** leads to a marked rate enhancement (**Table 5.3**, entry 7). Given that 1,2-diols do not significantly increase the activity of the catalyst, presumably the reaction rate increase in the presence of ascorbic acid is due to its ability to keep copper (I) in its reduced state and its concentration constant. The use of ascorbic acid or its sodium salt as an additive in copper

catalysed organic reactions is known, and its function is to retain the catalytic ability of copper (I) by providing a redox system which effectively reduces copper (II) or (III) back to copper (I).[299] The amino acids alanine (**L6**) and proline (**L7**) inhibit the reaction (**Table 5.3**, entries 8 and 9), but there was no sign of precipitation although the reaction solutions turned blue indicative of oxidation of Cu (I) to Cu (II). The inhibitory effect of the amino acids may simply be due to stabilisation of Cu (II) by the ligands and reduction of the electrode potential (E_0).

Table 5.3 The pseudo first order rate constant of copper (I) catalysed amination of iodobenzene with ligands in liquid ammonia at 25 ^oC[a]

entry	Cu(I) source	ligands	$10^5k_{obs}/s^{-1}$
1	CuI	–	3.26[b]
2	$Cu(CH_3CN)_4BF_4$	–	3.63
3	CuI	**L1**	4.32
4	CuI	**L2**	3.95
5	CuI	**L3**	4.00
6	CuI	**L4**	4.92
7	CuI	**L5**	19.6[b]
8	CuI	**L6**	0.037
9	CuI	**L7**	0.025
10	CuI	**L8**	5.23
11	CuI	**L9**	4.91

[a] Kinetics conditions: 50mM iodobenzene, 10mM Cu (I) salt, 10mM ligand, 40mg biphenyl as internal standard, 10ml LNH_3 at 25 ^oC. [b]Average of 2 runs.

In an attempt to distinguish between the role of ascorbic acid as a ligand and as a general reductant, the kinetics of the reaction were determined as a function of the concentration of ascorbic acid. With a constant copper (I) catalyst concentration, the rate of the amination of iodobenzene significantly increases with added ascorbic acid in liquid ammonia, but when the concentration of ascorbic acid reaches about twice of catalyst concentration, the rate levels out and becomes independent of further added ascorbic acid (**L5**) and (**Table 5.4**, **Figure 5.1**).

This rate saturation phenomenom implies some sort of association between copper (I) and ascorbic acid – in particular one or two moles of ascorbate may be complexed with copper (I). These observations also indicate the optimum ratio of ascorbic acid to copper (I) that is required for a relatively fast reaction rate. However, the rate enhancement is not great (ca. 5-fold) and rather than complex formation with Cu (I), the rate of ascorbic acid may simply be to reduce any copper (II) formed back to active copper (I).

Table 5.4 The effect of ascorbic acid concentration (**L5**) on the rate of the copper (I) CuI catalysed amination of iodobenzene in liquid ammonia at 25 ^{o}C.

[Iodobenzene]m/M	**[CuI]/mM**	**[L5]/mM**	**$10^4 k_{obs}/s^{-1}$**
50	10	0	0.326
50	10	10	1.96
50	10	20	2.15
50	10	40	2.22
50	10	50	2.23

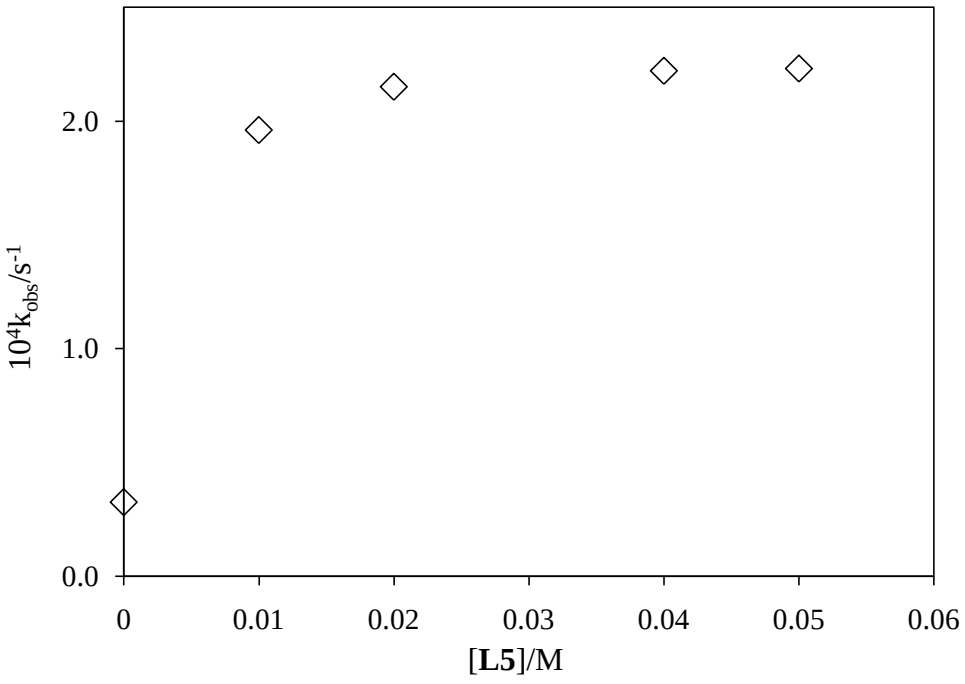


Figure 5.1 The effect of ascorbic acid concentration (**L5**) on the rate of the copper (I) CuI (10mM) catalysed amination of iodobenzene in liquid ammonia at 25 ^{o}C.

Further investigations of the kinetics of the amination of iodobenzene in liquid ammonia indicates that the rate of the reaction shows a first order dependence on the concentration of the copper (I) salt, both at lower and higher catalyst concentrations relative to the iodobenzene concentration (**Table 5.5**, **Figure 5.2**). This is consistent with a previous study of the copper (I) catalysed amidation of aryl iodides.[300]

Table 5.5 The dependence of the pseudo first order rate constants for the amination of iodobenzene on the copper (I) catalyst concentration in liquid ammonia at 25 °C

[a][Cu^{I}]/mM	$10^4k_{obs}/s^{-1}$	[b][Cu^{I}]/M	$10^4k_{obs}/s^{-1}$
5	1.25	25	5.50
10	2.23	40	8.64
20	3.82	50	10.7
40	9.60	70	13.1

[a] 50mM iodobenzene, 50mM ascorbic acid (**L5**) and various CuI concentration. [b] 10mM iodobenzene, 50mM ascorbic acid (**L5**) and various CuI concentration.

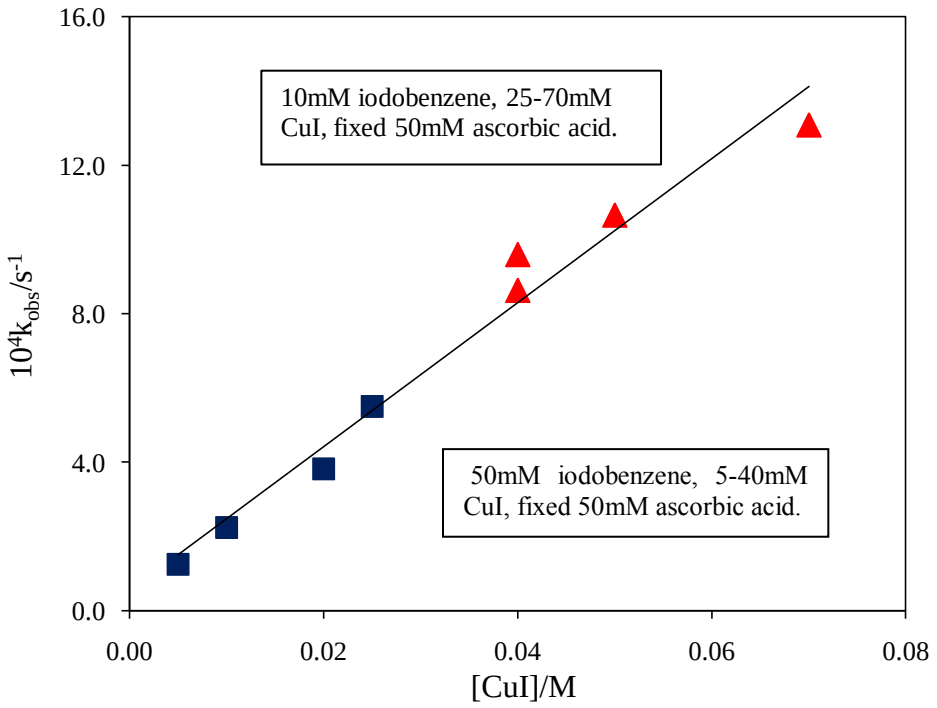


Figure 5.2 The first order dependence of k_{obs} of the amination of iodobenzene on copper (I) concentration in liquid ammonia at 25 °C

The first order rate constants for the copper (I) catalysed amination of 4-substituted phenyl iodides in liquid ammonia increase with electron withdrawing substituents (**Table 5.6**) and generate a Hammett ρ value of 0.49 (**Figure 5.3**). The small positive value of ρ indicates the generation of negative charge in the aryl ring in the transition state.

Table 5.6 The rate of copper (I) catalysed amination of 4-substituted phenyl iodide in liquid ammonia at 25 ^{o}C[a]

substituent	σ_p	$10^4 k_{obs}(s^{-1})$
4-MeO	-0.27	0.83
4-Me	-0.17	1.12
4-H	0	1.25
4-Cl	0.23	1.55
4-NO_2	0.78	2.95

[a] Reaction conditions: 50mM 4-substituted phenyl iodide, 5 mM CuI and 5mM ascorbic acid (**L5**) in 10ml liquid ammonia.

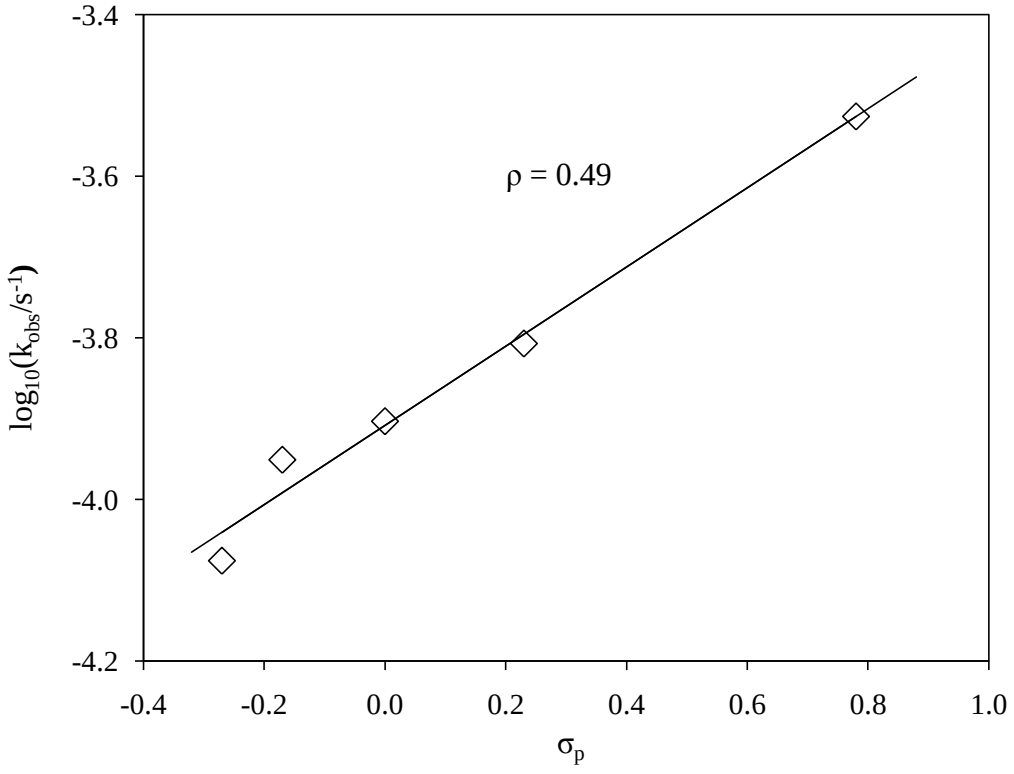


Figure 5.3 The Hammett plot for the copper (I) catalysed amination of iodobenzene in liquid ammonia at 25 ^{o}C. Reaction conditions: 0.05M iodobenzene, 5mM CuI and 5mM ascorbic acid in 10ml liquid ammonia.

The relatively small Hammett ρ = 0.49 contrasts with the much larger ρ = 2.3 for the analogous reactions catalysed by palladium (0) with phosphine ligands in toluene [301] suggesting that the C-I bond is not significantly broken in the transition state for the copper (I) catalysed amination of 4-substituted phenyl iodides in liquid ammonia.

The activation parameters provide a further characterisation of the copper (I) catalysed amination of aryl iodides in liquid ammonia. Linear Erying type plot (**Table 5.7**, **Figure 5.4**) gives $\Delta H^{\ddagger}$ = 65.6 kJ mol^{-1}, $\Delta S^{\ddagger}$ = -101.0 J K^{-1} mole^{-1} and $\Delta G^{\ddagger}$ = 95.7 kJ mol^{-1}. The entropy of activation is not as negative as one would expect for a termolecular reaction or one generating a charged transition state requiring heavy solvation.

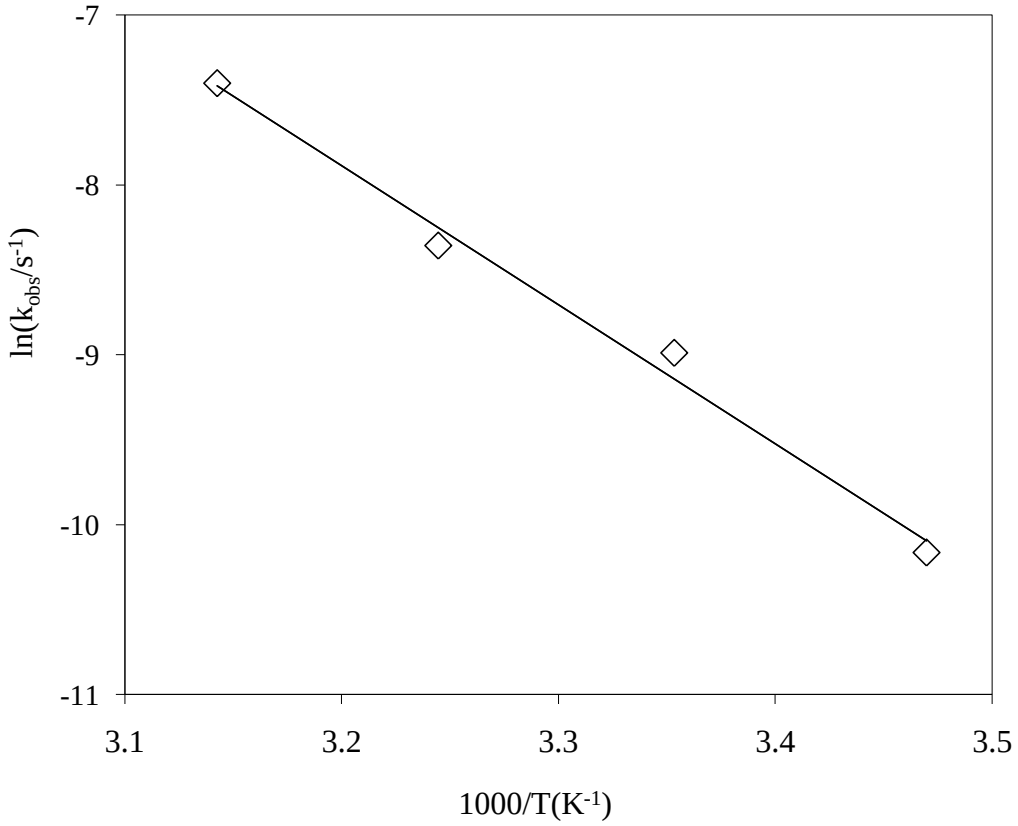


Figure 5.4 The Erying plot for the copper (I) catalysed amination of iodobenzene in liquid ammonia. Reaction conditions: 50mM iodobenzene, 5mM CuI and 5mM ascorbic acid in 10ml liquid ammonia.

Iodide anion is better solvated by liquid ammonia than the other halides, as showed by its relative small positive Gibbs transfer energy from water to ammonia, compared those larger

values for chloride and bromide anions.[302] Therefore it is less likely that the expulsion of iodide anion from the active complex would be the rate-limiting step as occurs with the nucleophilic substitution of nitrofluorobenzenes by phenoxide anions in liquid ammonia (chapter 4).

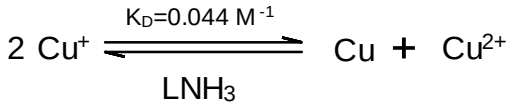
Table 5.7 The rate for the copper (I) catalysed amination of iodobenzene in liquid ammonia at various temperature[a]

temperature(K)	$10^4 k_{obs}(s^{-1})$
318.2	6.11
308.2	2.35
298.2	1.25
288.2	0.39

[a] 50mM iodobenzene, 5mM CuI and 5mM ascorbic acid (**L5**) in 10ml liquid ammonia.

To understand the mechanism of these catalysed reactions, it is important to know the active coordination state of copper (I) under our reaction conditions. The rate of the reaction appears generally insensitive towards several potential copper (I) ligands, except for the apparent inhibitory effects of amino acids, and the enhancement brought about by ascorbic acid (**Table 5.3**). With the large and effectively constant concentration of ammonia (35.5M, 298.2 K), copper (I) ion is presumably coordinated to ammonia and the added ligands do not compete with ammonia to form complexes with copper (I) cation.

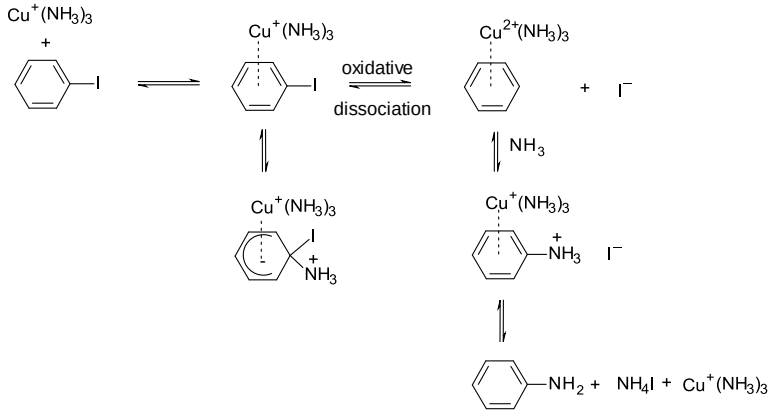
Based on EXAFS and ^{63}Cu NMR spectroscopy it is claimed that copper (I) ion is three-coordinated in liquid ammonia, $[Cu(NH_3)_3]^+$, possibly with a coplanar trigonal geometry. By contrast, in aqueous ammonia solution, the linear diamminecopper (I) complex, $[Cu(NH_3)_2]^+$, is the dominant species relative to $[Cu(NH_3)_3]^+$,[303] and even in highly concentrated aqueous ammonia solution, only 27% of copper (I) ion adopts three-coordinated coplanar structure.[304,305] Copper (I) ion undergoes disproportionation (**Scheme 5.2**) in liquid ammonia but with a small disproportion constant $K_D = 0.044M^{-1}$, the copper (I)-ammonia complex is the dominant species (>99%) at low concentration of copper (I) liquid ammonia solution (< 0.1M).[305]



Scheme 5.2

Copper (I) catalysed amination of iodobenzene in concentrated aqueous ammonia (30% w/w), at room temperature is much slower than that in liquid ammonia at 25 ^{o}C.[306] The pseudo first order rate constant, k_{obs} = 5.0× $10^{-6}s^{-1}$ for the copper (I) catalysed amination of iodobenzene in 10ml 30% w/w aqueous ammonia at 25 ^{o}C, using 0.5mmol iodobenzene, 1%mole CuI, 1 equivalent ascorbic acid to the copper catalyst. This 40 fold smaller than the analogous reaction under similar conditions in liquid ammonia (**Table 5.3** entry 7). Although the triamminecopper (I) is apparently the dominant species in liquid ammonia whereas the diamminecopper (I) is the major complex in aqueous ammonia, it is not known which has the greater catalytic activity.

In principle Cu^{+} can act as either an electron donor or acceptor, but based on the importance of the presence of ascorbic acid, it seems likely that in liquid ammonia Cu^{+} is acting as a reducing agent and so is itself oxidised to a state that at the end of the reaction requires reduction for catalysis to continue. Theoretical studies on the cation-π interactions of Cu^{+} and benzene indicate that, in the gas phase, Cu^{+} forms a η^2 complex with benzene, especially if a counter-ion is present.[307] Another theoretical study[300,301,308] on the copper (I) catalysed amidation of aryl halides, suggested a mechanism involving rate-limiting oxidative addition through a penta-coordinated copper (III) intermediate.

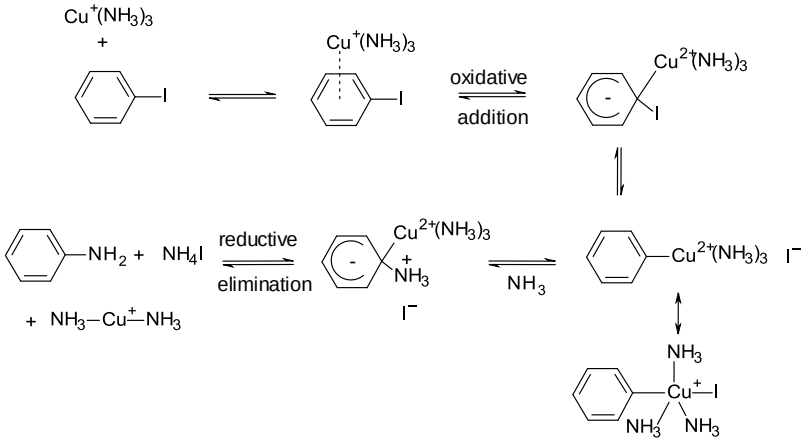


Scheme 5.3

A traditional view of this aromatic nucleophilic substitution reaction would regard the likely mechanism to involve initial copper (I)-π complex formation to be followed by dissociative or addition-elimination steps (**Scheme 5.3**). The latter seems intrinsically unlikely given the relative weak Lewis acid character of copper (I) and its ability to stabilise the negative charge on the aromatic ring. However, the dissociation of iodide ion effectively leaves what would normally be an unstable aromatic carbocation, but in this instance one which could be stabilised by electron transfers from Cu (I) to form a Cu (II) complex.

Comparison of previous mechanistic studies[300,301,309] on the copper (I) catalysed amidation of aryl halides and current kinetic data, a possible mechanism for the amination of aryl halides is proposed as in **Scheme 5.3**. The formation of triamminecopper (I)-aryl ring complex is rate determining step, small Hammett ρ value and activation parameters support this assumption.

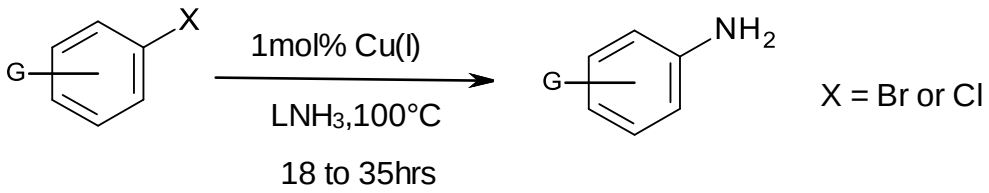
The difference between this mechanism (**Scheme 5.3**) and the type usually proposed for Pd (0) catalysed reactions are the timing of bond making and breaking. If Cu (I) is regarded as a nucleophile then catalysis could occur by a 'normal' type of addition step to generate a Meisenheimer type of σ-complex with negative charge distributed around the aromatic ring with copper now in the +2 oxidation state, followed by cleavage of the bond to the leaving group and then a repeat process involving nucleophilic displacement of the Cu^{2+} by reductive elimination and regeneration of the Cu (I) catalyst (**Scheme 5.4**).



Scheme 5.4

In liquid ammonia, the product of iodide expulsion from the Meisenheimer type intermediate may well be strongly bound to copper and is represented as a possible trigonal bipyramidal intermediate. The relatively small Hammett ρ = 0.49 suggests that the C-I bond is not significantly broken in the transition state and that there is a small generation of negative charge in the aryl ring which is compatible with the oxidative addition of the copper ion being rate limiting.

5.1.2 Copper (I) catalysed amination of aryl bromides and chlorides (**Scheme 5.5**)



Scheme 5.5

With 1 mol% CuI as catalyst in liquid ammonia at room temperature, less than 1% of bromobenzene is converted into aniline after 18 hours, however, under the elevated temperature, for example, 100 ^{o}C, the yield of the reaction increases to 96% after 18 hours (**Table 5.6**, entry 1) and the other substituted aryl bromides also can be smoothly converted to the corresponding anilines with good to excellent yields in liquid ammonia (**Table 5.6**).

Using the copper (0) powder as a catalyst for the amination of bromobenzene in aqueous ammonia it was reported that 5mol% of copper (0) was required at 100 ^{o}C for 24 hours and gives a lower yield of aniline (85%), compared with our method.[310] Some bromopyridine derivatives give excellent yields in liquid ammonia (**Table 5.6**, entries 12 and 13). 4-*t*-Butyl phenyl bromide gives a slightly lower yield (**Table 5.6**, entry 10), but is still compatible with that of palladium (II), (Pd[P(*o*-tol)$_3$]$_2$) catalysed amination with ammonia in 1,4-dioxane (65 ^{o}C, 15 hours, 88% yield).[290b] Interestingly, the amination of 3-fluoro-4-bromotoluene occurs only to displace bromide ion (**Table 5.6**, entry 13).

No diaryl or triaryl amine derivatives, which can occur as a result of further reaction of the product, are found under elevated temperatures for the copper (I) catalysed amination of aryl bromides in liquid ammonia. By contrast, these di and triaryl amines by-products are often

unavoidable when the strong bases are utilised for the palladium catalysed amination of aryl bromides or chloride in some conventional solvents, especially under high temperature.[288c,290a] At a similar temperature, the yields of the copper (I) catalysed amination of aryl bromides in liquid ammonia are generally higher than those previously reported by using aqueous ammonia solution or ammonia surrogates as nitrogen source. Furthermore, the amination of aryl bromides requires only 1% copper (I) catalyst in liquid ammonia, which is much lower than those demanded in conventionally used solvents.

Table 5.8 Amination of variety of aryl bromides and chlorides with copper (I) iodide catalyst in liquid ammonia at elevated temperature in liquid ammonia[a]

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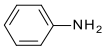
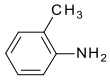
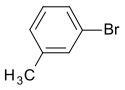
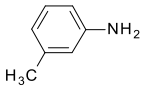
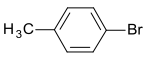
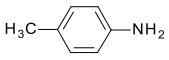
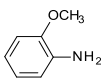
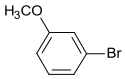
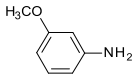
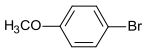
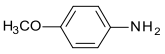
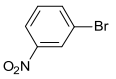
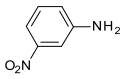
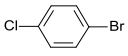
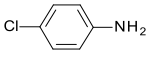
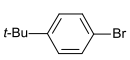
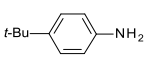
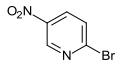
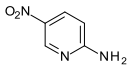
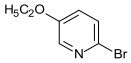
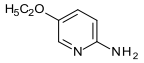
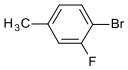
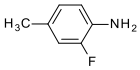
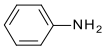
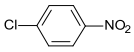
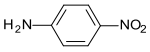
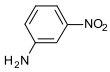
1			96
2			95
3			97
4			94
5			86
6			91
7			80
8			96
9			97
10			85

entry	substrate	product	yield(%)[b]
11			99
12			96
13			92
14			5<
15			74[c]
16			88[c]
17			63[c]

[a] General reaction conditions unless otherwise noted: 1mmol aryl halides, 1 mole % CuI, 1eq. ascorbic acid to the copper catalyst, in 1-1.5ml liquid ammonia at 100 ^{o}C for 18 hrs. [b] GC yields, except otherwise noted. [c] 36 hours, isolated yields.

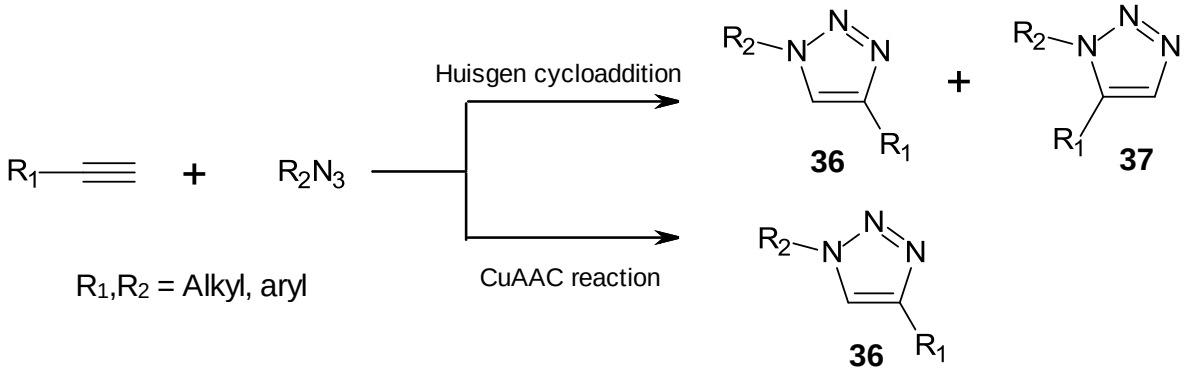
Unactivated chlorobenzenes are very inert under similar conditions to that used for the amination of aryl bromides in liquid ammonia (**Table 5.8**, entry 5). For example, even at 120 ^{o}C, with 10mol% copper (I) catalyst, less than 5% chlorobenzene is converted into aniline after 12 hours in liquid ammonia. This is as expected, based on the large dissociation energy of a sp^2 carbon-chlorine bond.[311] However, electron-withdrawing groups are activating so that nitrochlorobenzenes can be smoothly converted into corresponding aniline with only 1mol% copper (I) catalyst to give moderate yields in liquid ammonia (**Table 5.8**, entries 15 to 17).

In summary, we have developed a method for the amination of aryl halides in liquid ammonia using copper (I) catalysis which enables direct synthesis of a number of primary amines with excellent yields. This method does not require strong base and ligands as additives, which are often used for the similar metal catalysed amination of aryl halides in the conventionally used solvents. Most importantly, the amination in liquid ammonia has exclusive selectivity for the formation of primary amines, even under relative higher temperature. The amount of catalyst required for the reaction is relatively lower than that generally used, and the convenience of

products separation with liquid ammonia as reaction medium indicate its potential industrial application. The preliminary mechanistic investigation indicates that the rate of the amination is first order dependence on the concentration of copper (I) catalyst, and the formation of triamminecopper (I)-aryl ring intermediate is probably the rate limiting step in liquid ammonia. Due to strong coordination of solvent molecules to the copper (I) ion, the kinetics of the reaction are generally insensitive to the addition of other conventional ligands in liquid ammonia.

5.2 Copper (I) catalysed azide-alkyne cycloaddition ($Cu^{I}AAC$)

The 1,3-dipolar cycloaddition between azide and alkyne [3+2] was first discovered in 1893 by Michael and 70 years later thoroughly developed by Huisgen (and subsequently widely recognised as Huisgen 1,3-dipolar cycloadditions).[312] The reaction has a high activation barrier and consequently demanding reaction conditions are usually required, such as elevated temperature and pressure, and, in addition, the reaction gives a mixture of 1,4- and 1,5-substituted 1,2,3-triazoles (**36** and **37**, respectively, **Scheme 5.6**).



Scheme 5.6

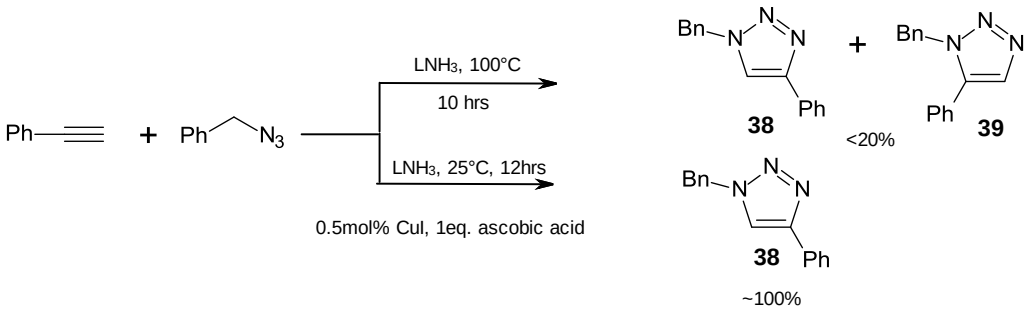
In 2002, Sharpless[313] and Meldal[314] independently improved the 1,3-Huisgen cycloaddition by using copper catalysts and successfully achieved amiable reaction conditions and exquisite regioselectivity. This variation of the Huisgen cycloaddition, was later described as CuAAC reactions standing for Cu-catalysed Azide-Alkyne Cycloaddition, or more commonly as "click chemistry",[315] which proceeds under ambient temperature and pressure to give exclusively 1,4-substituted 1,2,3-triazoles (**36**) (**Scheme 5.6**). This method has become a powerful and reliable tool for the synthesis of 1,2,3-triazole derivatives which are widely used in

pharmaceutical and agrochemical industry.[316] Recently, copper-free click chemistry between some strained alkynes, such as cyclooctynes, and azides has been reported.[317]

CuAAC reactions can be carried out in a variety of solvents, such as aqueous alcohol solvents, pure water, dipolar aprotic solvents or their aqueous solutions, but are often carried out under a basic atmosphere or, a strong base, such as Et_3N or DIPEA (N,N-diisopropylethylamine), which is required to facilitate the deprotonation of the terminal alkynes.

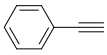
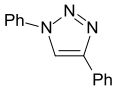
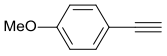
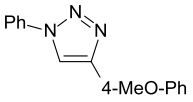
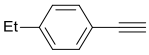
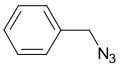
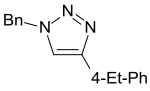
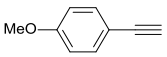
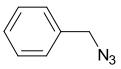
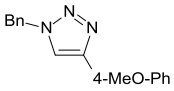
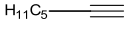
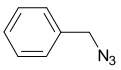
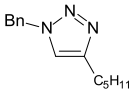
Liquid ammonia is a basic solvent and we have shown in this thesis that it behaves like a typical dipolar aprotic solvent in its solvent effects on organic reactions. One of the potential advantages of using liquid ammonia as reaction medium in the chemical industry is relative ease in separating the solvent from the products by vapourisation of ammonia.

When phenyl acetylene and benzyl azide are charged together in liquid ammonia at room temperature without a copper catalyst, there is no reaction even after several days. Furthermore, in the absence of a copper (I) catalyst, even at elevated temperatures (100 ^oC), and after 10 hours agitation, less than 20% of the starting material is converted into a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazoles (**38** and **39**, respectively) (**Scheme 5.7**) in a molar ratio of 2:1. However, the copper (I) catalysed 1,3-dipolar cycloaddition of phenyl acetylene and benzyl azide occurs smoothly at ambient temperature in liquid ammonia to give the regioselective 1,4-disubstituted product (**38**). This 'click reaction' in liquid ammonia requires only 0.5 mol% of copper (I) catalyst and the yields of these reactions are extraordinarily high. The amount of copper catalyst required for the Cu^IAAC reactions in liquid ammonia is much lower than those previously reported in conventionally used solvents[318] and both aromatic and aliphatic alkynes give excellent yields (**Table 5.9**). In addition, no acetylene dimer $(RC{\equiv}C)_2$ is found for the Cu^IAAC reactions in liquid ammonia, which is often observed when the reaction is performed in some conventionally used solvents. The ^1H NMR spectra of the products for the equi molar reaction of azides and acetylenes in liquid ammonia show that pure 1,4-disubstituted 1,2,3-triazoles (**38**) are obtained quantitatively by the vapourisation of ammonia after the reactions is complete, and there is no need for the further purification or additional separation procedures (Appendix C, **Figures N30**).



Scheme 5.7

Table 5.9 Copper (I) catalysed 'click reactions' of a variety of azides and acetylenes in liquid ammonia at room temperature[a]

entry	acetylene	azide	product(37)[b]	yield[c]
1				98
2				99
3				97
4				99
5				98

[a] General conditions unless otherwise noted are: 1mmol starting azides and 1mmol acetylenes, 0.5 mol% CuI and 1.0 eq. ascorbic acid to the catalyst, 1ml liquid ammonia, at 20 °C for 10hrs. [b] Products were confirmed by GC-MS and ^{1}H NMR. c. Isolated yields.

A variety of copper (I) salts can be used as catalyst for the click reaction in liquid ammonia (**Table 5.10**). In addition, copper (0) powder can also act as the catalyst, although this appears to be under heterogeneous conditions and gives a much lower yield (**Table 5.10**, entry 6), it is possible that some of the copper(0) dissolves in liquid ammonia to give ammonia solvated copper(I).

Table 5.10 Various copper salts catalysed 'click reactions' in liquid ammonia at room temperature[a]

entry	copper source	yields of 38(%)[b]
1	CuI(99.999%)	>99
2	CuCl(99%)	>99
3	Cu(OAc)(97%)	>99
4	$Cu(CH_3CN)_4BF_4$ (97%)	>99
5	$Cu(OAc)_2$(98%)[c]	>99(40[d])
6	copper powder	36.9

[a] General condition unless otherwise noted are: 1mmol phenyl azide, 1mmol phenyl acetylene, 0.5mol% copper catalyst, 1eq. ascorbic acid to the copper catalyst, 1ml liquid ammonia for 12 hrs, the product precipitated as white short crystal in needle form. [b] GC yields. [c] 2eq. ascorbic acid to the copper catalyst. [d] Without ascorbic acid.

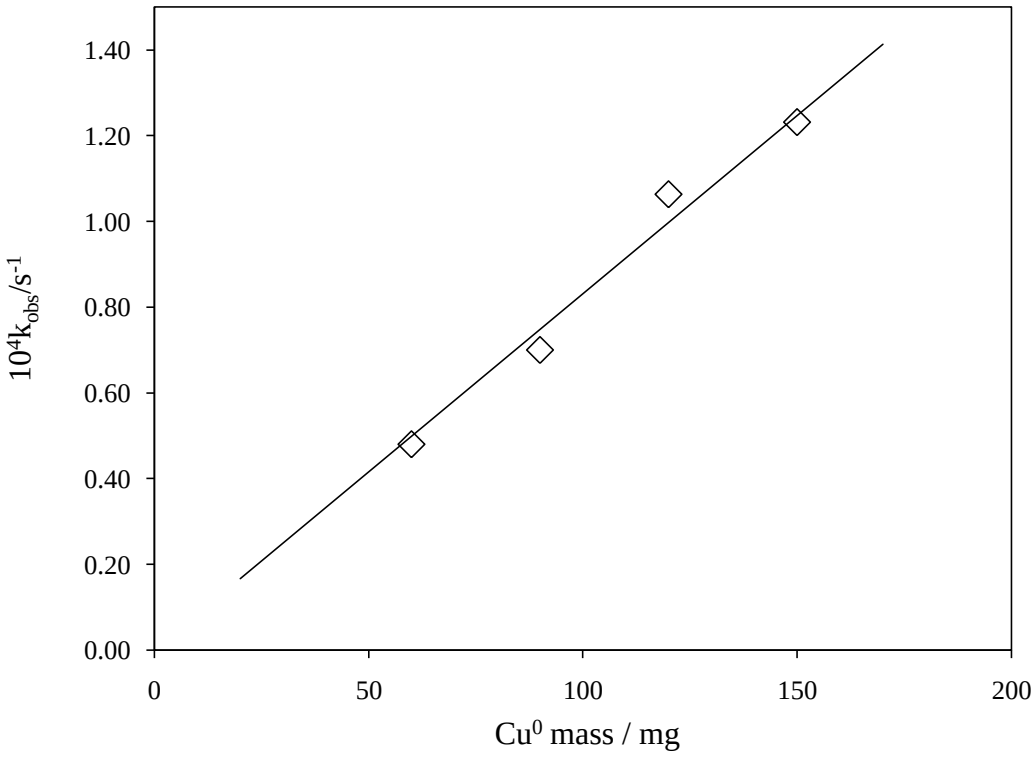


Figure 5.5 The observed pseudo first order rate constant as a function of the mass of copper (0) powder added for the CuAAC reaction in liquid ammonia. (Reaction conditions: 1mmol phenyl azide, 1mmol phenyl acetylene in 10ml liquid ammonia at 25 ^oC)

The rate of the copper (0) catalysed 'click reaction' in liquid ammonia is proportional to the amount of copper powder added, which is compatible with either some copper(0) dissolving or possibly the reaction occurring on the surface of the copper (0) catalyst in liquid ammonia (**Figure 5.5**, Appendix A, **Table A44**).

Generally, copper (II) salts that are used as the catalyst for CuAAC reactions are often done in aqueous binary solvents, such as in *t*-butyl alcohol-water system. This process often requires additional ancillary ligands to avoid the dimerisation of activated acetylene-copper complexes which occurs under air. In liquid ammonia, with 2 equivalent amount of ascorbic acid, Cu (II) catalysed CuAAC reaction does not need ancillary ligands and yields the same product as the Cu^{I}AAC reaction (**Table 5.10**, entry 5). Presumably, copper (II) is reduced to copper (I) by ascorbic acid in liquid ammonia, as in the absence of ascorbic acid, copper (II) catalysed 'click reactions' are slow and the starting materials are partially converted to the 1,4-disubstituted-1,2,3-triazole in liquid ammonia at room temperature, together with significant amounts of the acetylene dimer $(RC{\equiv}C)_2$.

Some preliminary mechanistic investigations of Cu^{I}AAC reaction of benzyl azide and phenyl acetylene in liquid ammonia show that the observed pseudo first order rate constant for the reaction has an apparent second order dependence on the copper (I) concentration (**Table 5.11**).

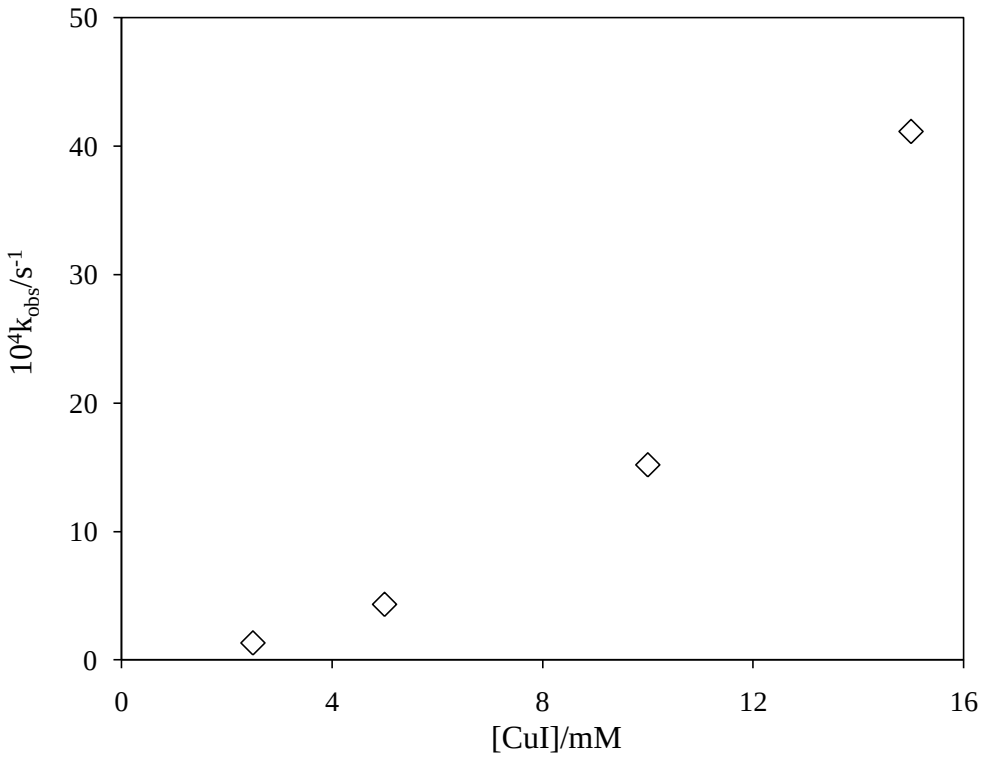


Figure 5.5a The dependence of the observed rate constant on the concentration of copper (I) catalyst for the Cu^IAAC reaction in liquid ammonia at 25 ^oC (Reaction conditions: 50mM phenyl azide and 50mM phenyl acetylene, fixed ascorbic acid concentration at 15mM, copper iodide concentration varies from 2.5-15mM)

The nonlinear relationship between k_{obs} and $[Cu^I]$ in **Figures 5.5a** indicates that the reaction in liquid ammonia has a greater than first order dependence on the catalyst concentration. Therefore the observed pseudo first order rate constant (k_{obs}) could possibly be expressed by **Equation 5.1**.

$$k_{obs} = k_1[Cu^I] + k_2[Cu^I]^2$$

$$\text{Thus, } k_{obs}/[Cu^I] = k_1 + k_2[Cu^I]$$

Equation 5.1

The plot of $k_{obs}/[Cu^I]$ vs. $[Cu^I]$ shows that there is no significant intercept which indicates there is no significant first order term in $[Cu^I]$ in the rate law. The slope of the plot gives the apparent second order rate constant $k_2 = 17.4M^{-1}s^{-1}$ (**Figures 5.5b**).

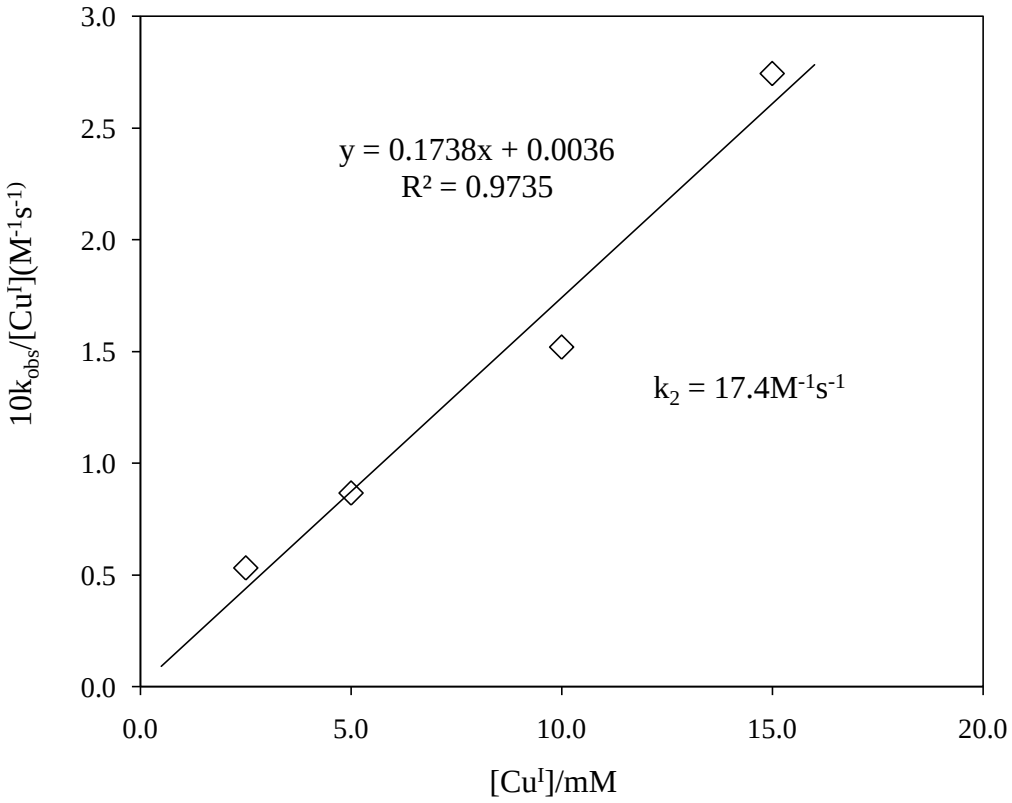


Figure 5.5b The dependence of the observed rate constant on the concentration of copper (I) catalyst for the Cu^{I}AAC reaction in liquid ammonia at 25 ^{o}C (Reaction conditions: 50mM phenyl azide and 50mM phenyl acetylene, fixed ascorbic acid concentration at 15mM, copper iodide concentration varies from 2.5-15mM)

Table 5.11 The dependence of the observed rate constant on the concentration of copper (I) catalyst for the Cu^{I}AAC reaction in liquid ammonia at 25 ^{o}C[a]

$[Cu^{I}]$/mM	**$10^{4}k_{obs.}/s^{-1}$**
2.5	1.30
5	4.33
10	15.2
15	41.2

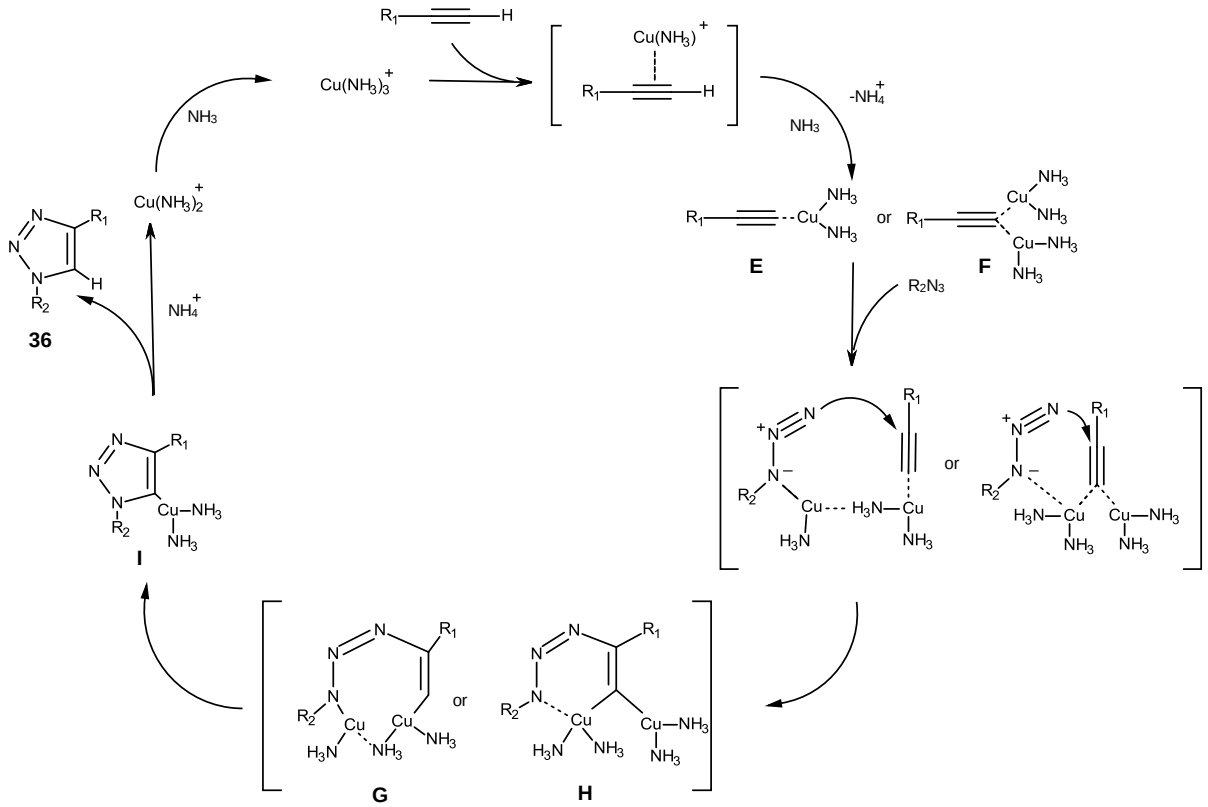
[a] Reaction conditions: 50mM phenyl azide and 50mM phenyl acetylene, fixed ascorbic acid concentration at 15mM, copper iodide concentration was varied from 2.5-15mM.

The azide only 'clicks' with terminal (CH) acetylene groups and there is no CuAAC reaction between internal alkynes and azide,[319] so, for example, no reaction is observed between

diphenylacetylene (PhC≡CPh) or 2-iodoethynylbenzene (PhC≡C–I) with benzyl azide in the presence of a copper (I) catalyst in liquid ammonia at room temperature. These observations suggest that the CuAAC reaction in liquid ammonia is a stepwise process involving two metal centres for the cycloaddition of azides and acetylenes, which is consistent with previous mechanistic studies of CuAAC in some conventional solvents.[320]

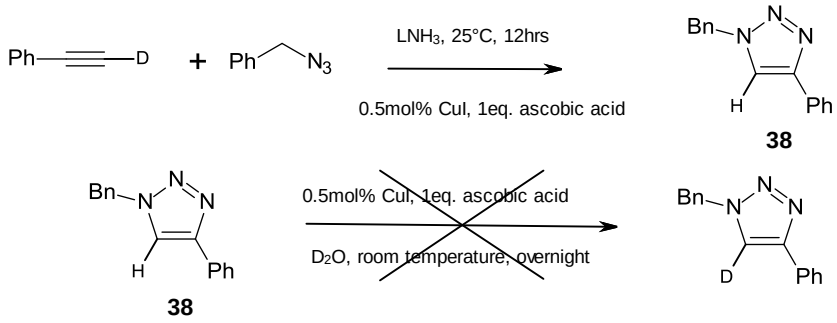
As described earlier in the copper (I) catalysed amination section, copper (I) salts mainly exist as tri-coordinated coplanar species, $[Cu(NH_3)_3]^+$, in liquid ammonia.[305] Acetylenes normally have pK_a range from 20 to 25 in water,[9] and are neutral in liquid ammonia at room temperature, as shown by the ^1H NMR spectrum of phenylacetylene in liquid ammonia (Appendix C, **Figure N31**). However, the theoretical calculations show that copper (I) coordination to the acetylene increases its acidity by up to 10^{10}-fold in water.[320a] Compared with other solvents, the basic nature of liquid ammonia facilitates the deprotonation of acetylene in the presence of copper (I) ions. Therefore, the formation of a coordinated copper (I)-acetylide ion complex in liquid ammonia could enhance the rate of reaction. However, it is worth noting that currently the exact structure of the copper-acetylene complex in liquid ammonia is still not clear, and we are not sure whether this complex exists in a copper monomer (**E**) or dimer form (**F**) which is crucial for the elucidation of the detailed reaction mechanism in liquid ammonia.

As stated earlier, the kinetic studies show that the Cu^IAAC process in liquid ammonia requires two copper (I) ions, which implies that one of these coordinated with the azide and the other to the acetylene. The reaction could then proceed via a six- or seven-membered copper-containing intermediate (**H** and **G**, respectively) to give a triazole-copper derivate **I**, which is followed by the fast protonation of **I** by ammonium ion to give the product **36** and the regenerated copper (I) catalyst (**Scheme 5.8**).



Scheme 5.8

In order to prove the existence of copper-acetylene complexes (**E** or **F**) in the Cu^{I}AAC reactions, deuteriated phenylacetylene (PhC≡C-D)[321] is used to 'click' with benzyl azide in liquid ammonia under the same conditions as introduced in **Table 5.9**. The ^{1}H NMR spectrum of the reaction product shows that there is no deuterium in the 1,4-disubstituted-1,2,3-triazole. In addition, the NMR results also show that there is no deuterium exchange between product (**38**) and D_2O, together with 0.5% CuI and 1eq. ascorbic acid to the copper catalyst, at room temperature for overnight (**Scheme 5.9**).



Scheme 5.9

These experimental observations described in **Scheme 5.9** indicate that the acetylene is deprotonated and copper atom substitutes the acetylene hydrogen to form **E** or **F** as the possible intermediate for the Cu^{I}AAC reactions in liquid ammonia.

In conclusion, the copper (I) catalysed 1,3-Huisgen cycloaddition reaction of azide and alkynes (Cu^{I}AAC) in liquid ammonia requires less catalyst than those in conventionally used solvents. The excellent yield, exclusive selectivity, and most importantly, the ease of separation of the product indicate the potential advantages of using liquid ammonia as the solvent for this reaction. The preliminary mechanistic investigation suggests that Cu^{I}AAC reaction in liquid ammonia is a stepwise process with the initial formation of copper (I)-acetylide ion complex, followed by its combination with copper (I) coordinated azide.

Table A1 The UV absorbance of 3-chlorophenol (10^{-4}M) under various concentration of $KClO_4$ in LNH_3 at room temperature

C_{KClO4}(M)	absorbance (317nm)	absorbance (257nm)
0	0.0528	0.240
0.005	0.150	0.467
0.01	0.239	0.675
0.05	0.360	0.920
0.1	0.379	1.022
0.2	0.385	1.025
0.3	0.392	1.026
0.4	0.399	1.027

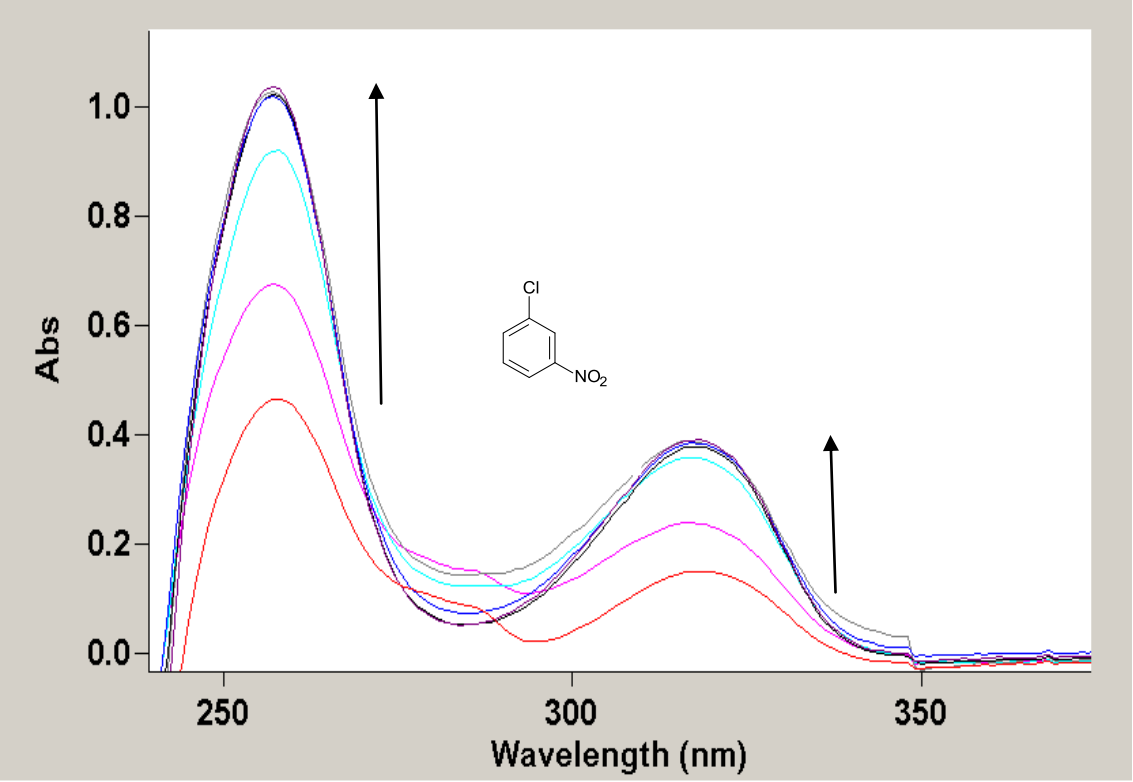


Figure A1 The UV absorbance of 3-chlorophenol (10^{-4}M) under various concentration of $KClO_4$ (0.005 to 0.4M) in LNH_3 at room temperature

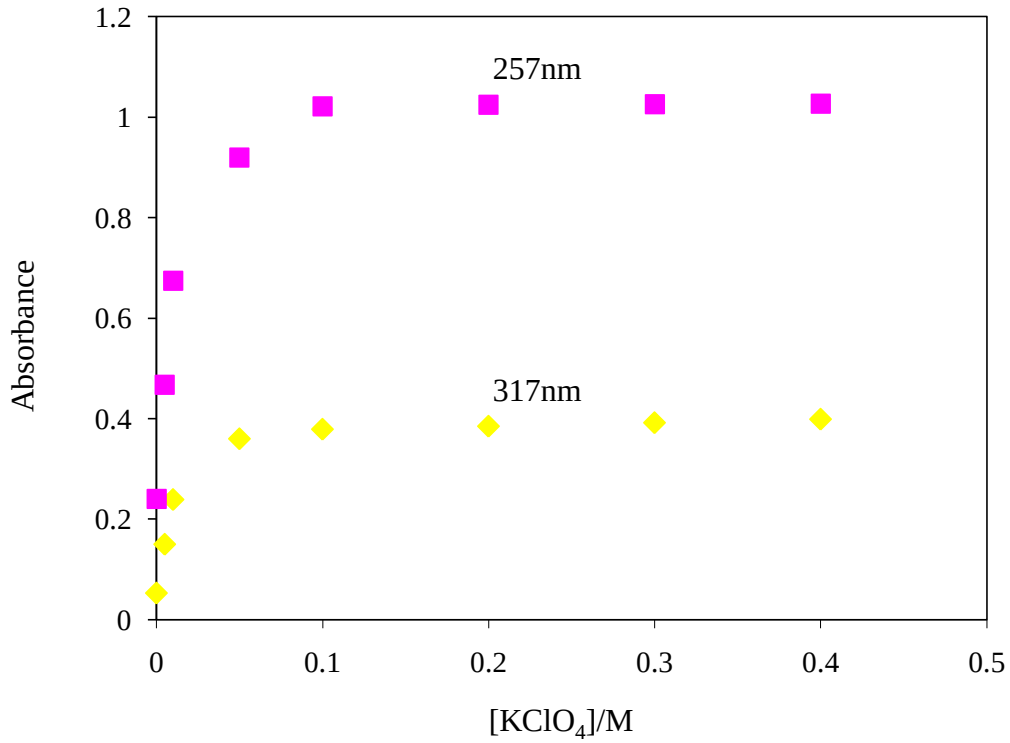


Figure A2 Various concentration of $KClO_4$ (0.005 to 0.4M) as salt effect on the ionisation of 3-chlorphenol (10^{-4}M) in LNH_3 at room temperature

Table A2 The UV absorbance of 3-chlorophenol (10^{-4}M) under various concentration of NaCl in liquid ammonia at room temperature

C_{NaCl}(M)	absorbance (317nm)	absorbance (257nm)
0.01	0.218	0.608
0.05	0.348	0.945
0.1	0.401	1.062
0.15	0.401	1.063
0.2	0.401	1.066

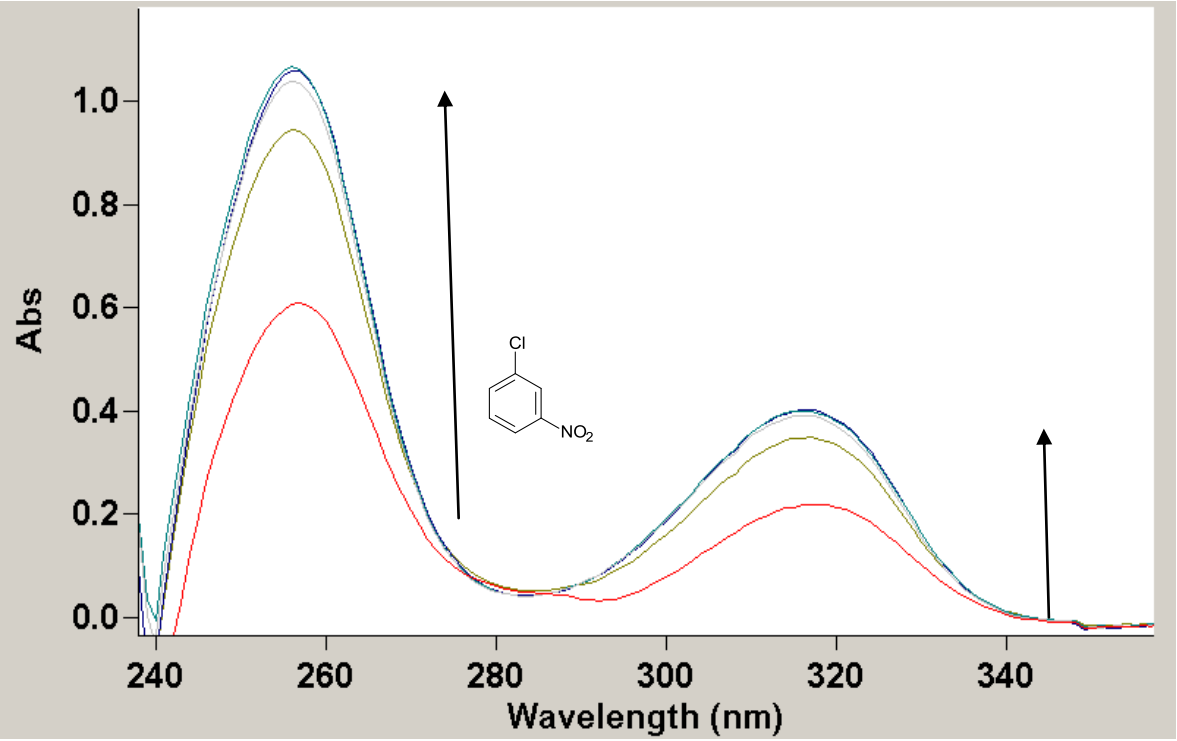


Figure A3 The UV absorbance of 3-chlorophenol (10^{-4}M) under various concentration of NaCl (0.01 to 0.2M) in LNH_3 at room temperature

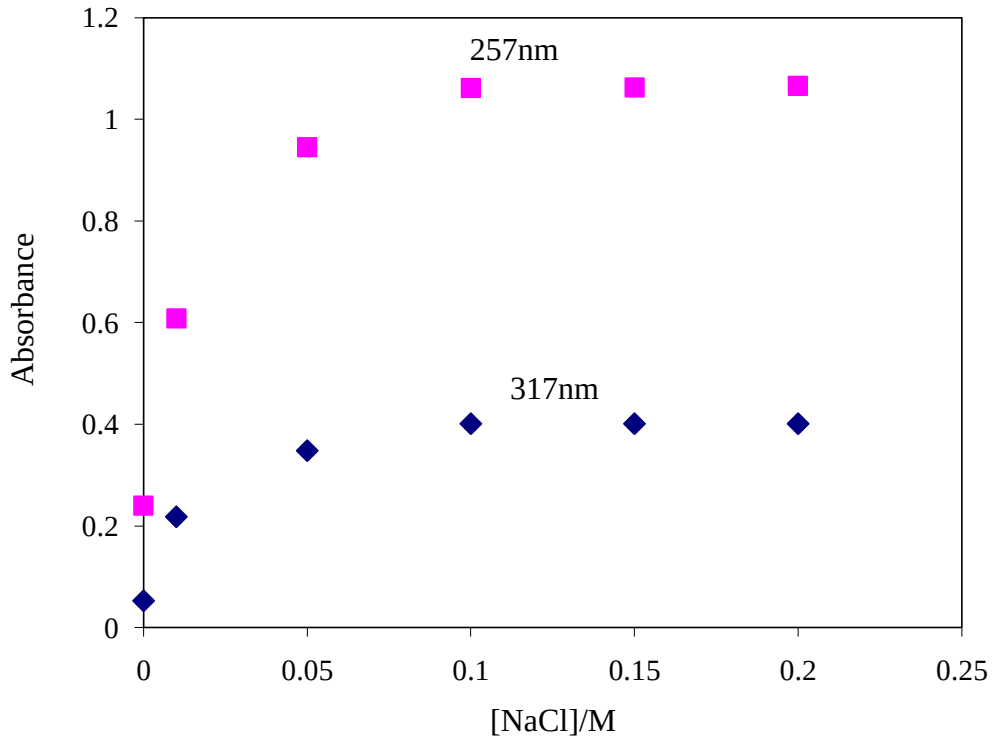


Figure A4 Various concentration of NaCl (0.01 to 0.2M) as salt effect on the ionisation of 3-chlorphenol (10^{-4}M) in LNH_3 at room temperature

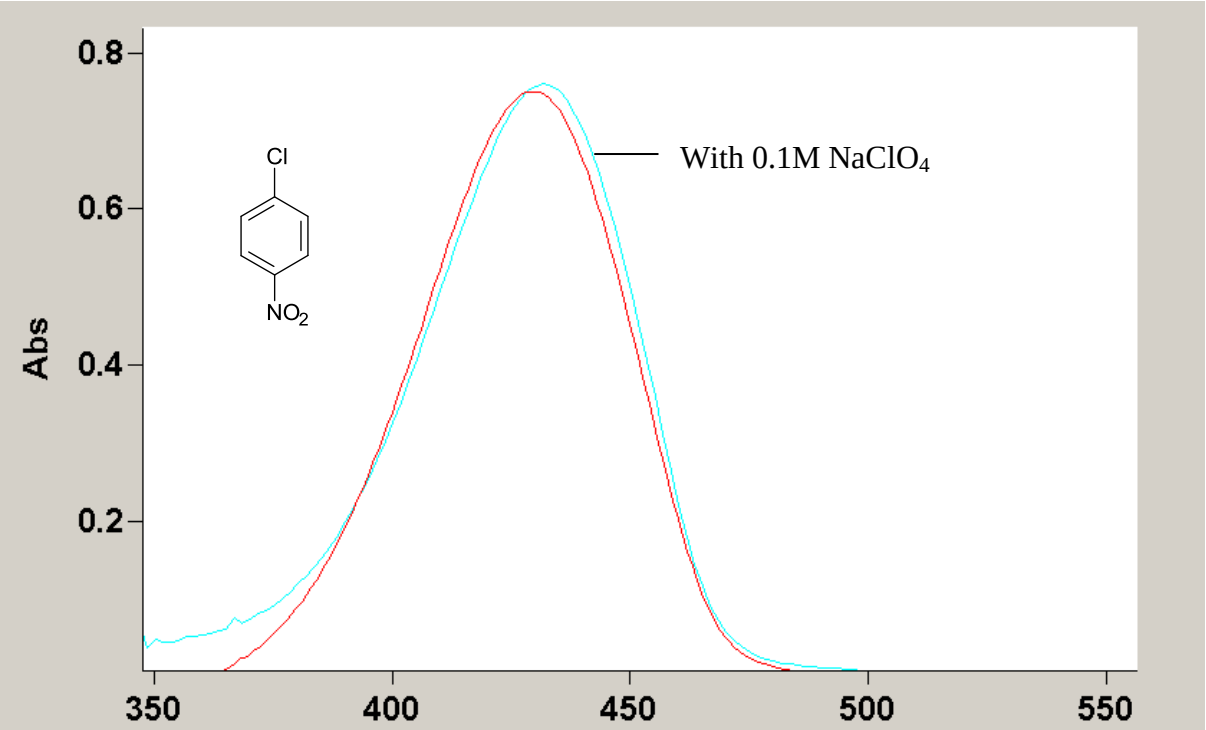


Figure A5a The UV absorbance of 2.5×10^{-4}M 4-nitorphenol with and without salt effects (0.1M $NaClO_4$) in LNH_3 at room temperature

Table A3 Linear relationship of pK_a of 4-methoxyphenol (3×10^{-4}M) with the square root of ionic strength (I, $KClO_4$) in LNH_3 at room temperature

I=C_{KClO4}(M)	$I^{1/2}$($M^{1/2}$)	Absorbance at λ_{max}	pK_a
0	0.00	0.035	6.59
0.1	0.32	0.063	6.07
0.2	0.45	0.109	5.58
0.3	0.55	0.127	5.44
0.4	0.63	0.168	5.18
0.5	0.71	0.205	4.99
0.8	0.89	0.264	4.74

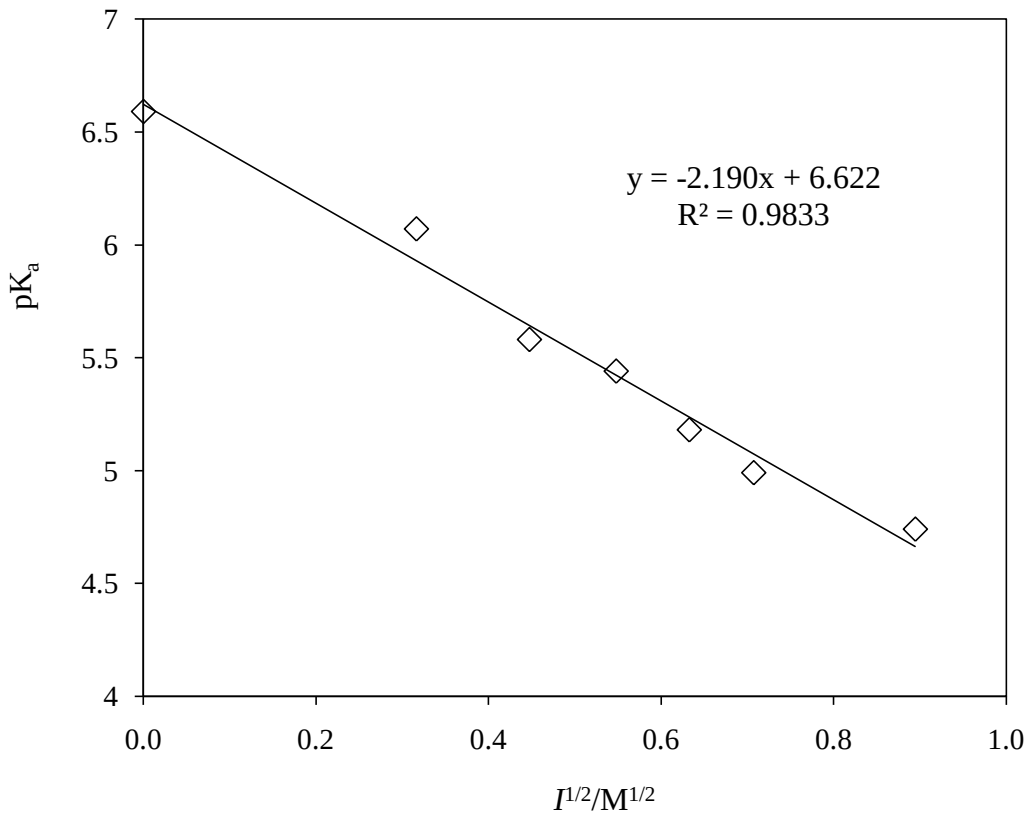


Figure A5 Linear relationship of pK_a of 4-methoxyphenol (3×10^{-4}M) with the square root of ionic strength (I, $KClO_4$) in LNH_3 at room temperature

Table A4 Linear relationship of pK_a of phenol (3×10^{-4}M) with the square root of ionic strength (I, $KClO_4$) in liquid ammonia at room temperature

I=C_{KClO4}(M)	$I^{1/2}$($M^{1/2}$)	Absorbance at λ_{max}	pK_a
0	0.00	0.000	6.02
0.1	0.07	0.140	5.01
0.2	0.10	0.246	4.66
0.3	0.22	0.321	4.16
0.4	0.45	0.349	4.07
0.5	0.54	0.369	4.00

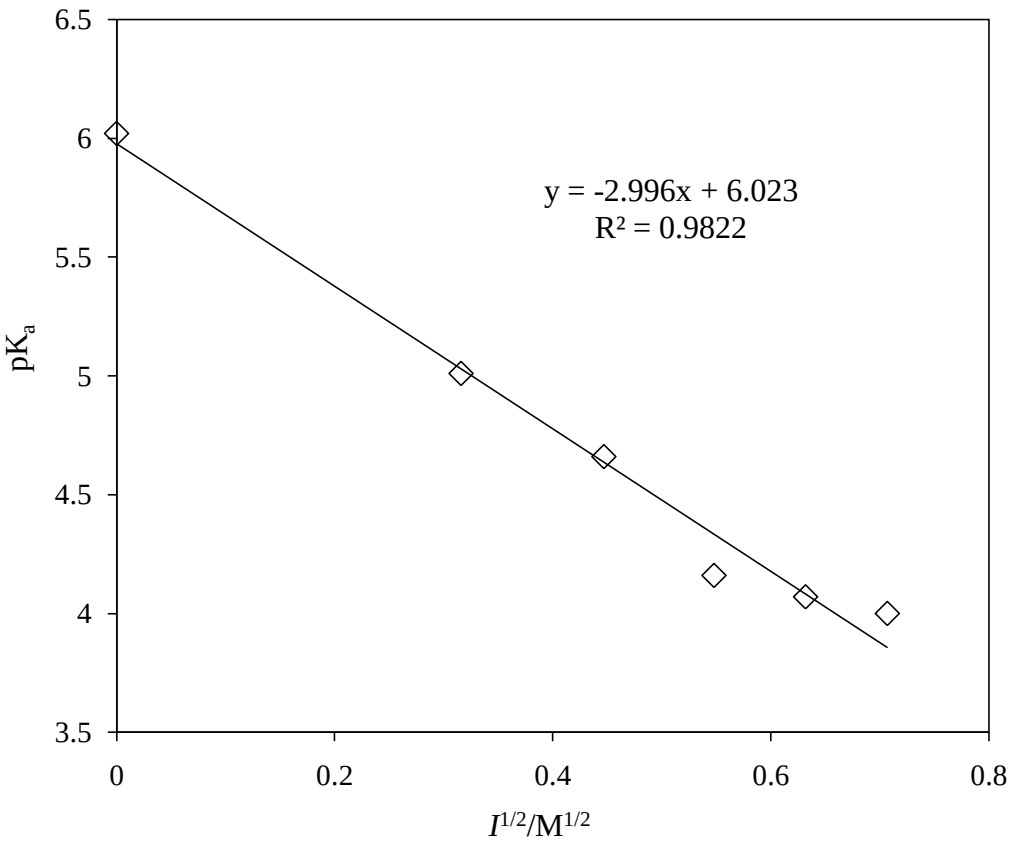


Figure A6 Linear relationship of pK_a of phenol (3×10^{-4}M) with the square root of ionic strength (I, $KClO_4$) in LNH_3 at room temperature

Table A5 Linear relationship of pK_a of 1-naphthol (1×10^{-4}M) with the square root of ionic strength (I, $KClO_4$) in liquid ammonia at room temperature

I=C_{KClO4}(M)	$I^{1/2}$($M^{1/2}$)	Absorbance at λ_{max}	pK_a
0	0.00	0.152	6.02
0.005	0.32	0.288	5.01
0.01	0.45	0.431	4.66
0.05	0.55	0.681	4.16
0.2	0.63	0.756	4.07
0.3	0.71	0.833	4.00

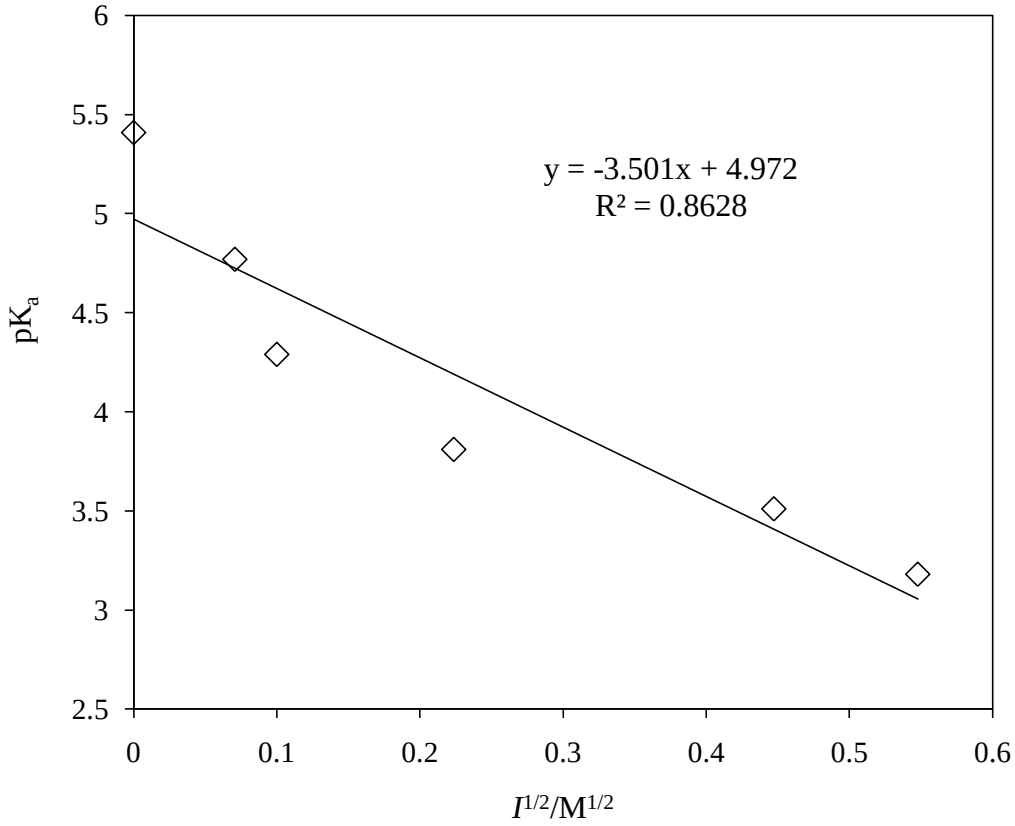


Figure A7 Linear relationship of pK_a of 1-naphthol (1×10^{-4}M) with the square root of ionic strength (I, $KClO_4$) in LNH_3 at room temperature

Table A6 Linear relationship of pK_a of 4-chlorophenol (1×10^{-4}M) with the square root of ionic strength (I, $KClO_4$) in liquid ammonia at room temperature

I=C_{KClO4}(M)	$I^{1/2}$($M^{1/2}$)	Absorbance at λ_{max}	pK_a
0	0.00	0.056	4.49
0.05	0.07	0.155	3.91
0.1	0.10	0.220	3.48
0.2	0.22	0.281	2.86
0.3	0.32	0.304	2.05

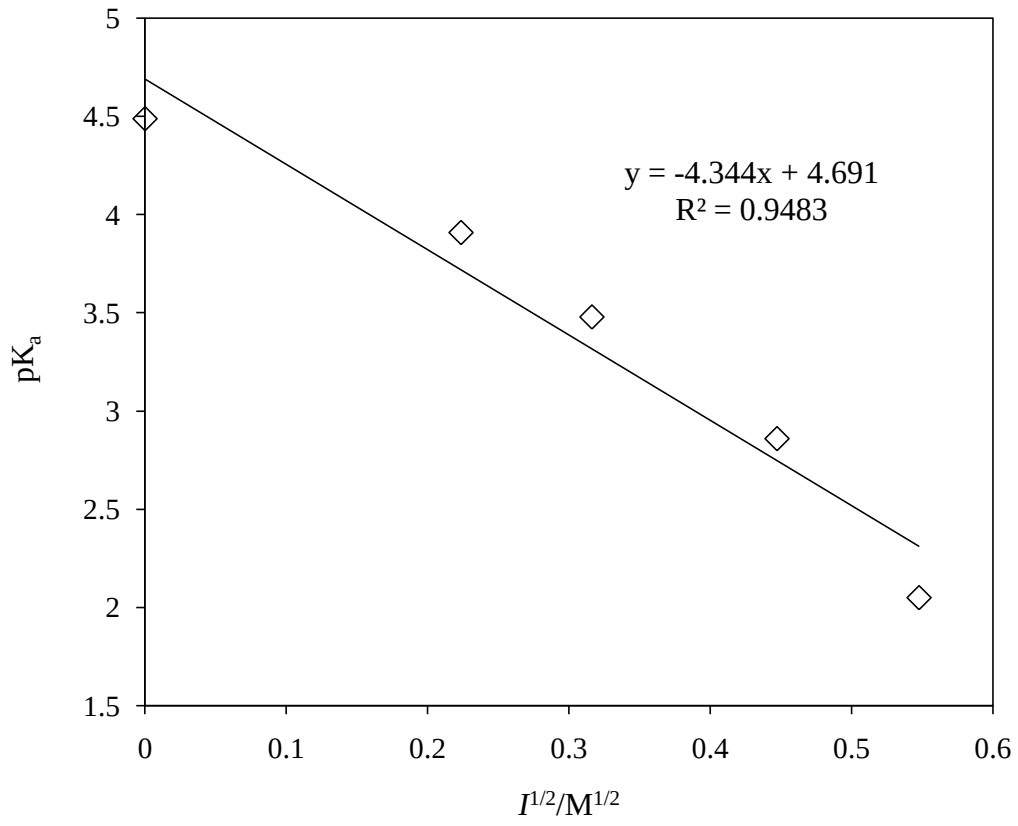


Figure A8 Linear relationship of pK_a of 4-chlorophenol (1×10^{-4}M) with the square root of ionic strength (I, $KClO_4$) in LNH_3 at room temperature

Table A7 Linear relationship of pK_a of 3-chlorophenol (1×10^{-4}M) with the square root of ionic strength (I, $KClO_4$) in liquid ammonia at room temperature

$I=C_{KClO4}$(M)	$I^{1/2}$($M^{1/2}$)	Absorbance at λ_{max}	pK_a
0	0.00	0.053	4.56
0.005	0.07	0.150	4.12
0.01	0.10	0.239	3.72
0.05	0.22	0.360	2.87
0.1	0.32	0.379	2.56

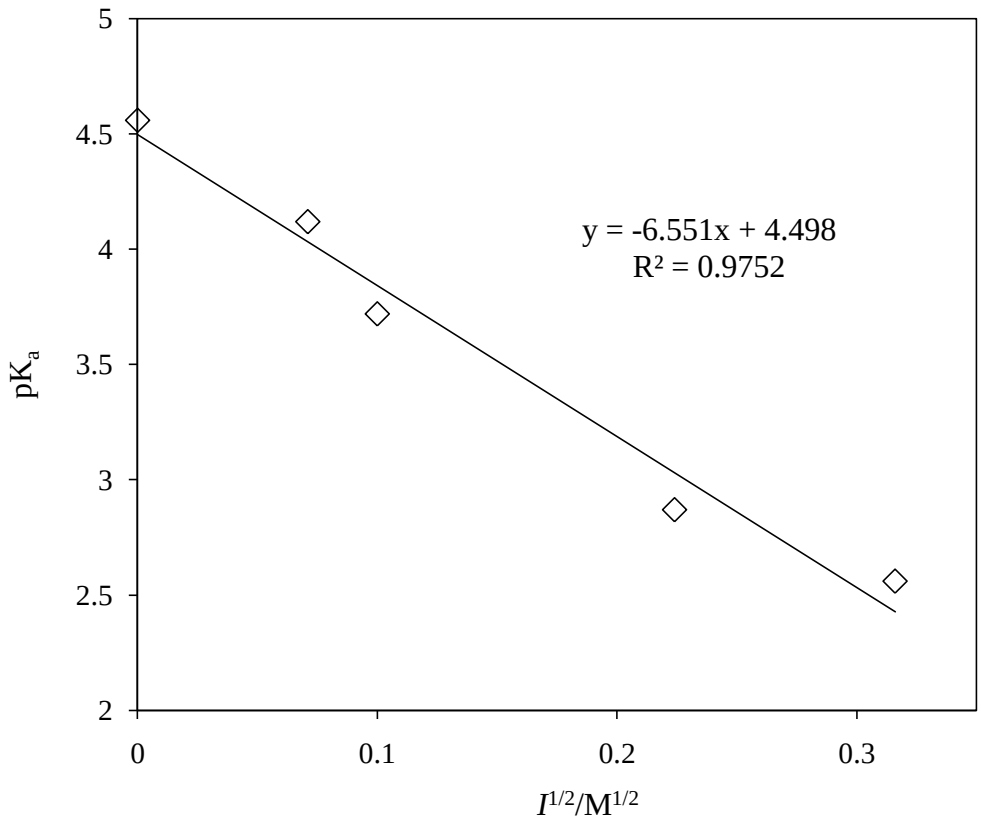


Figure A9 Linear relationship of pK_a of 3-chlorophenol (1×10^{-4}M) with the square root of ionic strength (I, $KClO_4$) in LNH_3 at room temperature

Table A8 Linear relationship of pK_a of 4-carbomethoxy phenol (5×10^{-5}M) with the square root of ionic strength (I, $KClO_4$) in liquid ammonia at room temperature

$I=C_{KClO4}$(M)	$I^{1/2}$($M^{1/2}$)	Absorbance at λ_{max}	pK_a
0	0.00	1.41	4.04
0.01	0.10	1.57	3.84
0.05	0.22	1.71	3.56
0.1	0.32	1.78	3.40

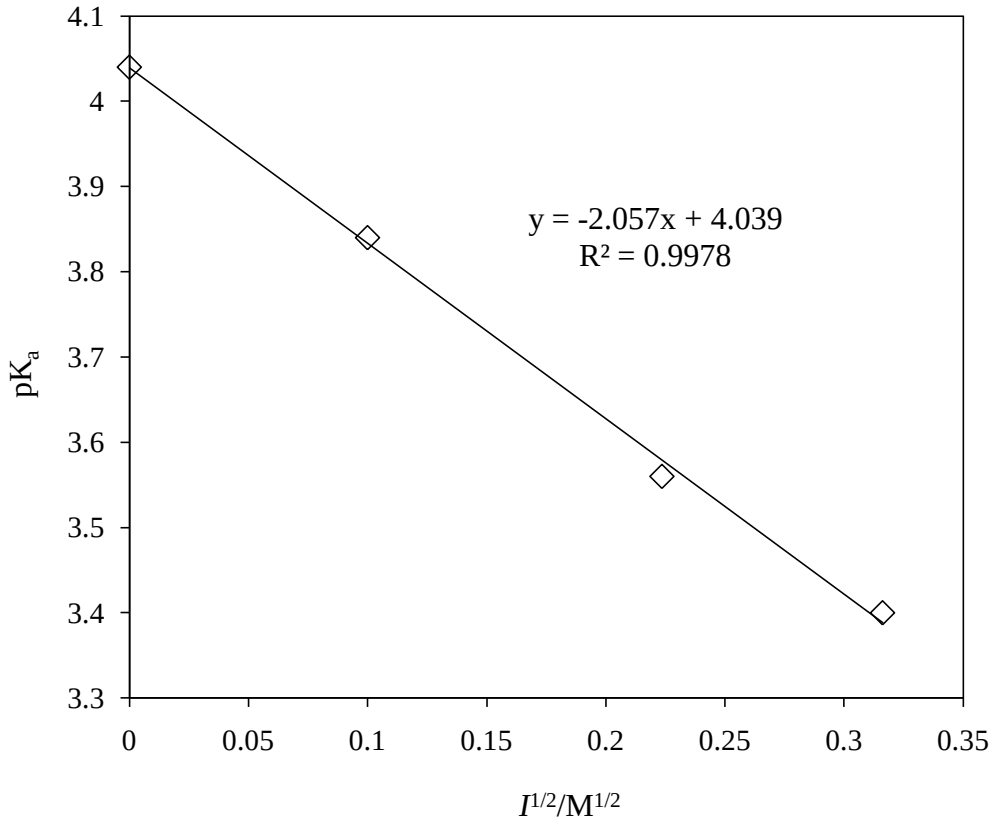


Figure A10 Linear relationship of pK_a of 4-carbomethoxy phenol (5×10^{-5}M) with the square root of ionic strength (I, $KClO_4$) in LNH_3 at room temperature

Table A9 Linear relationship of pK_a of 3-nitrophenol (1×10^{-4}M) with the square root of ionic strength (*I,* $KClO_4$) in liquid ammonia at room temperature

$I=C_{KClO4}$(M)	$I^{1/2}$($M^{1/2}$)	Absorbance at λ_{max}	pK_a
0	0.00	0.123	3.63
0.005	0.07	0.136	3.38
0.01	0.10	0.150	2.98
0.05	0.22	0.157	2.60

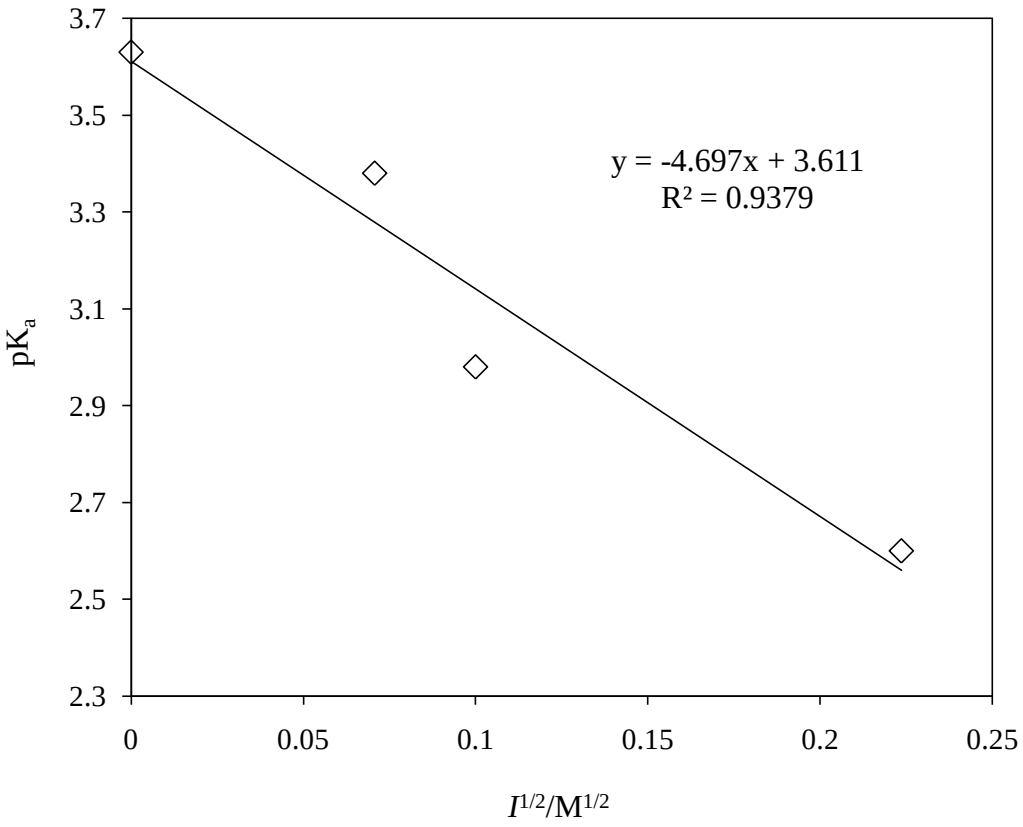


Figure A11 Linear relationship of pK_a of 3-nitrophenol (1×10^{-4}M) with the square root of ionic strength (*I,* $KClO_4$) in LNH_3 at room temperature

Table A10, Figure A12 Titration of 4-carbomethoxy phenol (5×10^{-5}M) with NH_4Cl salt in liquid ammonia at room temperature

[NH_4Cl]/M	**Absorbance**
0	1.500
1.00×10^{-5}	1.420
2.50×10^{-5}	1.318
5.00×10^{-5}	1.176
1.25×10^{-3}	0.927
2.50×10^{-3}	0.846
3.75×10^{-3}	0.757
5.00×10^{-3}	0.734
1.00×10^{-2}	0.781
5.00×10^{-2}	0.782

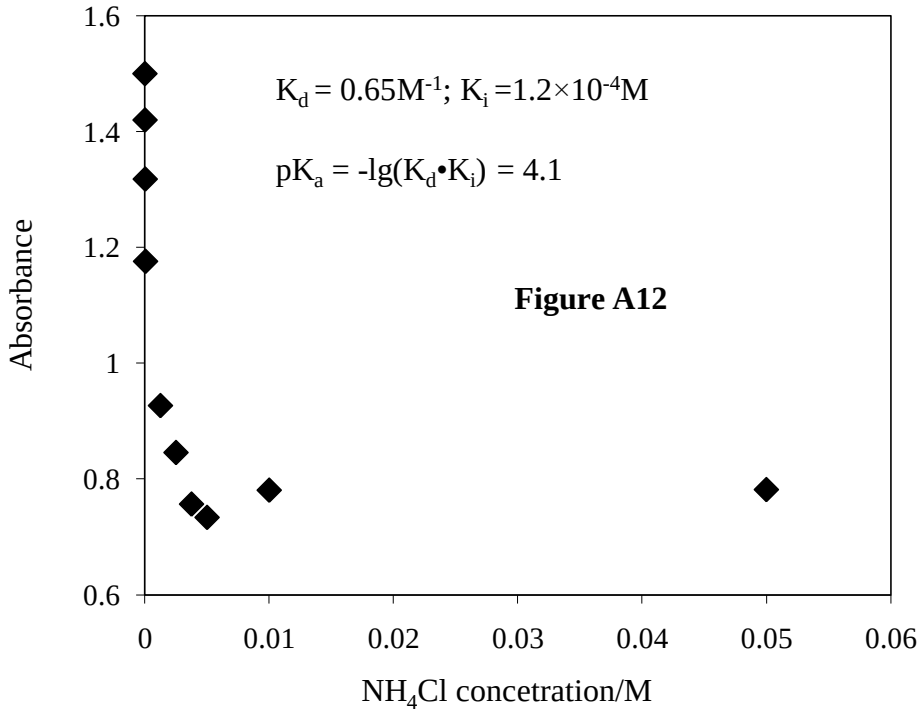


Table A11, Figure A13 Titration of 4-carbomethoxyphenol (5×10^{-5}M) with NH_4Cl salt (I=0.2M, NaCl) in liquid ammonia at room temperature

[NH_4Cl]/M	**[NaCl]/M**	**Absorbance**
0	0.20	1.89
0.01	0.19	1.41
0.03	0.17	1.29
0.04	0.16	1.10
0.05	0.15	1.03
0.10	0.10	0.914
0.15	0.05	0.872
0.20	0	0.874

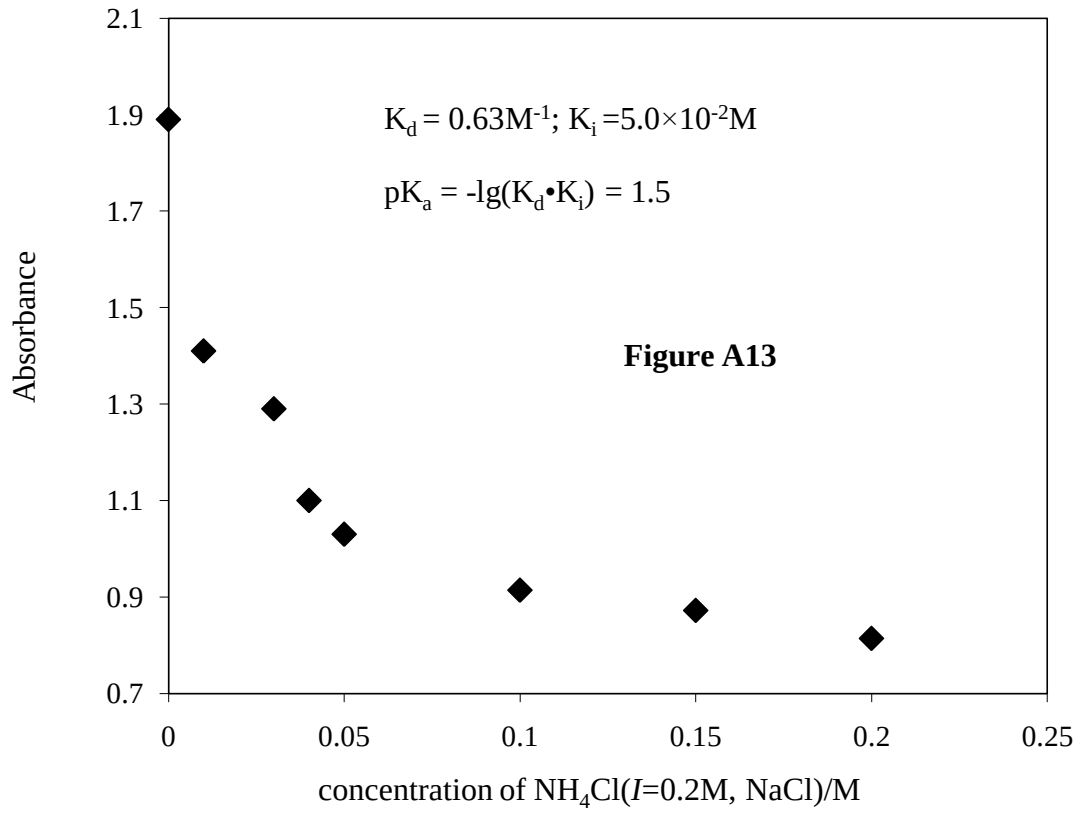


Figure A13

Table A12, Figure A14 Titration of 4-nitrophenol (2.5×10^{-5}M) with NH_4Cl salt in liquid ammonia at room temperature

[NH_4Cl]/M	**Absorbance**
0	0.942
0.01	0.889
0.02	0.875
0.05	0.815
0.10	0.796
0.50	0.792
1.00	0.790
2.00	0.799

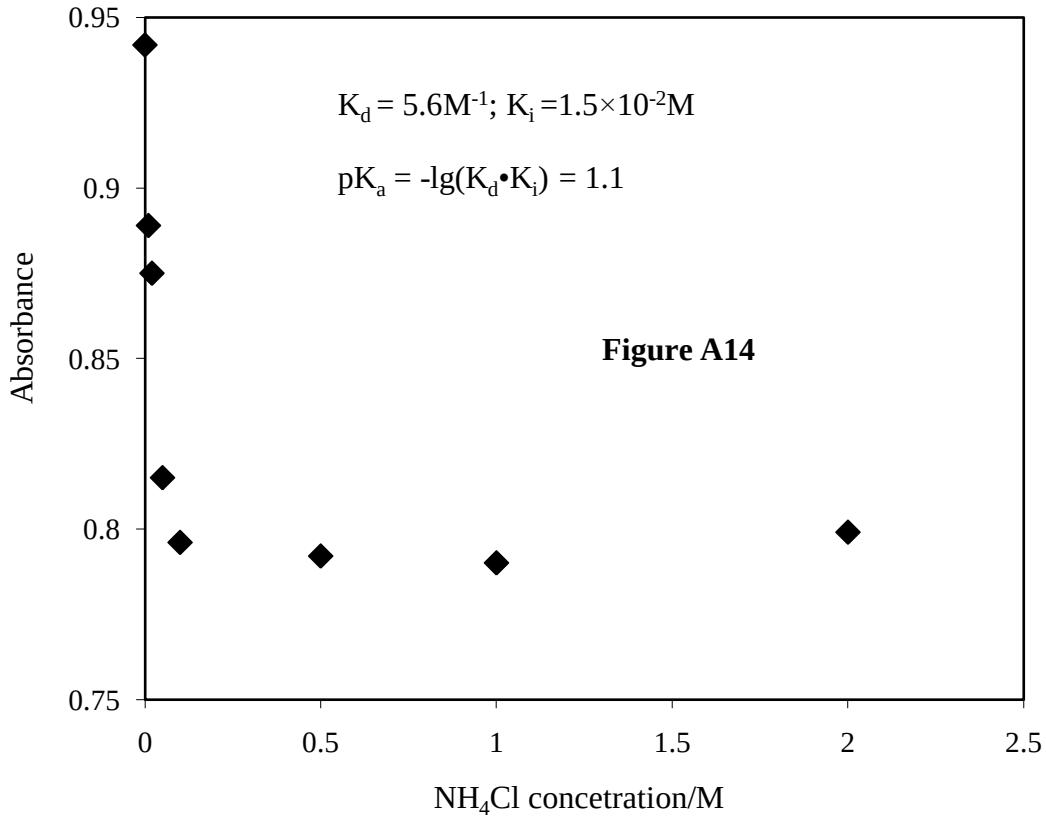


Figure A14

Table A13, Figure A15 Titration of 4-nitrophenol (2.5×10^{-5}M) with NH_4Cl salt (I=0.2M, NaCl) in liquid ammonia at room temperature

[NH_4Cl]/M	**[NaCl]/M**	**Absorbance**
0	0.20	1.085
0.005	0.195	1.079
0.03	0.17	0.988
0.05	0.15	0.914
0.07	0.13	0.905
0.10	0.10	0.902
0.15	0.05	0.819
0.20	0	0.811

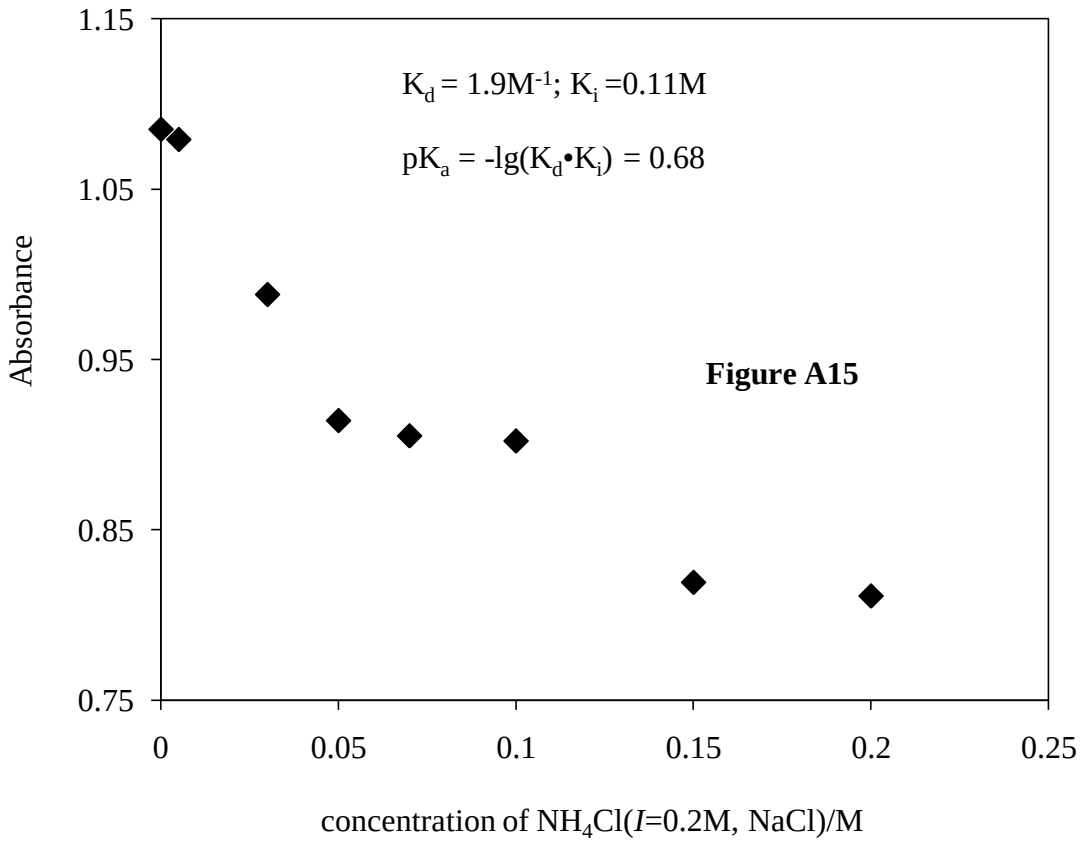


Figure A15

Table A14 Solvolysis rate of benzyl chloride in liquid ammonia at different temperature

temperature(K)	**$10^4 k_{obs}(s^{-1})$**	**$10^5 k_2(M^{-1}s^{-1})$**
268.2	1.28	0.338
283.2	3.25	0.881
298.2	8.89	2.48
308.2	13.3	3.79

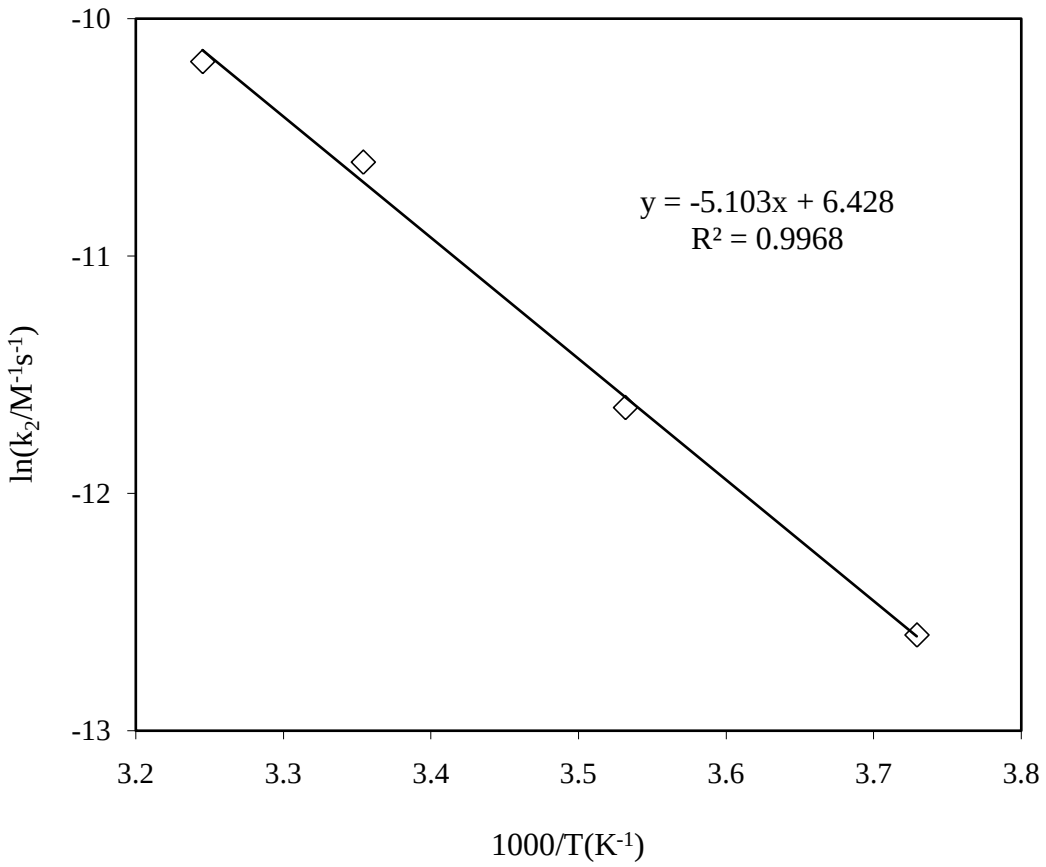


Figure A16 Erying plot for the solvolysis of benzyl chloride in LNH_3

Table A15 Solvolysis rate of 4-chlorobenzyl chloride in liquid ammonia at different temperature

temperature(K)	**$10^4 k_{obs}(s^{-1})$**	**$10^5 k_2(M^{-1}s^{-1})$**
268.2	1.48	0.391
283.2	4.36	1.18
298.2	9.81	2.74
308.2	16.8	4.78

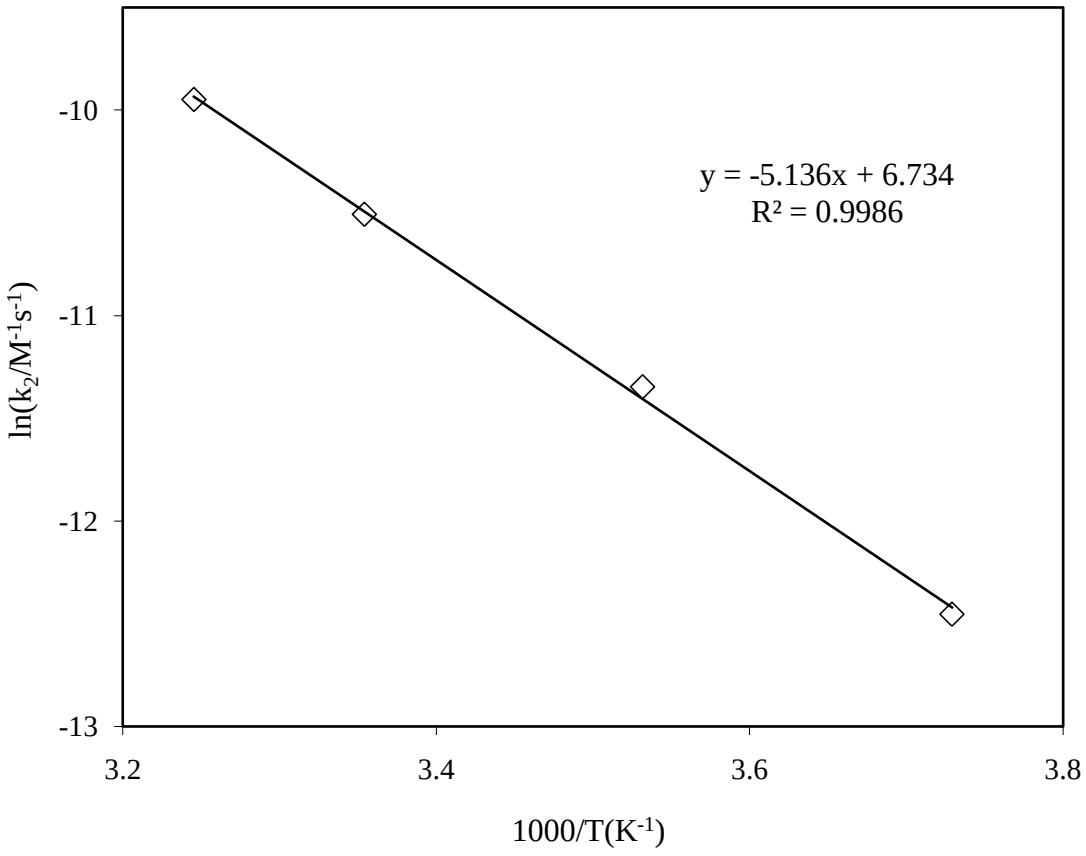


Figure A17 Erying plot for the solvolysis of 4-chlorobenzyl chloride in LNH_3

Table A16 Solvolysis rate of 4-nitrobenzyl chloride in liquid ammonia at different temperature

temperature(K)	**$10^4 k_{obs}(s^{-1})$**	**$10^5 k_2(M^{-1}s^{-1})$**
268.2	2.42	0.636
283.2	6.71	1.82
298.2	15.3	4.27
308.2	22.9	6.52

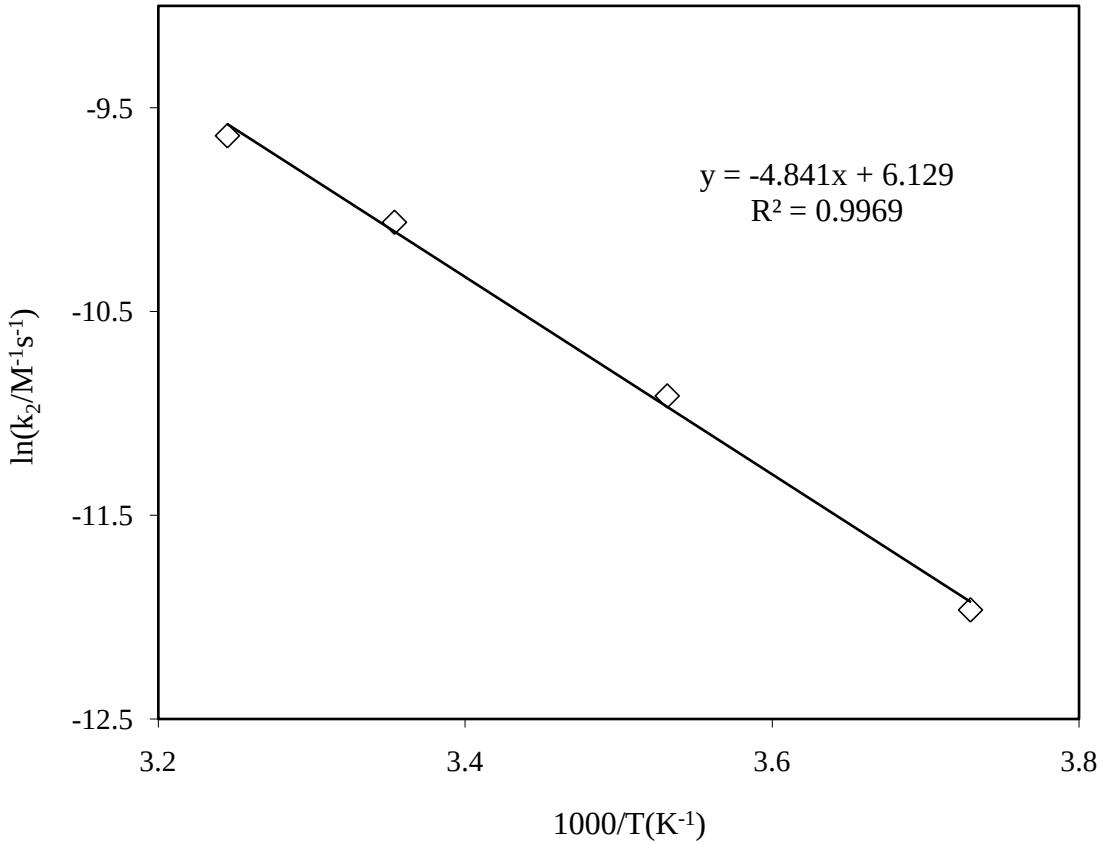


Figure A18 Erying plot for the solvolysis of 4-nitrobenzyl chloride in LNH_3

Table A17 Solvolysis rate of 4-methoxybenzyl chloride in liquid ammonia at different temperature

temperature(K)	**$10^4 k_{obs}(s^{-1})$**	**$10^5 k_2(M^{-1}s^{-1})$**
268.2	2.72	0.717
283.2	7.99	2.16
298.2	19.1	5.33
308.2	32.3	9.23

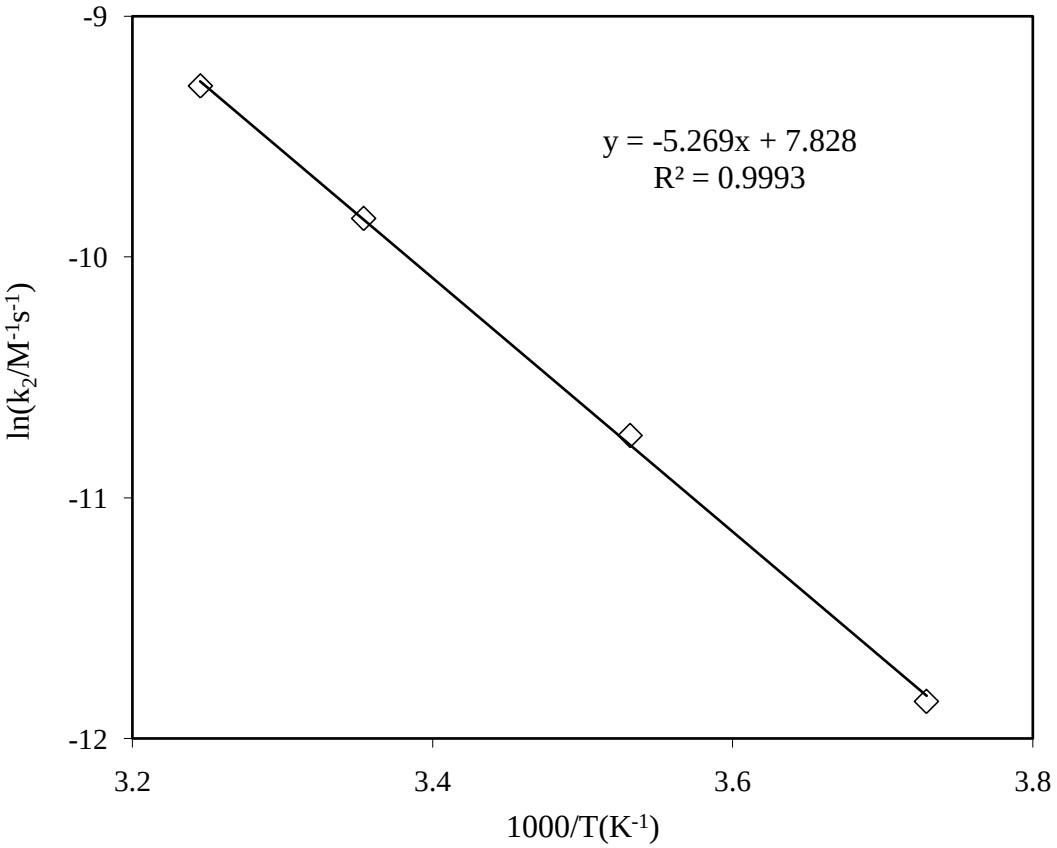


Figure A19 Erying plot for the solvolysis of 4-methoxybenzyl chloride in LNH_3

Table A18 Solvolysis rate of α-methyl benzyl chloride in liquid ammonia at different temperature

temperature(K)	**$10^5 k_{obs}(s^{-1})$**	**$10^7 k_2(M^{-1}s^{-1})$**
298.2	0.671	1.87
308.2	1.62	4.53
318.2	3.98	11.1

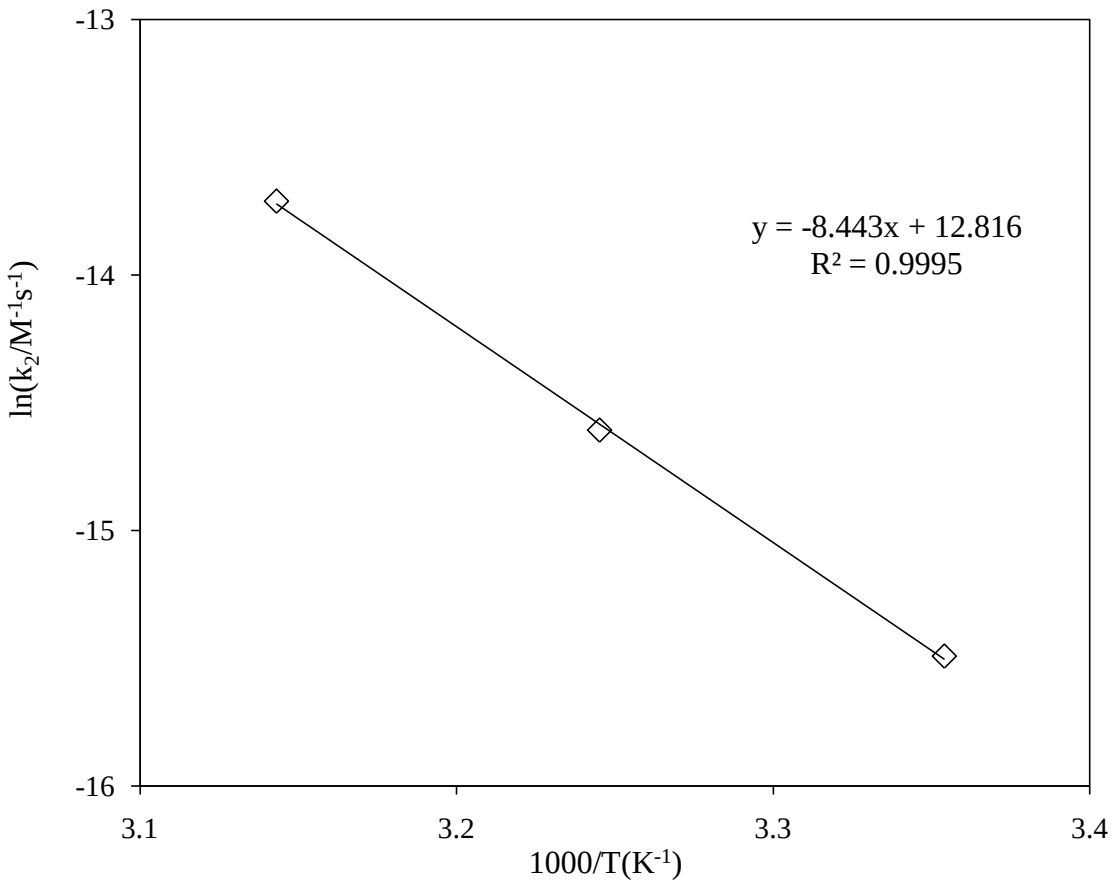


Figure A20 Erying plot for the solvolysis of α-methyl benzyl chloride in LNH_3

Table A19 Salt effects on the solvolysis rates of 4-NFB and 2-NFB in LNH_3

substrate	temperature	salt	salt concentration/M	$10^5 k_{obs}/s^{-1}$
4-NFB	20	$NaNO_3$	0	0.79
			0.5	1.32
			1	1.55
			2	2.32
			3	3.17
4-NFB	20	NH_4Cl	1	1.42
			2	1.88
			3	2.28
2-NFB	25	$NaNO_3$	0	21.5
			0.5	22.7
			1	24.7
			2	27.3

Table A20 Calculated ground state free energy of solvation for 4-NFB and 2-NFB in different solvents[a]

substrate	computational method	water	ethanol	DMSO	DMF
4-NFB	HF/6-31+G*	-15.97	-28.02	-24.52	-26.84
	DFT/B3LYP[b]	-16.88	-28.71	-24.80	-27.12
2-NFB	HF/6-31+G*	-23.98	-35.40	-32.26	-34.47
	DFT/B3LYP[b]	-25.05	-36.13	-32.45	-34.66

[a] Energy unit: kJ/mol. [b] basis set: 6-31+G*.

Table A21 Solvolysis of 4-NFB in LNH_3 at different temperature

T(K)	k_{obs}/s^{-1}
293.2	7.86×10^{-6}
333.2	1.24×10^{-4}
353.2	3.90×10^{-4}
373.2	1.51×10^{-3}
393.2	2.06×10^{-3}

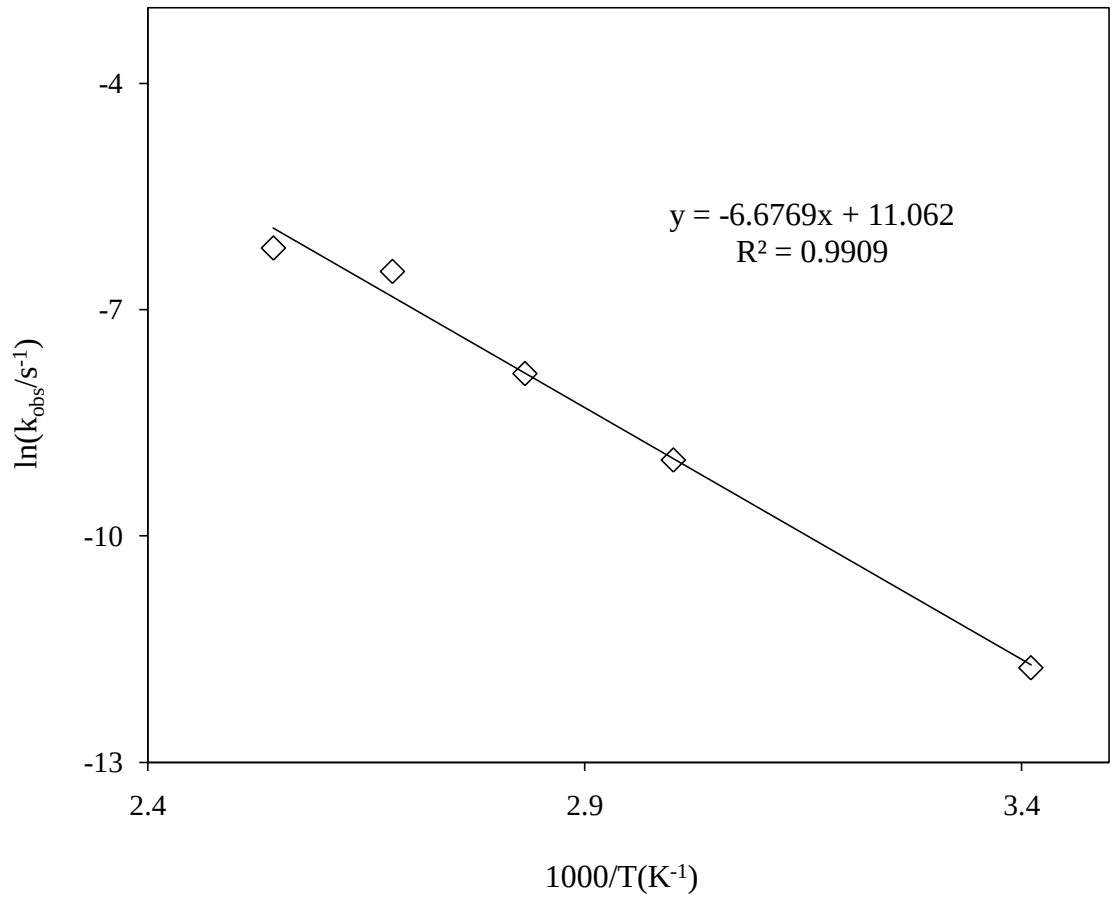


Figure A21 Erying plot for the solvolysis of 4-NFB in LNH_3

Table A22 Solvolysis of 2-NFB in LNH_3 at different temperature

T(K)	k_{obs}/s^{-1}
263.2	1.16×10^{-5}
298.2	2.13×10^{-4}
308.2	4.02×10^{-4}
318.2	8.32×10^{-4}

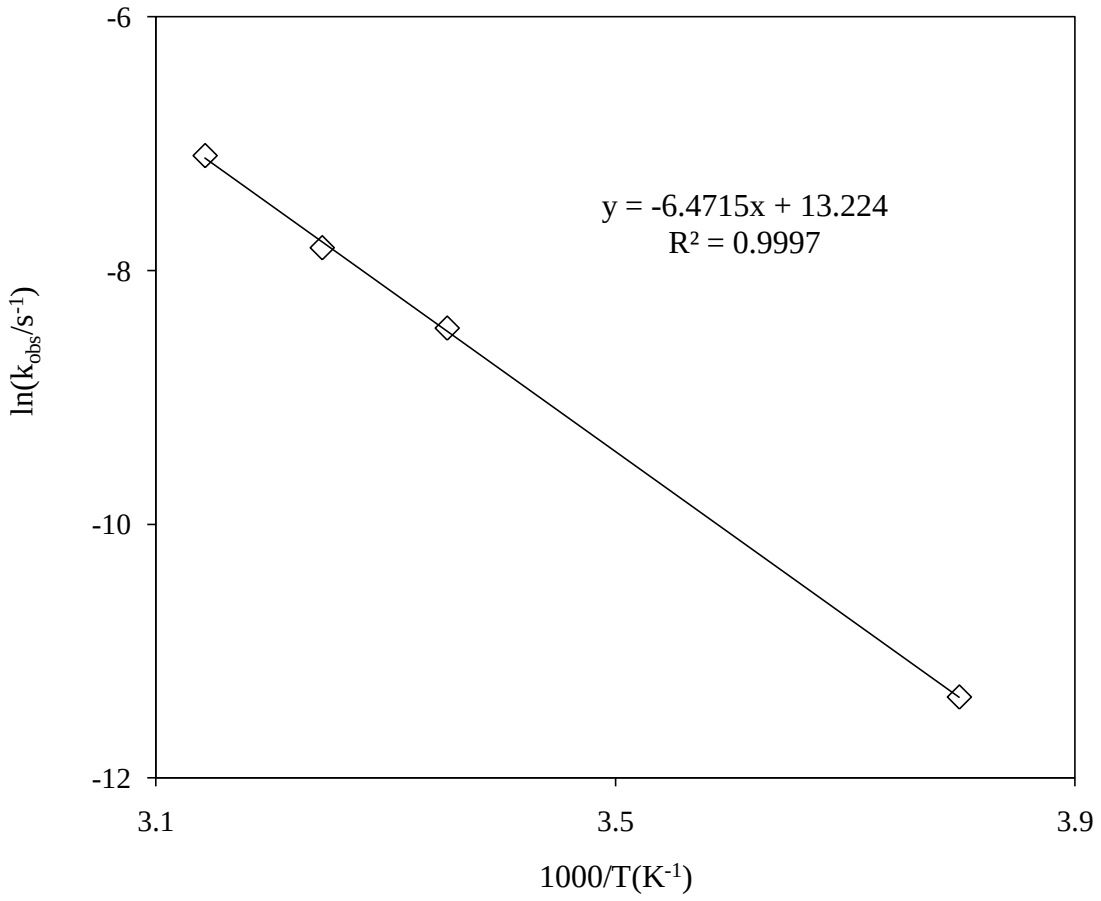


Figure A22 Erying plot for the solvolysis of 2-NFB in LNH_3

Table A23 Solvolysis of 2,4-DFNB in LNH_3 at different temperature

T(K)	k_{obs}/s^{-1}
288.2	4.14×10^{-3}
296.2	6.29×10^{-3}
308.2	1.30×10^{-2}
318.2	2.15×10^{-2}

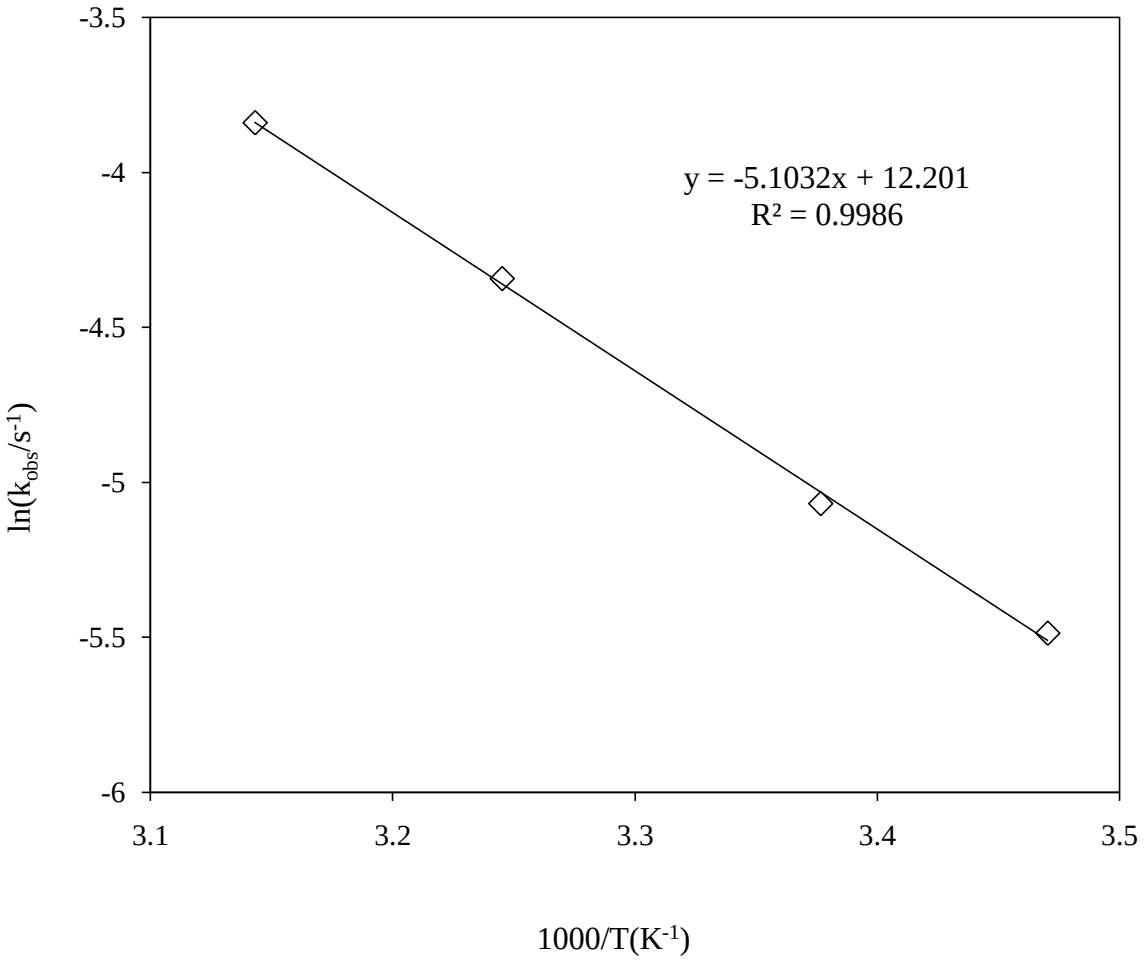


Figure A23 Erying plot for the solvolysis of 2,4-DFNB in LNH_3

Table A24 The rate for benzyl chloride with different concentration of phenoxide in liquid ammonia at 25 ^{o}C (I = 0.3 M, $KClO_4$)

[phenoxide]/M	**[$KClO_4$]/M**	**$10^3 k_{obs}/s^{-1}$**
0	0.3	1.18
0.05	0.25	2.41
0.1	0.2	3.23
0.2	0.1	4.38
0.3	0	5.30

Table A25 Second order rate constant for 4-substituted benzyl chloride with phenoxide anion in liquid ammonia at 25 ^{o}C

substituent	**σ_p**	**$10^2 k_2(M^{-1}s^{-1})$**
4-MeO	-0.27	4.02
4-Me	-0.17	1.48
4-H	0	2.01
3-MeO	0.12	2.22
4-Cl	0.23	4.93
4-COOMe	0.45	5.28
4-CN	0.66	13.4

Table A26 The rate for 4-methoxybenzyl chloride with different concentration of phenoxide in liquid ammonia at 25 ^{o}C (I = 0.1 M, $KClO_4$)

[PhO^-]/M	**[$KClO_4$]/M**	**$10^3k_{obs}/s^{-1}$**
0	0.1	2.07
0.05	0.05	4.18
0.075	0.025	5.52
0.1	0	7.19

Table A27 The rate for the benzyl chloride with different concentration of morpholine in liquid ammonia at 25 ^{o}C

[morpholine]/M	**$10^3k_{obs}/s^{-1}$**
0	8.89
0.1	1.30
0.2	1.60
0.4	2.38
0.75	3.62
1.0	4.18

Table A28 Second order rate constant for 4-substituted benzyl chloride with sodium triazolate in liquid ammonia at 25 ^{o}C

substituent	**σ_p**	**$10^2k_2(M^{-1}s^{-1})$**
4-MeO	-0.27	0.917
4-Me	-0.17	0.863
4-H	0	0.942
4-Cl	0.23	1.58
4-COOMe	0.45	1.70
4-NO_2	0.78	6.59

Table A29 Second order rate constant for 4-substituted benzyl chloride with piperidine in liquid ammonia at 25 ^{o}C

substituent	**σ_p**	**$10^2k_2(M^{-1}s^{-1})$**
4-Me	-0.17	1.79
4-H	0	1.70
4-Cl	0.23	1.34
4-COOMe	0.45	1.27
4-CN	0.66	1.96
4-NO_2	0.78	2.06

Table A30 Second order rate constant for 4-substituted benzyl chloride with diethyl malonate anion in liquid ammonia at 25 ^{o}C

substituent	**σ_p**	**$10^3k_2(M^{-1}s^{-1})$**
4-MeO	-0.27	6.92
4-Me	-0.17	3.04
4-H	0	2.27
4-Cl	0.23	6.67
4-CN	0.66	10.93
4-NO_2	0.78	12.76

Table A31 pK_a's of carbon acids in water and DMSO at 25 ^oC

acid	**pK_a(aq.)**	**pK_a(DMSO)**
acetone	19.3	26.5
dimedone	5.25	11.2
acetoacetone	9.0	13.3
2-acetylcyclohexanone	10.1	14.1
$CH_3COCHMeCOCH_3$	11	15.1
ethyl acetylacetate	10.7	14.2
diethyl malonate	12.9	16.4
CH_3COCH_2COPh	9.4	14.2
$EtCH(CO_2Et)_2$	15.0	18.7
meldrum's acid	4.8	7.3
ethyl acetate	25.6	29.5
nitroethane	8.6	17.0
1-nitropropane	9.0	17.2
2-nitropropane	7.74	16.8
nitromethane	10.29	17.2
$PhCH_2NO_2$	6.88	12.2
$(4\text{-}MePh)CH_2NO_2$	7.11	12.33
$(4\text{-}NO_2Ph)CH_2NO_2$	5.89	8.62
$(3\text{-}NO_2Ph)CH_2NO_2$	6.3	10.04
$(4\text{-}CNPh)CH_2NO_2$	6.17	9.31
acetonitrile	28.9	31.3
malononitrile	11.2	11.1
EtO_2CCH_2CN	11.2	13.1
benzyl cyanide	22.0	21.9
CH_3CH_2CN	30.9	32.5

Table A32 The rate for reaction between 4-NFB and various concentration of sodium phenoxide in LNH_3 at 25 ^oC (I=0.3M, $KClO_4$)

concentration of phenoxide(M)	**$10^3 k_{obs}/s^{-1}$**
0	1.66×10^{-2}
0.05	2.52
0.1	4.81
0.2	6.87
0.3	9.71

Table A33 Solvolysis of 4-NFB in LNH_3 at different temperature

T(K)	**k_{obs}/s^{-1}**
293.2	7.86×10^{-6}
333.2	1.24×10^{-4}
353.2	3.90×10^{-4}
373.2	1.51×10^{-3}
393.2	2.06×10^{-3}

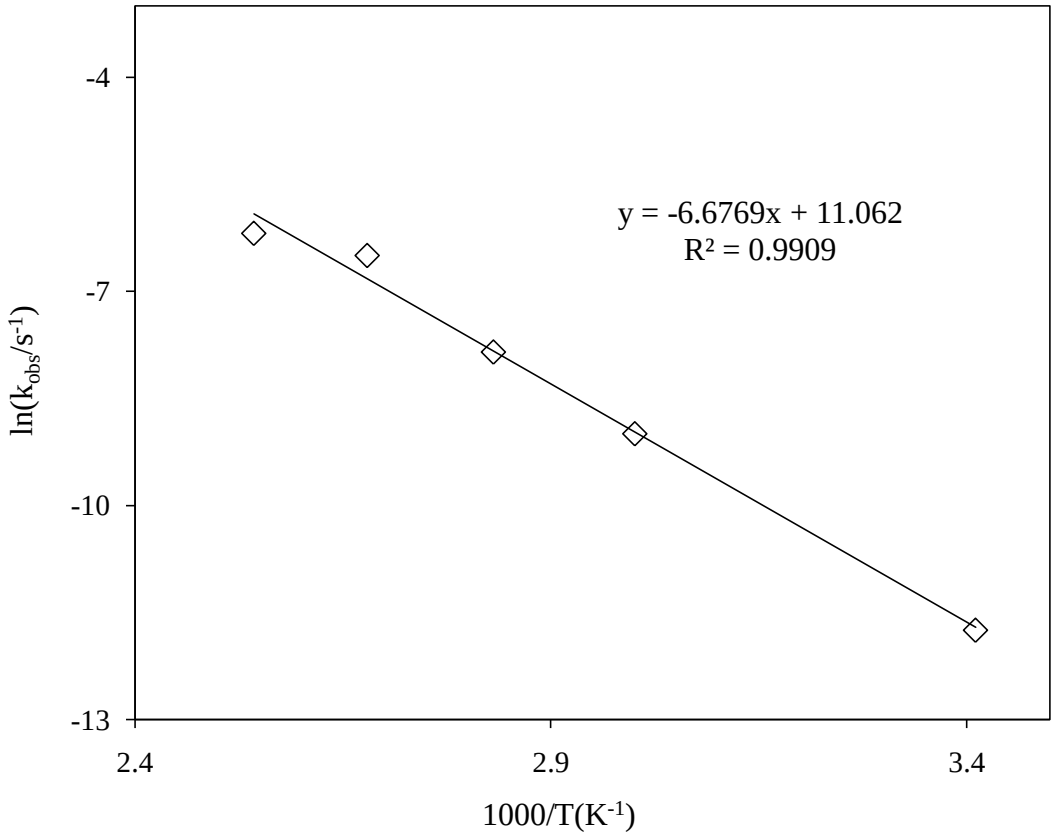


Figure A24 Erying plot for the solvolysis of 4-NFB in LNH_3

Table A34 The second order rate constant for the reaction between 4-NFB and 4-substituted phenoxide in LNH_3 at 25 ^{o}C

4-substituted phenoxide	**pK_a(aq.)**	**$pK_a(LNH_3)$**	**$k_2(M^{-1}s^{-1})$**
4-MeO	10.27	6.62	0.330
4-t-Bu	10.31	6.67	0.108
4-H	9.99	6.02	0.0528
4-Cl	9.20	4.69	0.0237
4-COOMe	8.47	4.04	5.31×10^{-4}
4-CN	7.95	2.71	4.22×10^{-5}

Table A35 Salt effect on the rate of reaction between 4-NFB and phenoxide anion in LNH_3 at 25 ^oC

$[NaNO_3]$/M	**$10^3k_{obs}/s^{-1}$**
0	5.28
0.2	3.33
0.5	2.90
1	2.38
1.5	1.93

Table A36 The rate for the reaction between 4-NFB and various concentration of morpholine in LNH_3 at 25 ^oC

morpholine concentration(M)	**$10^4k_{obs}(s^{-1})$**
0	0.0786
0.2	0.967
0.5	2.275
0.75	3.058

Table A37 A comparison of the second order rate constant for the reaction between sodium azide and 4-NFB in various solvents

solvent	**temperature(^oC)**	**$k_2(M^{-1}s^{-1})$**	**$k_{rel.}$**
methanol	25	6.3×10^{-8}	1
nitromethane	25	2.0×10^{-4}	3100
liquid ammonia[b]	25	3.8×10^{-4}	6000
acetonitrile	25	5.0×10^{-4}	8000
DMSO	25	5.0×10^{-4}	8000
DMF	25	2.0×10^{-3}	31000

[a] Except the rate in liquid ammonia, all the other data is from ref. 28. [b] The rate of the reaction was measured under pseudo first order conditions by using excess of 4-NFB, following the increasing of 4-NAB. The ratio between 4-NFB and sodium azide was 10:1, less than 1% 4-NAB decomposed under such condition.

Table A38 A comparison of the second order rate constants for the reaction between piperidine and 4-NFB in various solvents

solvent	**temperature(^{o}C)**	**$k_2(M^{-1}s^{-1})$**	**$k_{rel.}$**	**reference**
benzene[a]	25	7.8×10^{-6}	1	322
liquid ammonia	25	2.3×10^{-3}	300	this work
tetrahydrofuran[b]	25	3.9×10^{-3}	500	323
DMSO	25	9.0×10^{-3}	1150	276d

[a] The reaction is base catalysed, the second order rate constant increases exponentially with increasing of piperidine concentration, the rate cited here is when the concentration of piperidine equals 0.92M. [b] Base catalysis mechanism was also observed, the rate cited is when the concentration of piperidine equals 1.0 M.

Table A39 The rate for the reaction between 4-NFB and various concentration of sodium azide in LNH_3 at 25 ^{o}C (*I*=3M, $NaNO_3$)

concentration of sodium azide(M)	**$10^4k_{obs}/s^{-1}$**
0	0.248
0.5	0.559
1	0.869
1.5	1.223
2.5	1.810
3	2.158

Table A40 The rate for the solvolysis of 4-NAB under various concentration of $KClO_4$ in LNH_3 at 25 ^{o}C

concentration of potassium perchlorate(M)	**$10^4k_{obs}/s^{-1}$**
0	0.0511
0.5	0.848
1	1.78
1.5	2.53

Table A41 pK_a of phenol in acetonitrile (AN) against its aqueous pK_a at 25 ^oC

phenol	**pK_a(aq.)**	**pK_a(AN)**
3.5-dinitrophenol	6.66	20.50
4-nitrophenol	7.14	20.90
4-cyanophenol	7.95	22.77
3-nitrophenol	8.35	23.85
3,4-dichlorophenol	8.51	24.06
4-bromophenol	9.36	25.53
3-chlorophenol	9.02	25.04
3-trifluoromethylphenol	9.04	24.90
4-chlorophenol	9.20	25.44
phenol	9.99	27.20
4-methylphenol	10.28	27.45
4-*tert*-butylphenol	10.31	27.48

Table A42 pK_a of phenol in DMSO against its aqueous pK_a at 25 ^oC

phenol	**pK_a(aq.)**	**pK_a(DMSO)**
3,5-dinitrophenol	6.66	10.60
4-nitrophenol	7.14	11.00
4-cyanophenol	7.95	13.01
4-acetylphenol	8.05	13.68
3-nitrophenol	8.36	13.75
3-chlorophenol	9.02	15.83
3-trifluoromethylphenol	9.04	14.30
3-acetylphenol	9.19	15.14
3-fluorophenol	9.28	15.88
4-bromophenol	9.36	15.50
phenol	9.99	16.47
3-methylphenol	10.1	16.86
4-methoxyphenol	10.27	17.58
4-methylphenol	10.28	16.96

Table A43 pK_a of phenol in methanol against its aqueous pK_a at 25 ^oC

phenol	**pK_a(aq.)**	**pK_a(Methanol)**
3,4-dinitrophenol	5.42	9.46
3,5-dinitrophenol	6.66	10.20
4-nitrophenol	7.14	11.24
4-cyanophenol	7.95	13.27
3,5-dichlorophenol	8.18	12.94
3-nitrophenol	8.36	12.40
3-bromophenol	9.01	13.30
3-chlorophenol	9.02	13.10
4-chlorophenol	9.20	14.88
4-bromophenol	9.36	14.93
phenol	9.99	14.76
3-methylphenol	10.10	14.48
3,5-dimethylphenol	10.20	14.62
4-*tert*-butylphenol	10.31	14.52

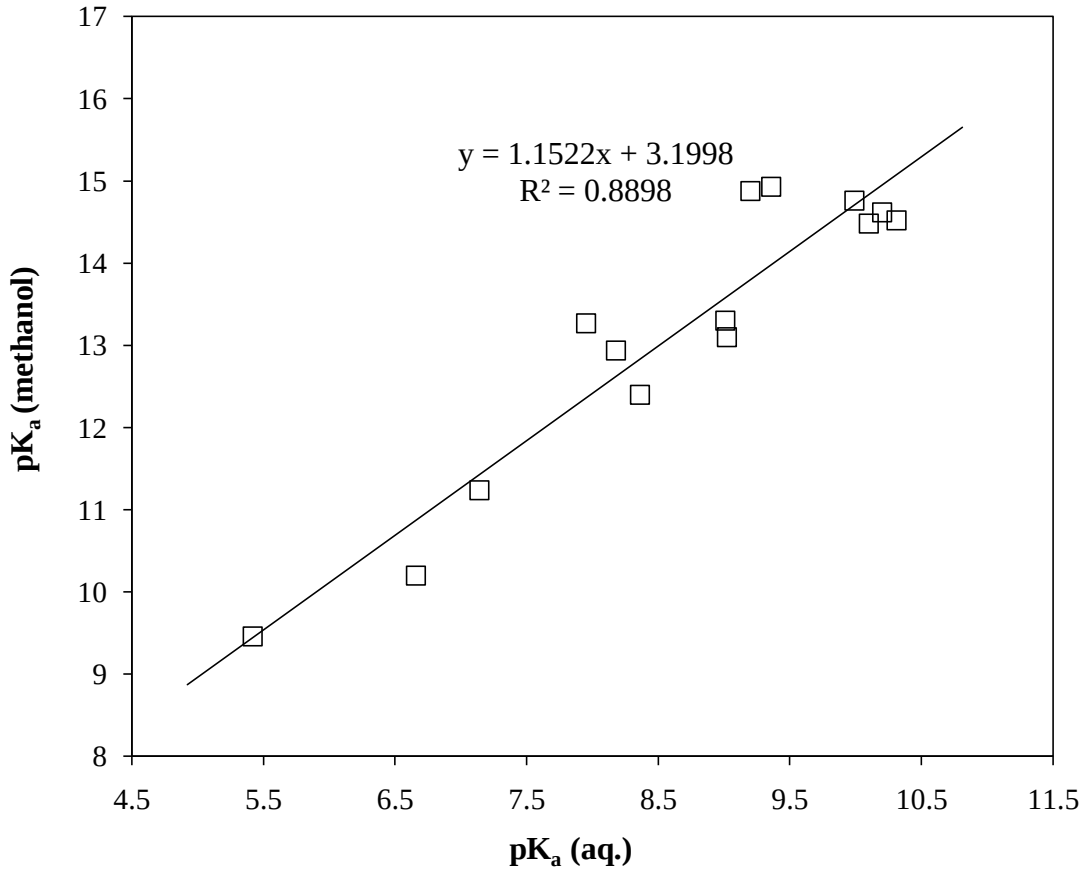


Figure A25 pK_a of phenol in methanol against its aqueous pK_a at 25 ^oC.

Table A44 The observed rate constant increases linearly with the increasing mass of copper power added for the CuAAC reaction in liquid ammonia at 25 ^oC[a]

Cu^0/mg	**$10^4 k_{obs.}/s^{-1}$**
60	0.48
90	0.70
120	1.06
150	1.23

[a] Reaction conditions: 1mmol phenyl azide, 1mmol phenyl acetylene in 10ml liquid ammonia at 25 ^oC.

Derivation 1:

Modeling the influence of added ammonium ion on the ionisation and ion-pairing behaviour of phenols in liquid ammonia

Two simultaneous equilibria need to be considered: deprotonation of the phenol by ammonia to give the ion pair, and dissociation of the ion pair to give the free phenolate and ammonium ions.

$$ArOH + NH_3 \overset{K_i}{\longleftrightarrow} \{ArO^-NH_4^+\}_{ip} \overset{K_d}{\longleftrightarrow} ArO^- + NH_4^+$$

These equilibria can be defined by the equilibrium constants K_i and K_d.

$$K_i = \frac{[ArO^-NH_4^+]_{ip}}{[ArOH]} \qquad K_d = \frac{[ArO^-][NH_4^+]}{[ArO^-NH_4^+]_{ip}}$$

We require a smooth function that describes the ionisation process at low (spectroscopic) concentration, where the only ammonium ion present is that produced by dissociation of the ion pair, through to conditions where ammonium ion is added to the solution. Solutions containing stoichiometric initial concentrations of phenol (c) and ammonium ion (Z) (added as ammonium chloride) are made up. Both equilibria must be satisfied, and from the mass balance across the phenol/ion pair equilibrium alone.

$$[ArOH]_T = [ArOH] + [IP], \text{ so } \frac{[ArOH]}{[ArOH]_T} = \frac{1}{1+K_i} \text{ and } \frac{[IP]}{[ArOH]_T} = \frac{K_i}{1+K_i}$$

Proceeding as usual for a dissociation process:

	NH_3 + ArOH	$\overset{K_i}{\longleftrightarrow}$	$\{ArO^-NH_4^+\}_{ip}$	$\overset{K_d}{\longleftrightarrow}$	ArO^- +	NH_4^+
Initial concs.	c		0		0	Z
Equilibrium	$\frac{c(1-x)}{1+K_i}$		$\frac{cK_i(1-x)}{1+K_i}$		cx	cx + Z

$$\text{Whence } K_d = \frac{(cx)(cx+Z)}{\frac{cK_i(1-x)}{1+K_i}} = \frac{x(cx+Z)(1+K_i)}{K_i(1-x)}$$

This transforms to the quadratic:

$$c(1 + K_i)x^2 + x(Z + K_iZ + K_iK_d) - K_iK_d = 0$$

which can be implemented on Excel with Z as the variable.

For the modeling the influence of added ammonium ion on the ionisation and ion-pairing behaviour of phenols in liquid ammonia under constant ionic strength (NaCl), the modeling was based on the approximation that the extinction coefficient of ion pair for ionised phenol does not change with the nature of counter-ion.

Derivation 2:

The pK_a of aminium cations are less than -1 in liquid ammonia at room temperature

The conclusion is based on that the UV absorbance of 1mM 3-chlorophenol in liquid ammonia at its λ_{max} increases less than 5% when 0.1M triethylamine is added as base.

Consider the equilibrium of ionisation of triethylamine in liquid ammonia:

$$Et_3\overset{+}{N}H + NH_3 \rightleftharpoons Et_3N + NH_4^+$$

$$K_a(\text{aminium}) = \frac{[Et_3N][NH_4^+]}{[Et_3NH^+]}$$

If the added 0.1M triethylamine has little effect on the ionisation of 1mM 3-chlorophenol as observed, therefore the total ammonium ion concentration can be calculated from the known initial concentration of 3-chlorophenol and its pK_a in liquid ammonia, which is 1.65×10^{-4}M.

The NMR results show that amine hydrochloride salts are fully deprotonated in liquid ammonia at room temperature, therefore, the ratio between free amine and protonated amine must more than 10^3 in liquid ammonia. Therefore the pK_a (aminium) must less than -1 in liquid ammonia at room temperature.

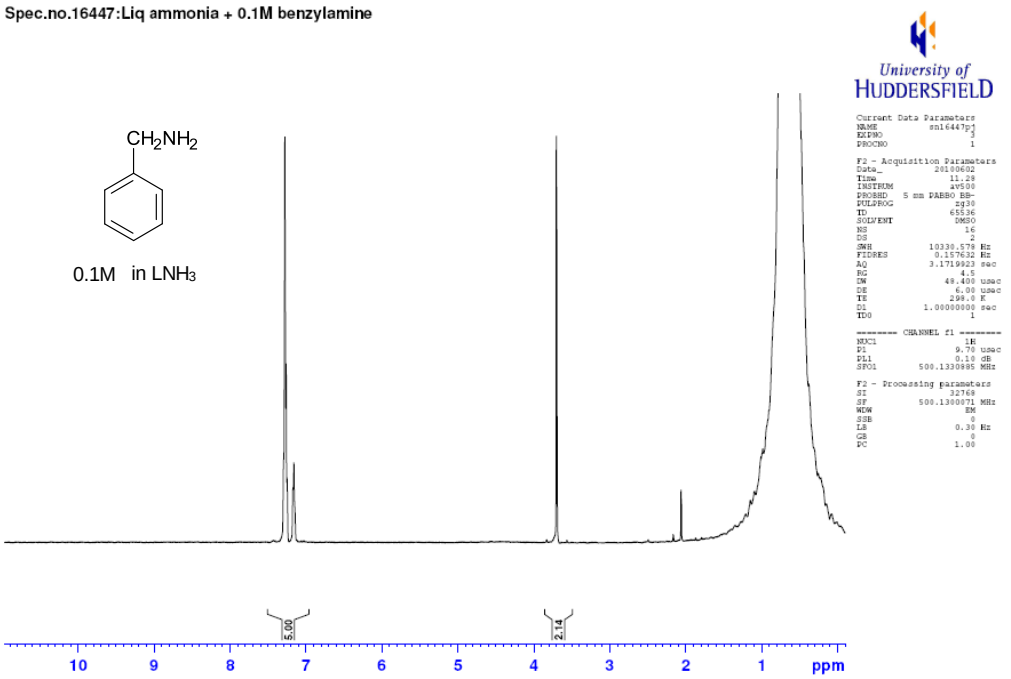


Figure N1 ^{1}H NMR Spectrum of 0.1M benzylamine in liquid ammonia at 25 ^{o}C

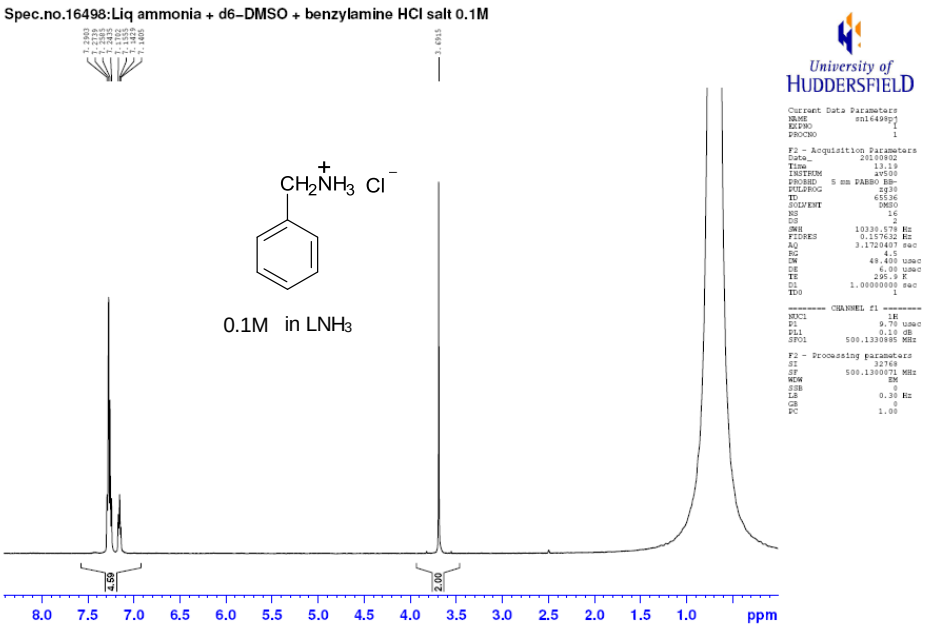


Figure N2 ^{1}H NMR Spectrum of 0.1M benzylamine hydrochloride in liquid ammonia at 25 ^{o}C

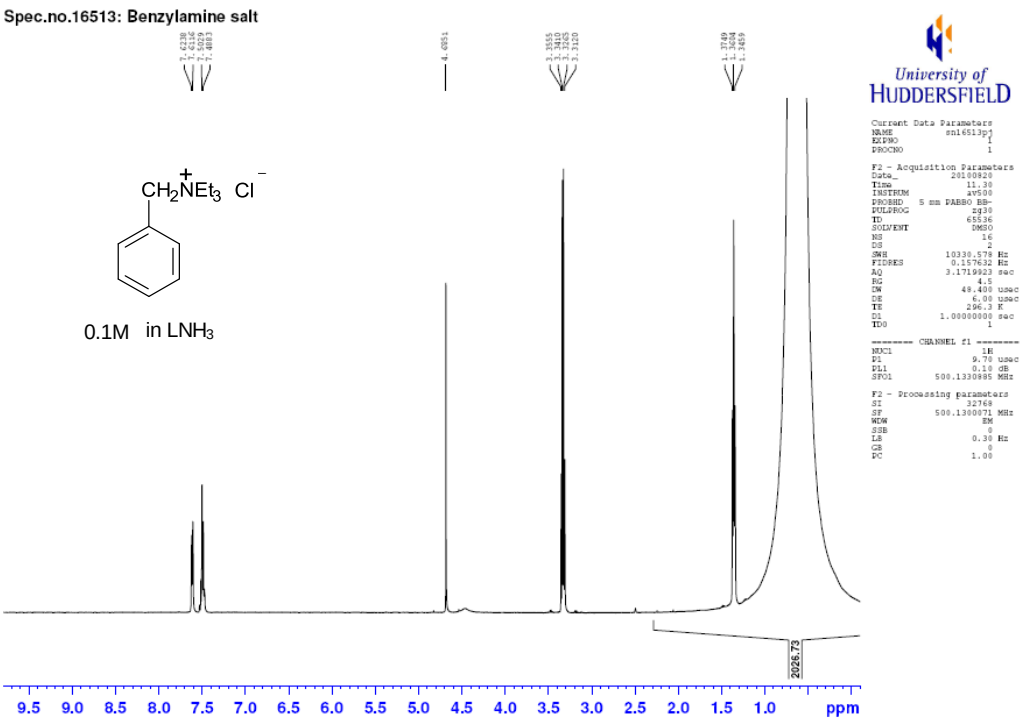


Figure N3 ^{1}H NMR Spectrum of 0.1M triethylbenzylammonium chloride in liquid ammonia at 25 ^{o}C

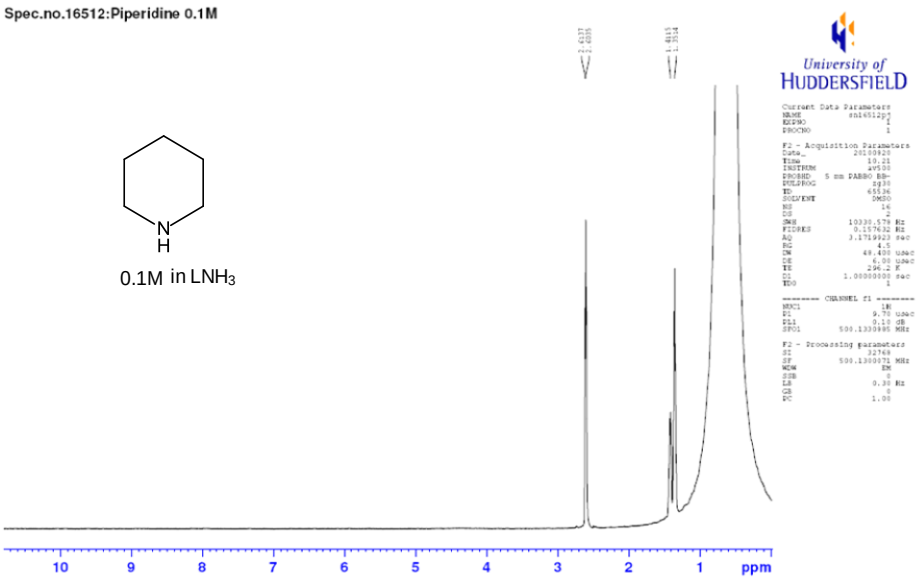


Figure N4 ^{1}H NMR Spectrum of 0.1M piperidine in liquid ammonia at 25 ^{o}C

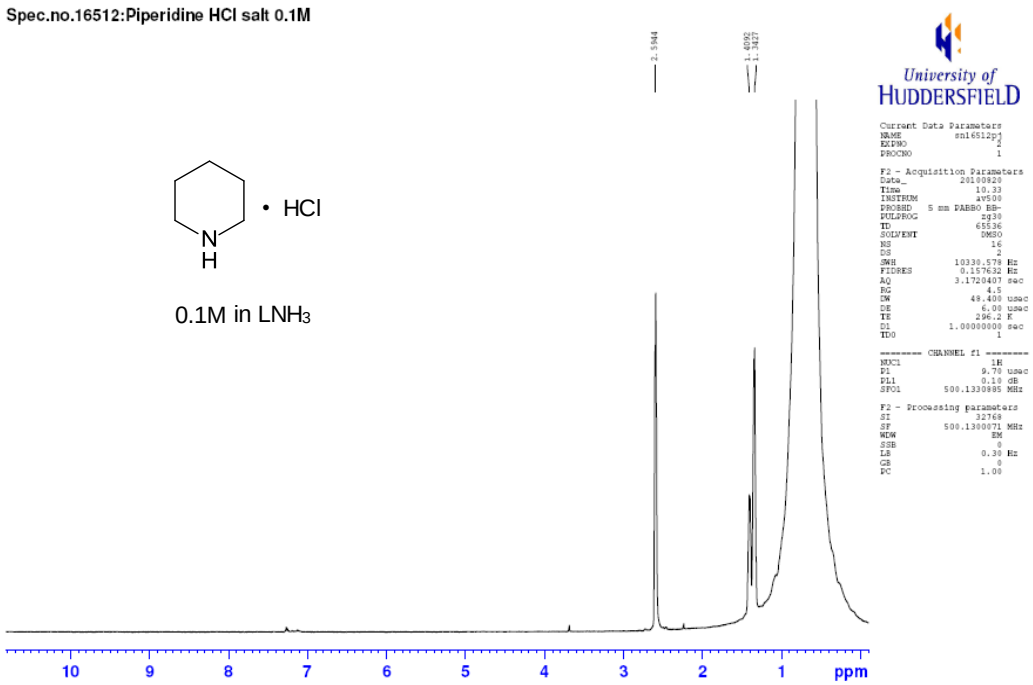


Figure N5 ^{1}H NMR Spectrum of 0.1M piperidine hydro chloride in liquid ammonia at 25 ^{o}C

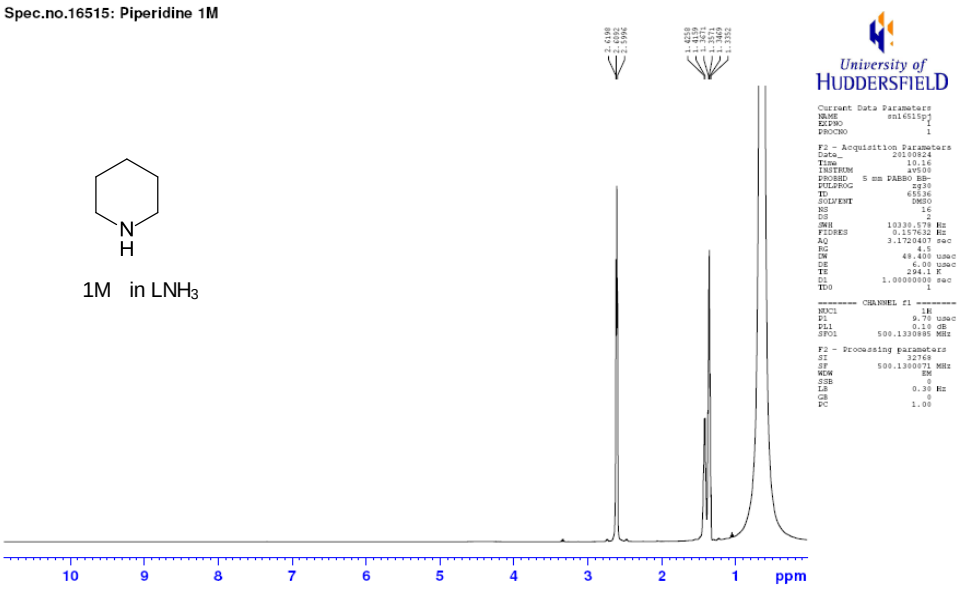


Figure N6 ^{1}H NMR Spectrum of 1 M piperidine in liquid ammonia at 25 ^{o}C

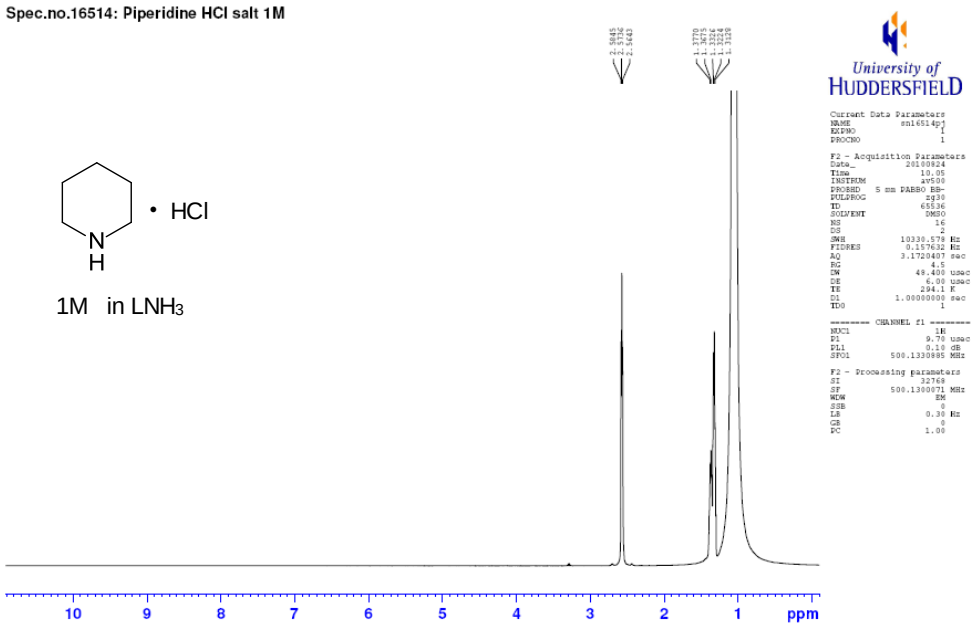


Figure N7 ^{1}H NMR Spectrum of 1M piperidine hydrochloride in liquid ammonia at 25 ^{o}C

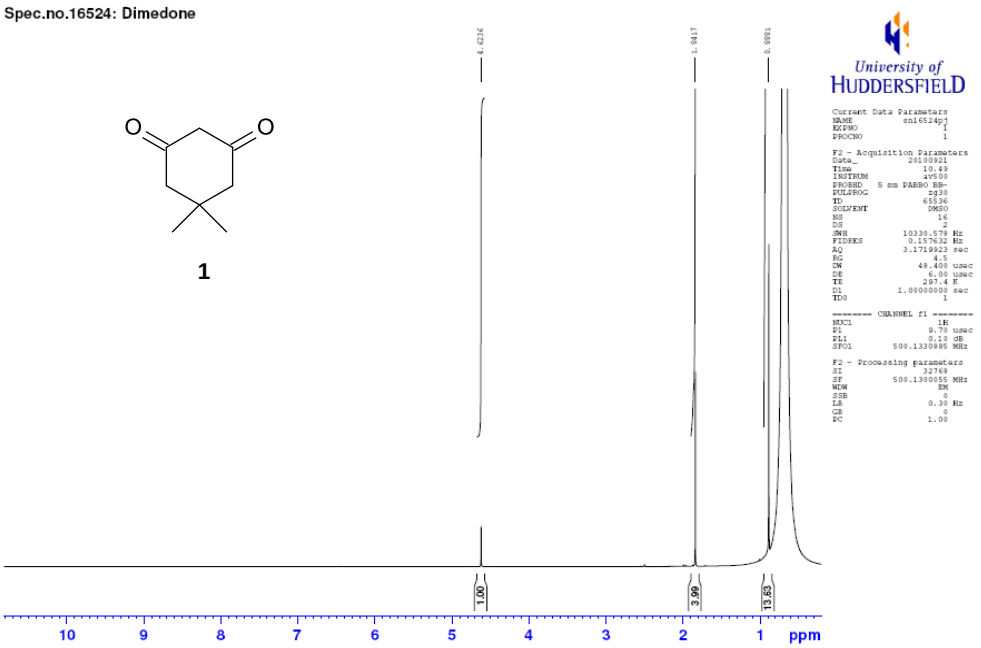


Figure N8 ^{1}H NMR Spectrum of 0.1M dimedone (5,5-dimethylcyclohexane-1,3-dione) in liquid ammonia at 25 ^{o}C

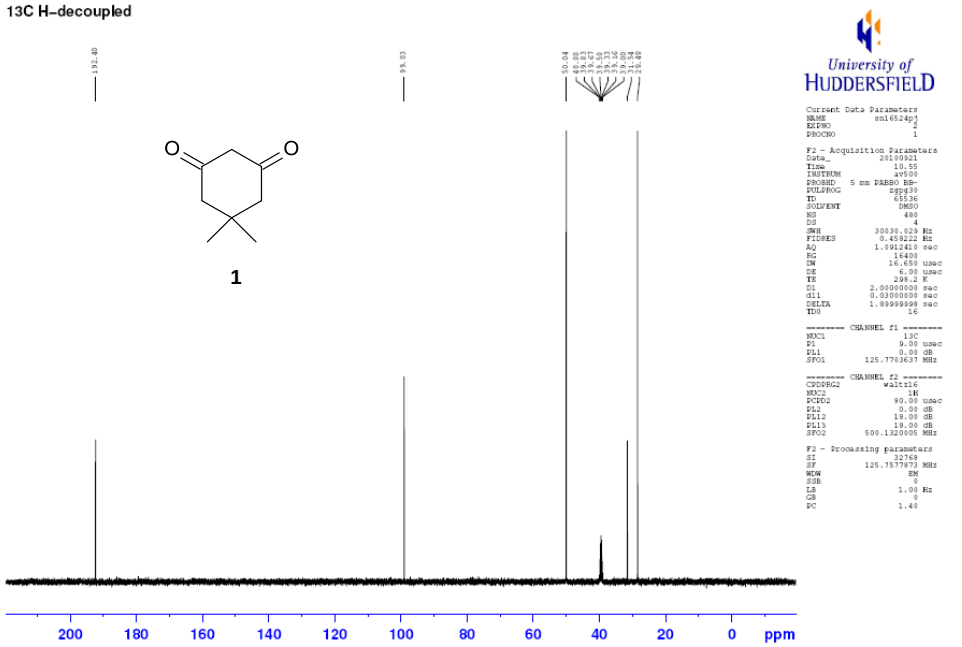


Figure N9 ^{13}C NMR Spectrum of 0.1M dimedone (5,5-dimethylcyclohexane-1,3-dione) in liquid ammonia at 25 ^{o}C

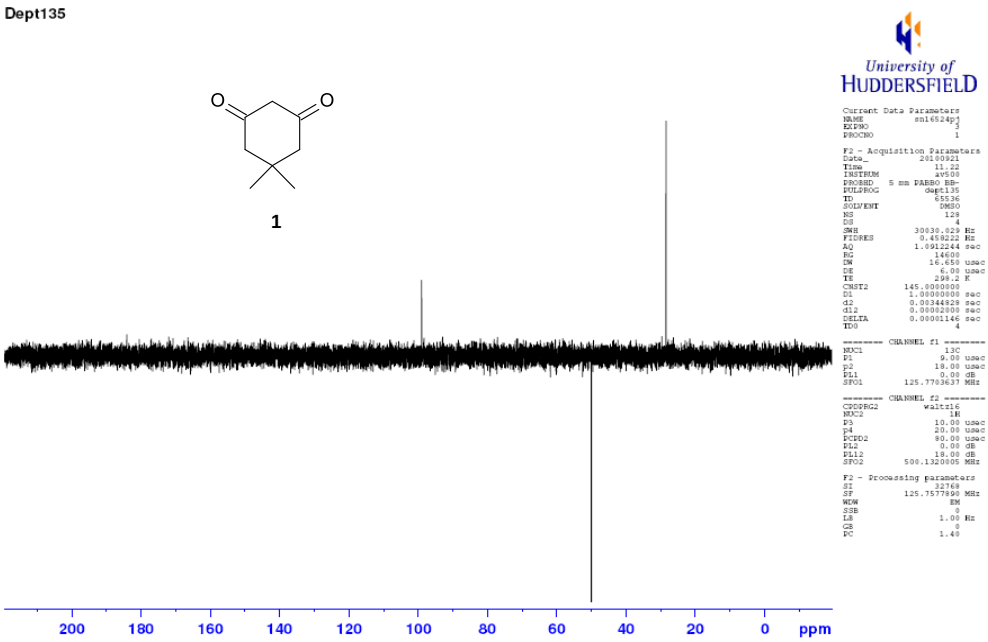


Figure N10 DEPT 135 Spectrum of 0.1M dimedone (5,5-dimethylcyclohexane-1,3-dione) in liquid ammonia at 25 ^{o}C

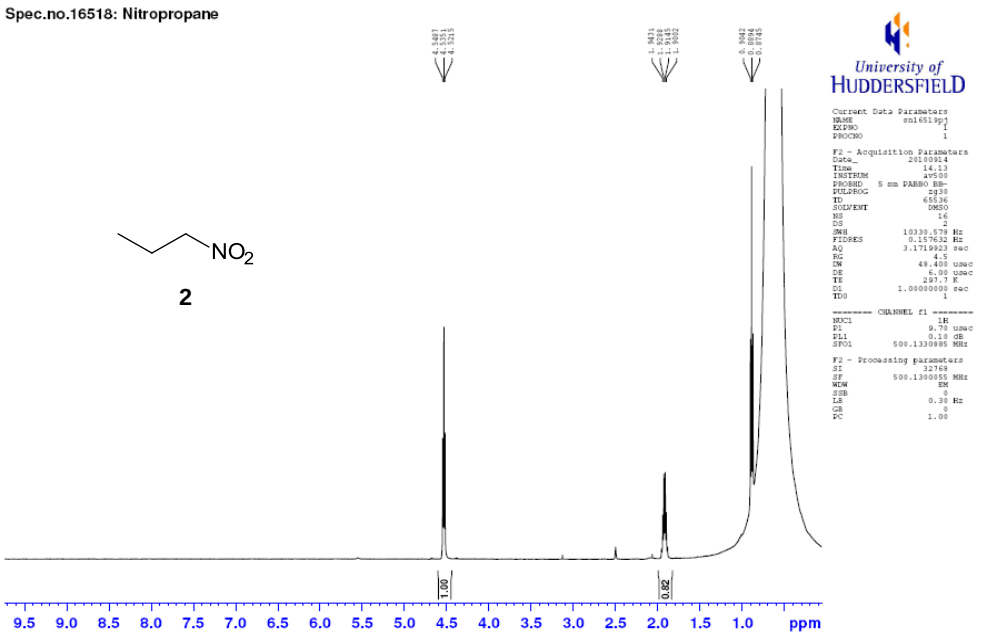


Figure N11 ^{1}H NMR Spectrum of 0.1M 1-nitropropane in liquid ammonia at 25 ^{o}C

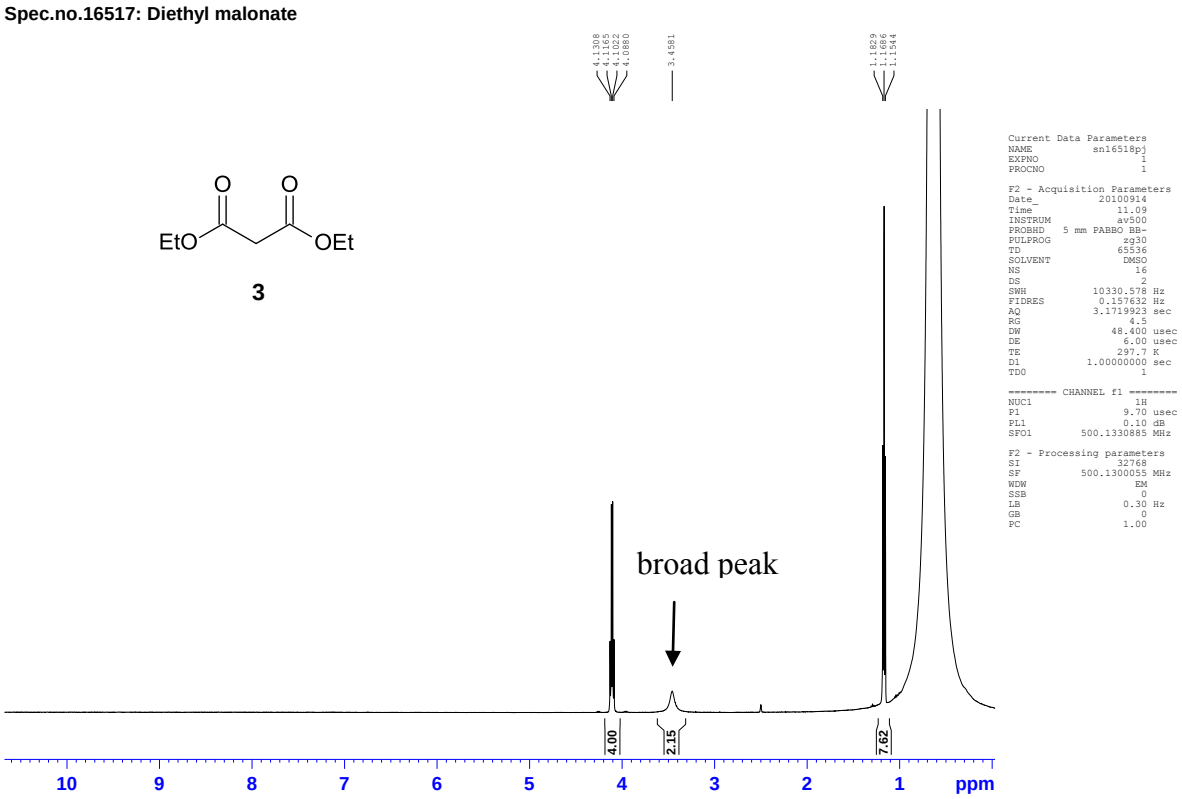


Figure N12 ^{1}H NMR Spectrum of 0.1M diethyl malonate ester in liquid ammonia at 25 ^{o}C

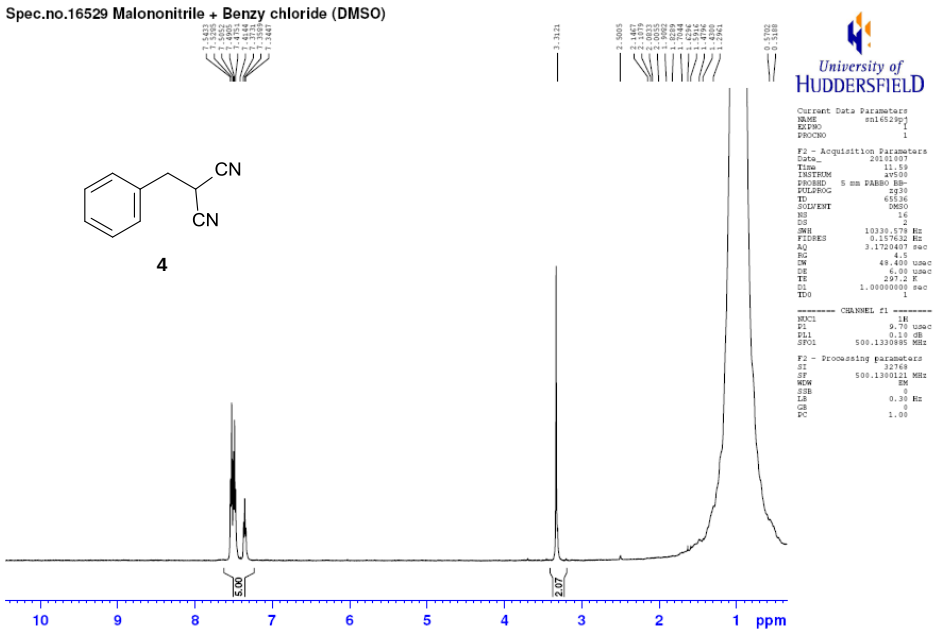


Figure N13 ^{1}H NMR Spectrum of 0.1M benzylmalonodinitrile ester in liquid ammonia at 25 ^{o}C

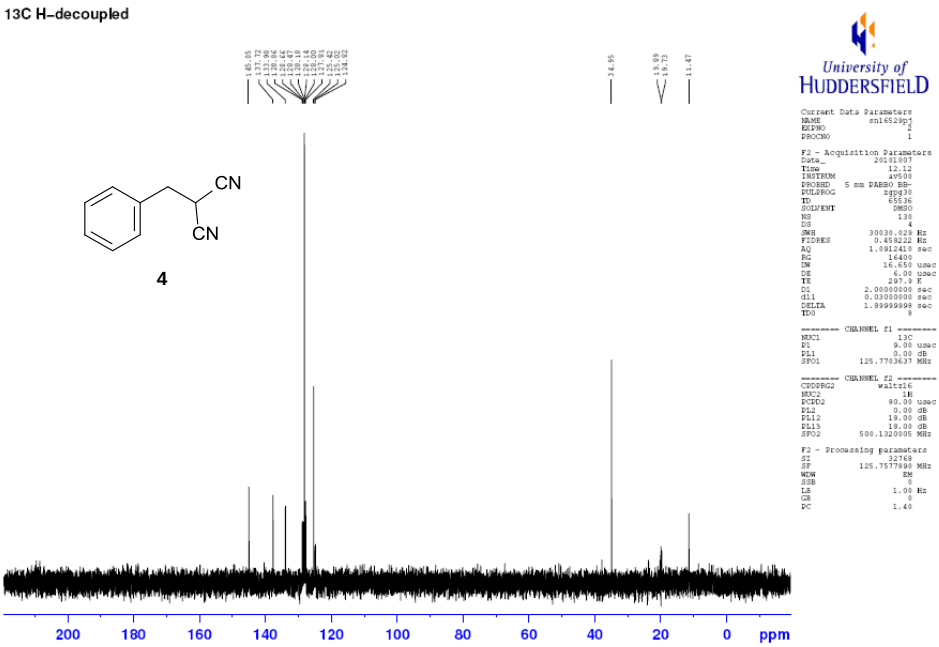


Figure N14 ^{13}C NMR Spectrum of 0.1M benzylmalonodinitrile ester in liquid ammonia at 25 ^{o}C

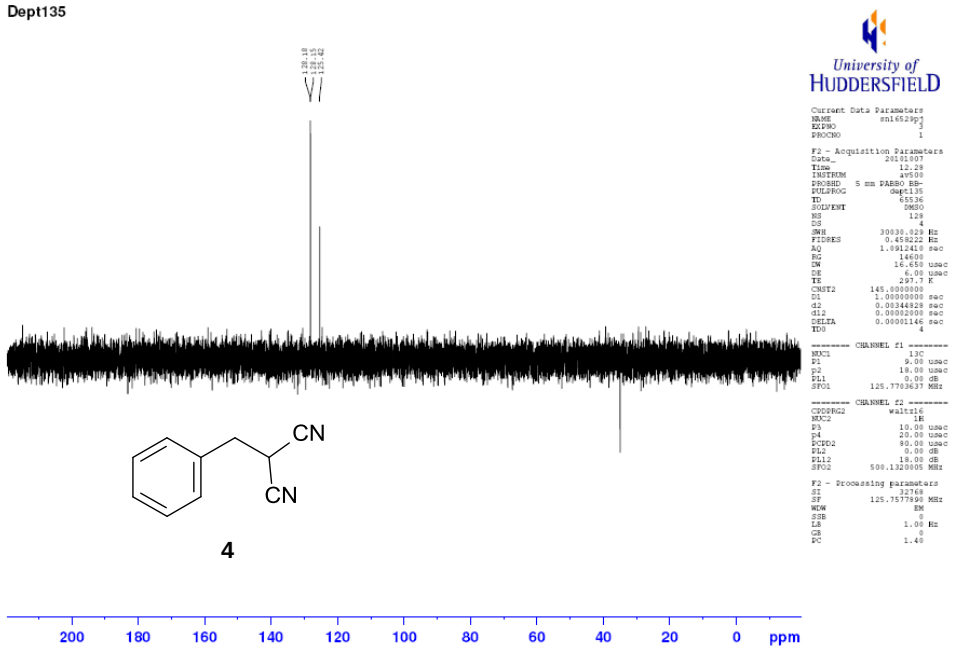


Figure N15 DEPT 135 Spectrum of 0.1M benzylmalonodinitrile ester in liquid ammonia at 25 ^{o}C

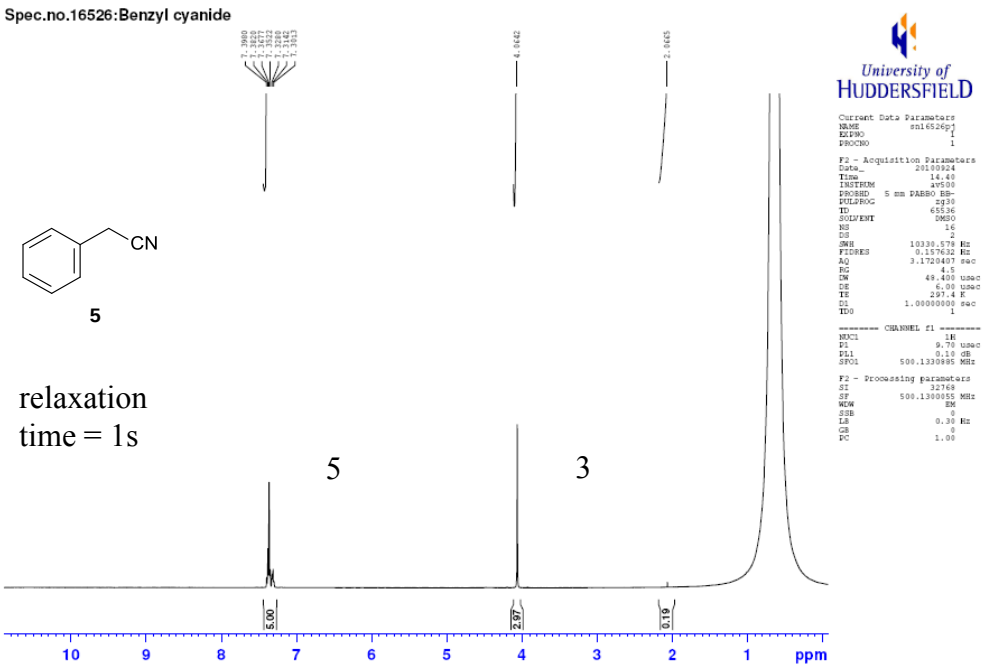


Figure N16 ^{1}H NMR Spectrum of 0.1M benzyl cyanide in liquid ammonia at 25 ^{o}C, integration aromatic H : methylene H = 5:3, relaxation time = 1s

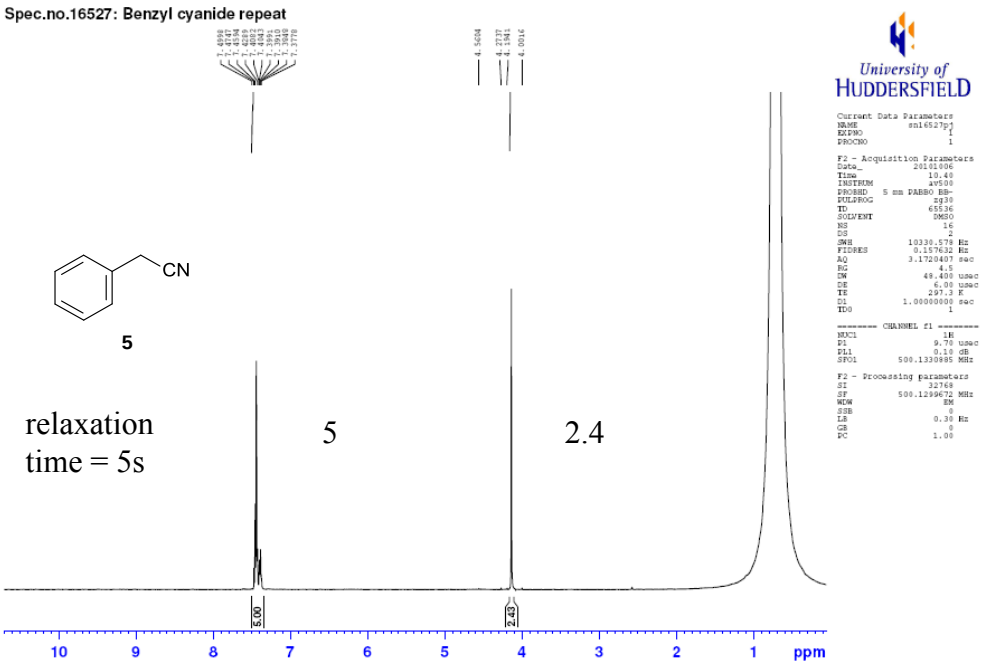


Figure N17 ^{1}H NMR Spectrum of 0.1M benzyl cyanide in liquid ammonia at 25 ^{o}C, integration aromatic H : methylene H = 5:2.4, relaxation time = 5s

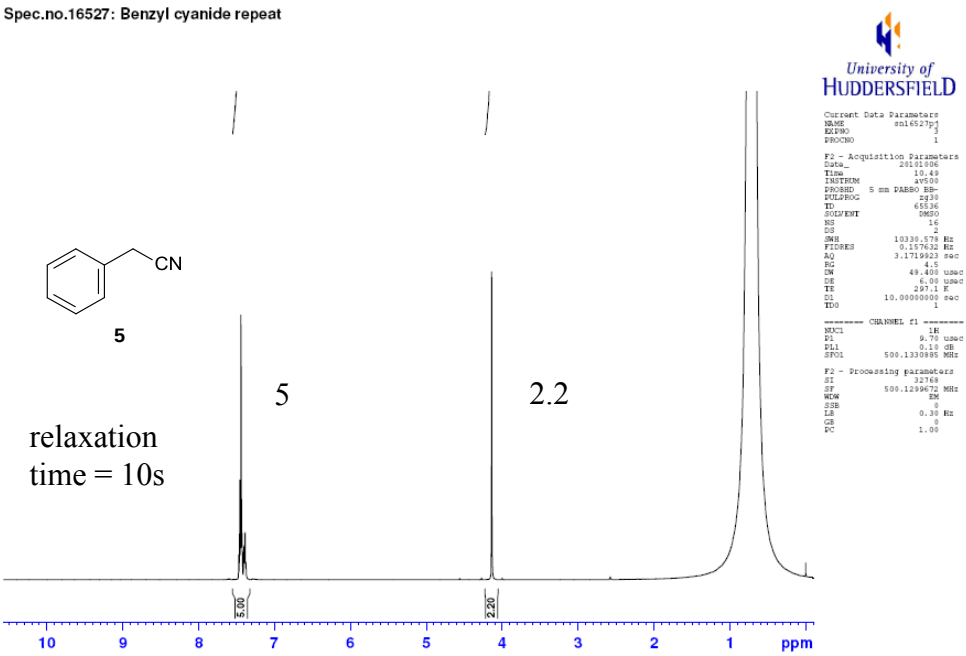


Figure N18 ^{1}H NMR Spectrum of 0.1M benzyl cyanide in liquid ammonia at 25 ^{o}C, integration aromatic H : methylene H = 5:2.2, relaxation time = 10s

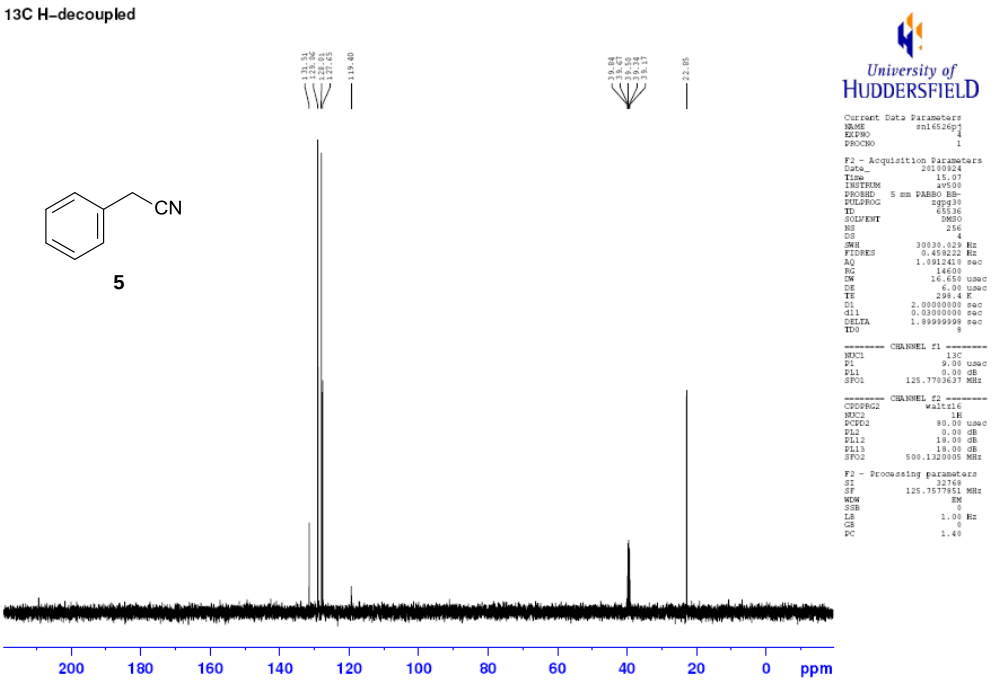


Figure N19 ^{13}C NMR Spectrum of 0.1M benzyl cyanide in liquid ammonia at 25 ^{o}C

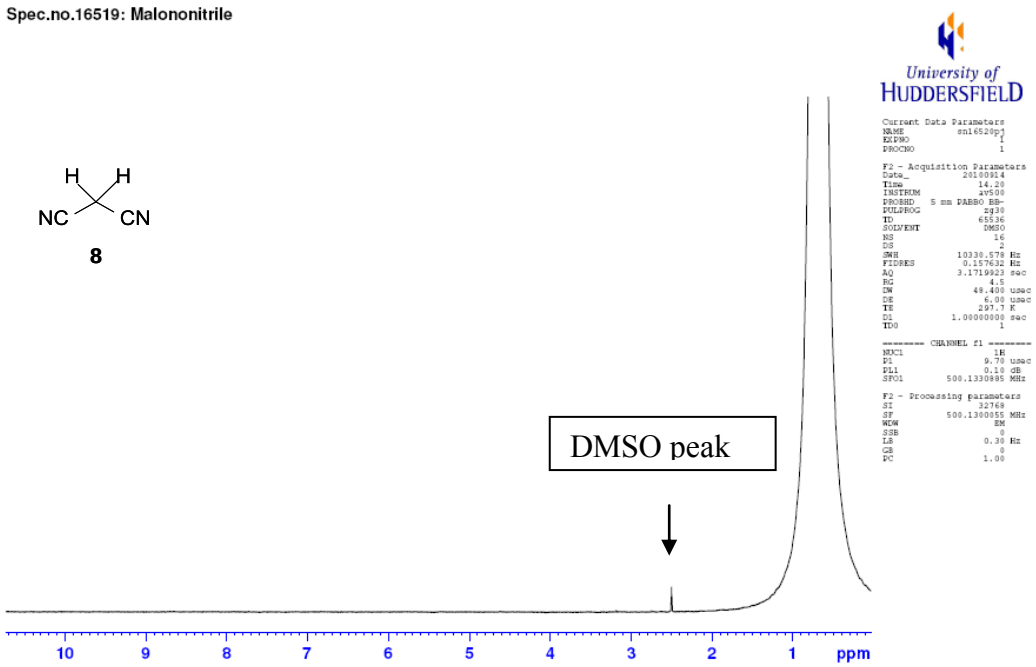


Figure N20 ^{1}H NMR Spectrum of 0.1M malonodinitrile in liquid ammonia at 25 ^{o}C

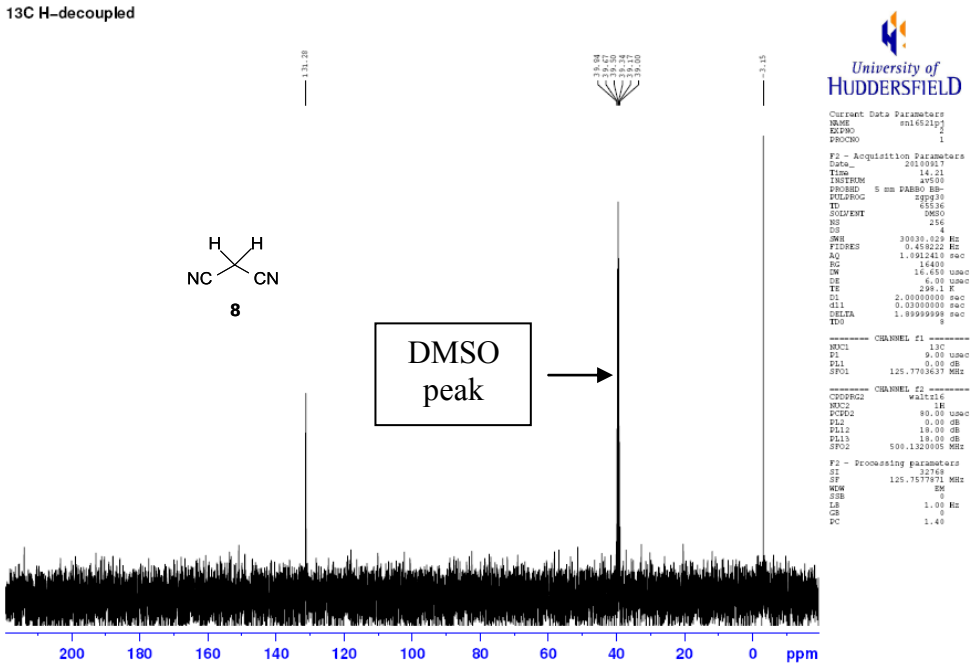


Figure N21 ^{13}C NMR Spectrum of 0.1M malonodinitrile in liquid ammonia at 25 ^{o}C

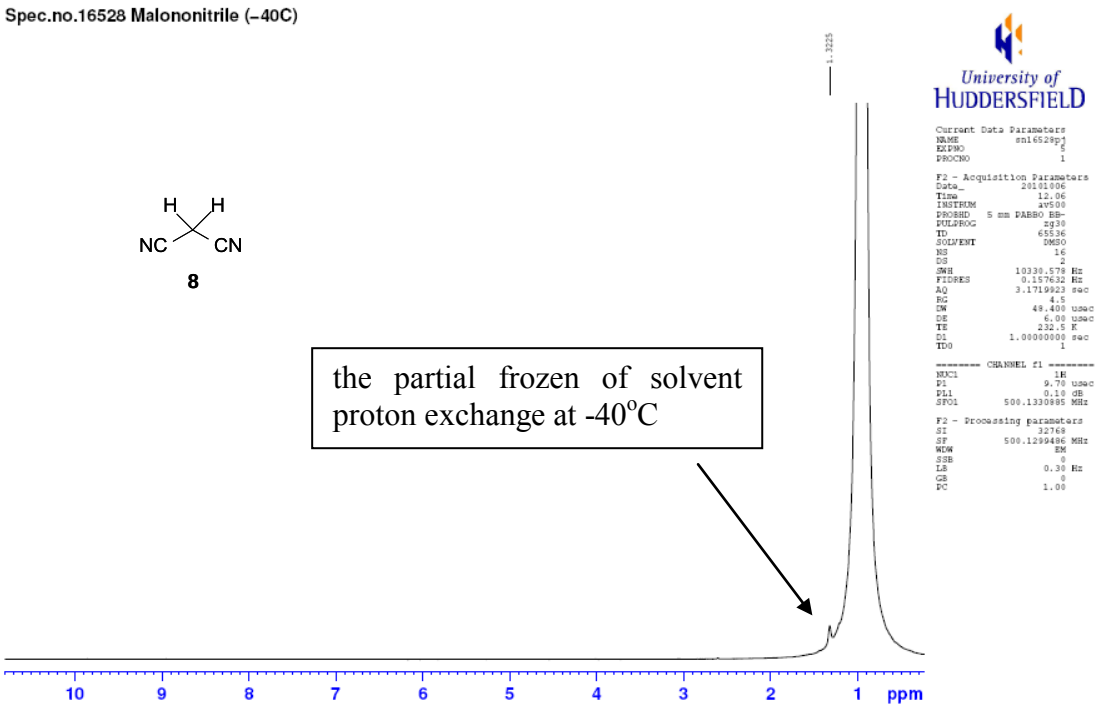


Figure N22 ^{1}H NMR Spectrum of 0.1M malonodinitrile in liquid ammonia at -40 ^{o}C

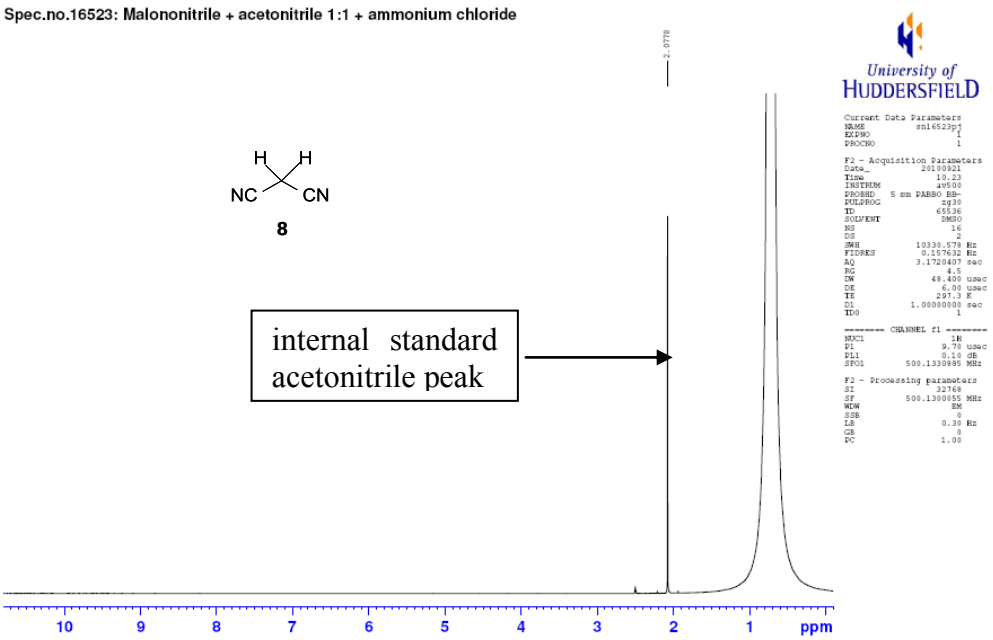


Figure N23 ^{1}H NMR Spectrum of 0.1M malononitrile with 0.1M NH_4Cl and acetonitrile as internal reference in liquid ammonia at 25 ^{o}C

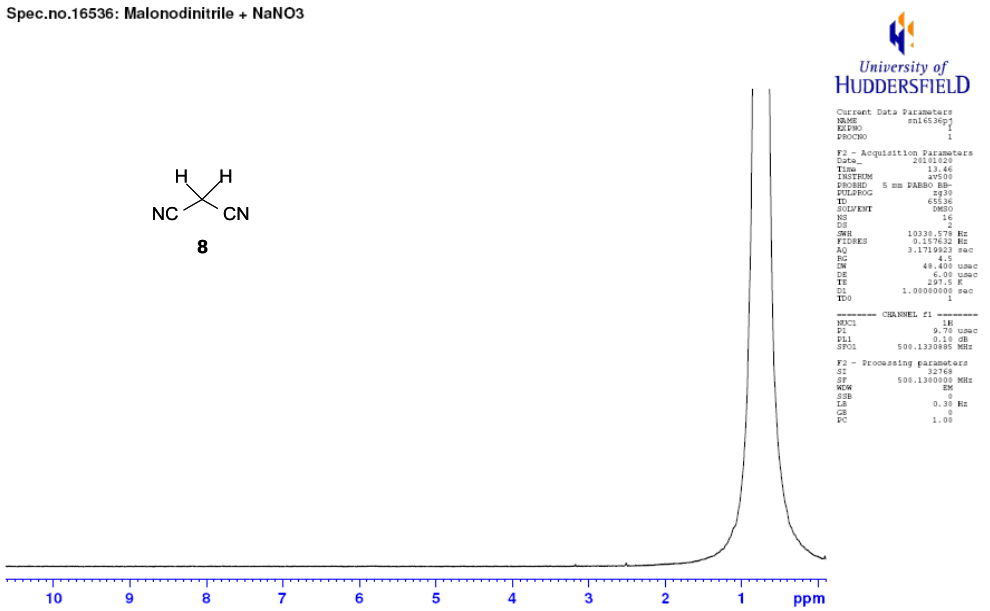


Figure N24 ^{1}H NMR Spectrum of 0.1M malononitrile with 1M $NaNO_3$ in liquid ammonia at 25 ^{o}C

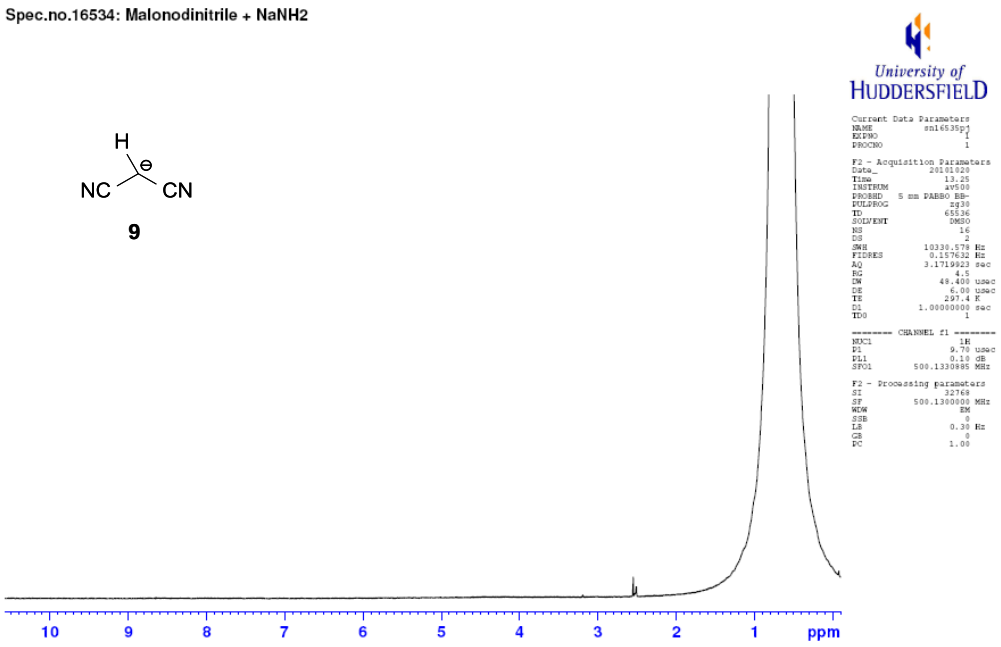


Figure N25 ^{1}H NMR Spectrum of 0.1M malononitrile with 2 eq. $NaNH_2$ in liquid ammonia at 25 ^{o}C

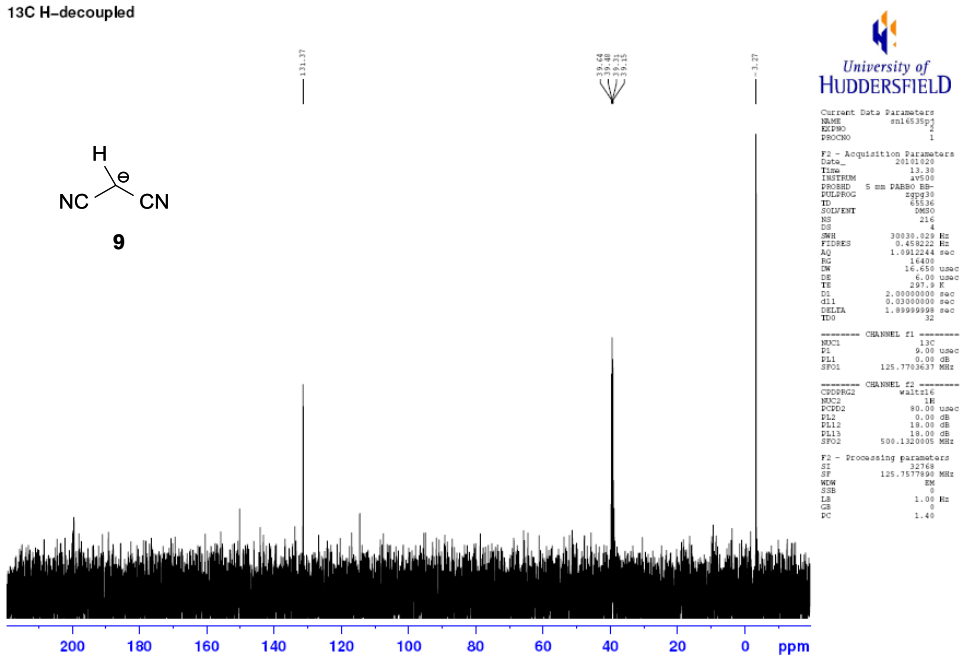


Figure N26 ^{1}H NMR Spectrum of 0.1M malononitrile with 2 eq. $NaNH_2$ in liquid ammonia at 25 ^{o}C

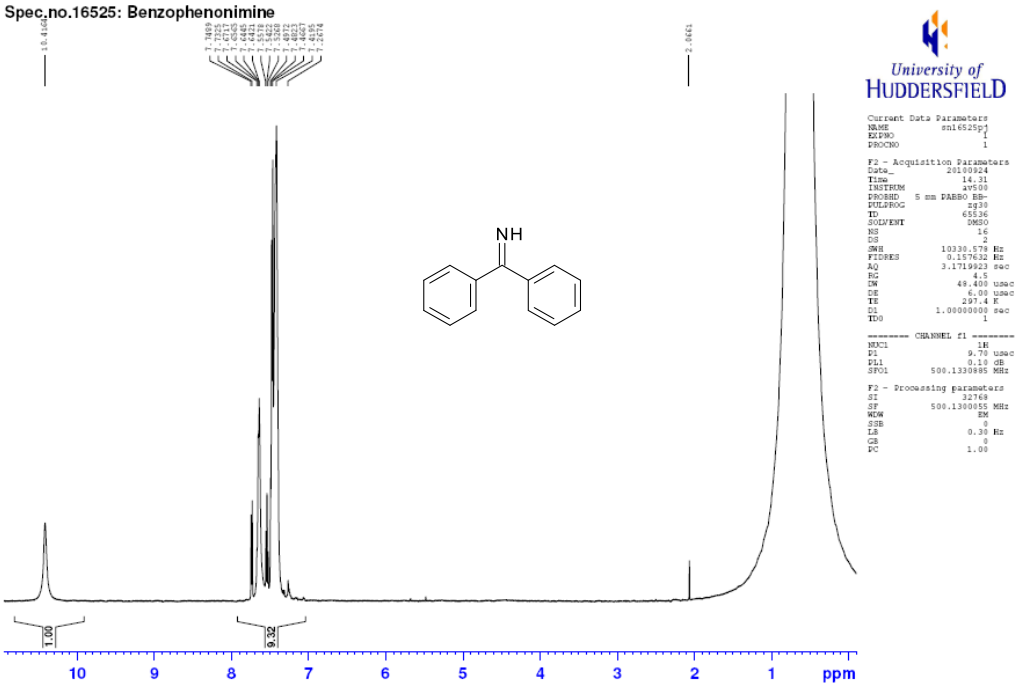


Figure N27 ^{1}H NMR Spectrum of 0.1M benzophenone imine in liquid ammonia at 25 ^{o}C

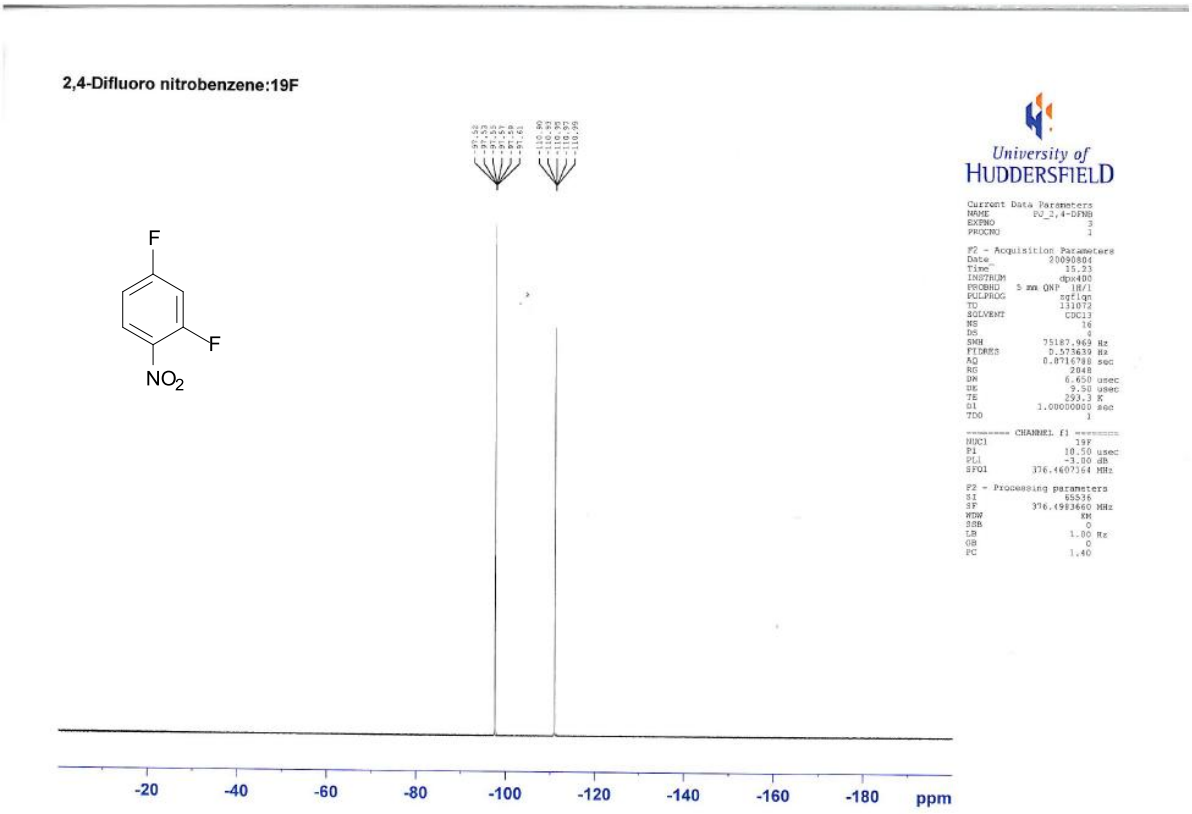


Figure N28 ^{19}F NMR Spectrum of 2,4-difluoronitrobenzene in DMSO-d_6 at 25 ^{o}C

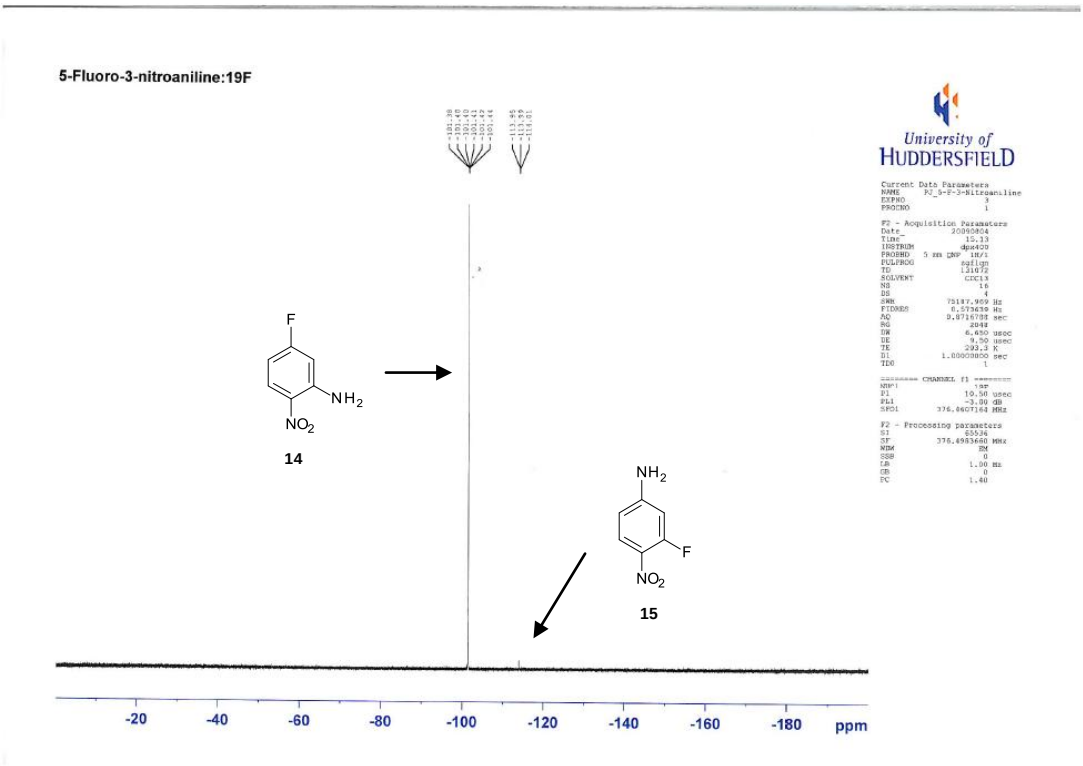


Figure N29 The products analysis for the solvolysis of 2,4-difluoronitrobenzene in liquid ammonia at 25 ^{o}C by ^{19}F NMR spectrum (DMSO-d$_6$)

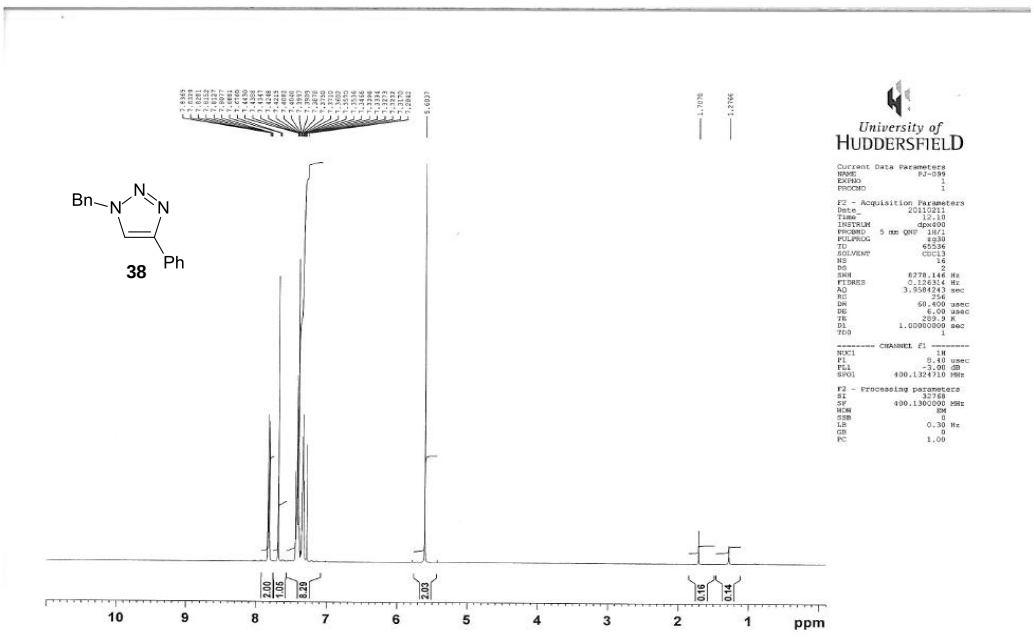


Figure N30 The ^{1}H NMR spectrum for the reaction product of Cu^{I}AAC in liquid ammonia at room temperature [benzyl azide with phenyl acetylene (1:1), after the vapourisation of ammonia, no purification procedure was performed, the product was directly dissoved in DMSO-d$_6$ for the NMR study]

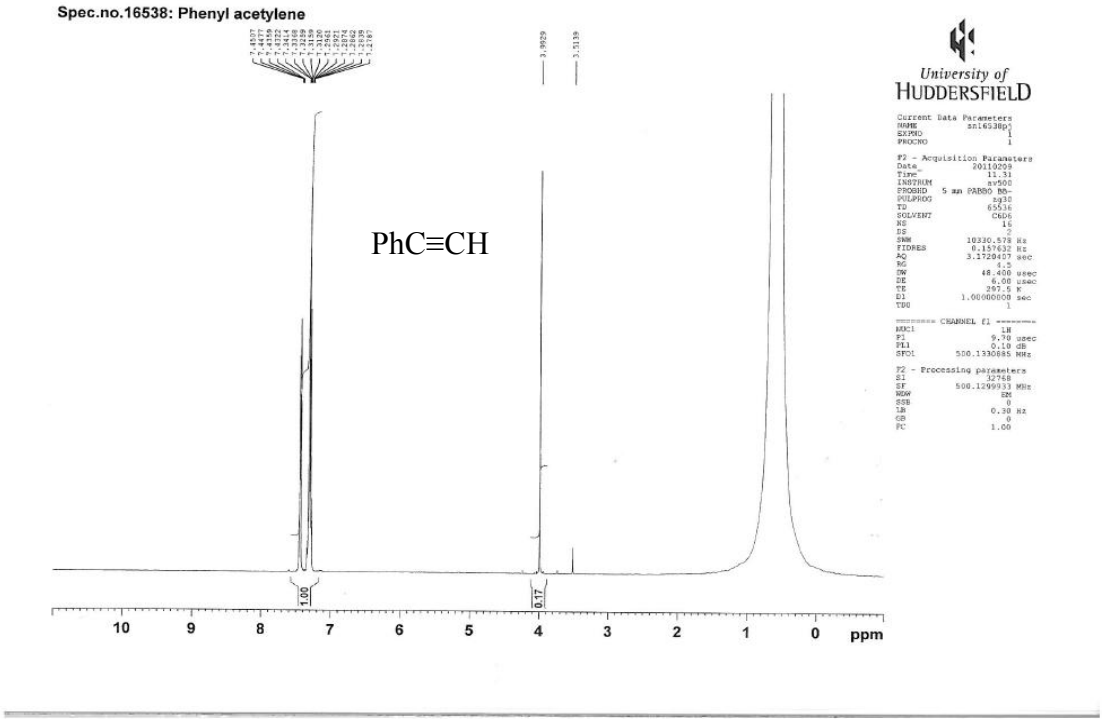


Figure N31 The ^{1}H NMR spectrum of phenylacetylene in liquid ammonia at 25 ^{o}C

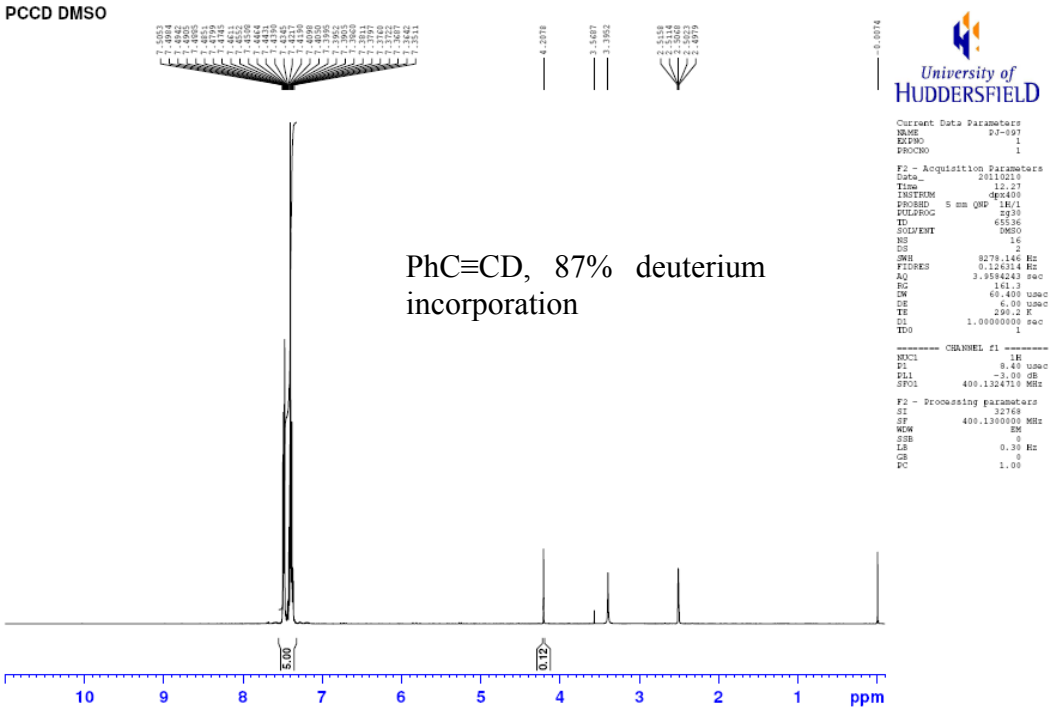


Figure N32 The ^{1}H NMR spectrum of phenylacetylene-d in DMSO-d_6 at 25 ^{o}C, 87% duterium incorporation (ca.)

OPERATING PROCEDURE AND RISK ASSESSMENT

Equipment

Several glass pressure vessels of different volume capacity (3 to 35ml); a 30ml glass burette, a 40ml glass tank; a SGE 10ml pressure syringe; several Omnifit™ 2-way valves and 3-way valves; a pressure UV cell; a pressure NMR glass tube.

General procedure

As described in Experiment section

Properties of liquid ammonia

Vapor pressure of liquid ammonia at 25 ^{o}C, 9.89 bar; at 30 ^{o}C, 11.7 bar.
Flammability limits in air 15 - 25% v/v (can explode).

Perceived hazards

- Catastrophic failure of vessel with ejection of glass and liquid/vapour into the working area.
- Splashing with ammonia liquid could lead to burns; inhalation of ammonia vapour at high concentration will cause unconsciousness.
- Unexpected pressure increase due to gas evolution in unvented vessels.

Risk mitigation

The glassware used is purpose made and the glassblower is aware of the intended use and required operating pressure. Glassware is pressure tested before use to at least twice the working pressure. A limit of 20 mm diameter is applied to new glassware.

Glassware under pressure is shielded at all times by Perspex sheet of at least 8 mm thickness.

The inventory of liquid ammonia in any glass reaction vessel is restricted to 12 ml., and to 20 ml in feed vessels.

There will be no lone working with pressurised glassware.

All reactions will be assessed for possible exothermicity and generation of permanent gases as part of the individual experimental risk assessment, and appropriate measures taken e.g., control of reactant concentrations and methods of reactant addition.

PPE

Goggles will be worn at all times when manipulating liquid ammonia. A full face shield will always be available and will be used when judged appropriate.

Pressure Test Standard Procedures

1. Pressure test below 10 bar.

- Connect the vessel to the Omnifit parts and the lid.
- Connect the vessel to an air or nitrogen cylinder with pressure gauges.
- Submerge the vessel in a bucket filled with water
- Gradually increasing the pressure to about 8-10 bar, see if any bubble comes out from the vessel (**MUST WEAR PROTECTION GOGGLES WHEN DOING THIS!**).

If no obvious bubbling is observed, close all the Omni valves connected to the vessel, leave the vessel in water for overnight, and monitor the pressure through a pressure gauge

2. Pressure test above 10 bar.

- Connect the vessel to Omnifit parts and the lid.
- Connect the vessel to an HPLC pump, and make the water as eluent.
- Submerge the vessel in a steel bucket filled with water.
- Set the flow rate of the HPLC pump to 0.5-1ml/min.
- Set the pump pressure up-limit to certain value, generally 20 bar.

If the pump automatically shut-down after reaching the up-limit, then the vessel is safe under that pressure.

Repeat the procedures described above after 2-3 months, keep the records routinely.

Date Signature (Research student)

Signature (Supervisor)

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[321] The preparation of deuterium rich phenylacetylene (PhC≡C-D): 1.02g phenylacetylene was agitated in 5ml sodium deuteroxide (30%w/w) at 40^{o}C for overnight; the reaction mixture was neutralized with concentrated HCl, and then extracted with DCM, dried with $NaSO_4$. The solvent was removed in vacuum and the residue liquid was distilled under pressure (2-3 mmHg, 45-50^{o}C) to give 0.9g (89% yield) colourless liquid. The ^{1}H NMR spectrum showed that the deuterium incorporation was 87% (ca.) (Appendix C, **Figure N32**).

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