

## A Comprehensive Study of mechanisms of organic reactions in Liquid Ammonia

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**ABSTRACT:** Liquid ammonia is a potentially useful solvent for a variety of organic reactions and so understanding the kinetics and mechanisms of these processes is important. In contrast to the hydrolysis rates of the substituted benzyl halides in water which vary  $10^7$ -fold, the rates of the solvolysis of substituted benzyl chlorides in liquid ammonia at 25 °C have little or no dependence upon ring substituents and vary only 2-fold between 4-methoxy- and 4-nitro- derivatives. The Hammett  $\rho$ -value is practically zero, which suggests there is no significant charge developed on the central carbon in the transition state. Activation energies for solvolysis of 4-nitro-, 4-methoxy-, 4-chloro- and unsubstituted benzyl chloride in liquid ammonia vary from 40.3 to 43.8 kJ mol<sup>-1</sup> in the order of NO<sub>2</sub> < H < Cl < OMe and entropies of activation ( $DS^\ddagger$ ) are very negative varying from 188 J K<sup>-1</sup> mol<sup>-1</sup> to 202 J K<sup>-1</sup> mol<sup>-1</sup>. The solvolysis rates of benzyl halides in liquid ammonia increase linearly with increasing concentration of potassium perchlorate and ammonium chloride. All of these observations are indicative of a bimolecular concerted S<sub>N</sub>2 mechanism proceeding through a transition state structure with complementary charge development on the entering and leaving groups and little or no change in charge on the central benzylic carbon. Benzyl chloride undergoes substitution with oxygen and nitrogen nucleophiles also by an S<sub>N</sub>2 process as shown by the dependence of the rate on the concentration of the nucleophile. A Brønsted type relationship for a series of amine nucleophiles show a  $b_{\text{nuc}}$  of 0.33 suggesting an early type transition state with a small amount of charge development on the amine nitrogen. Contrary to commonly accepted views, it appears that the liquid ammonia behaves like a dipolar aprotic solvent in nucleophilic substitution reactions. The nucleophilic substitution reaction in liquid ammonia shows high (>99%) selectivity towards O-benylation of phenoxide ion, and with 1,2,4-triazolate anion gives predominantly (92%) substitution in the 1-position.

## Introduction

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

Liquid ammonia is a promising candidate to replace dipolar aprotic solvents in a number of applications. It has a boiling point of  $33\text{ }^{\circ}\text{C}$  and a vapor pressure of 10 bar at  $25\text{ }^{\circ}\text{C}$ ,<sup>2</sup> and although it is similar in many ways to conventional dipolar aprotic solvents, it is much easier to recover and can be handled with care in small scale laboratory glassware over a useful temperature range. Despite the low dielectric constant of liquid ammonia (16.0 at  $25\text{ }^{\circ}\text{C}$ ),<sup>3</sup> many synthetically useful salts are highly soluble, *e.g.*  $\text{NH}_4\text{N}_3$ , 67.3 g per 100 g at  $36\text{ }^{\circ}\text{C}$ .<sup>4</sup> Moreover many organic compounds have appreciable solubility, *e.g.* biphenyl has a moderate solubility in liquid ammonia, while anisole is totally miscible with liquid ammonia.<sup>5</sup> In some respects, the solvation properties of liquid ammonia are very different from those of water. The nitrogen lone pair makes ammonia a good hydrogen bond acceptor and liquid ammonia strongly solvates cations, as evidenced, for example, by  $^{23}\text{Na}$  chemical shifts.<sup>6</sup> However, unlike water, it is not a good hydrogen bond donor<sup>7</sup> and does not significantly solvate anions, as shown by the high single ion transfer energies from water.<sup>8</sup> Liquid ammonia thus renders anionic nucleophiles more “naked” than in water which are therefore expected to be more reactive. The normalized donor number ( $\text{DN}^{\text{N}}$ ) of liquid ammonia is 1.52, greater than that of HMPTA (1.0),<sup>9</sup> while its autoprotolysis constant gives a  $\text{p}K_{\text{a}}$  of 33 ( $50\text{ }^{\circ}\text{C}$ ), compared with 14 for water ( $25\text{ }^{\circ}\text{C}$ ).<sup>10</sup>

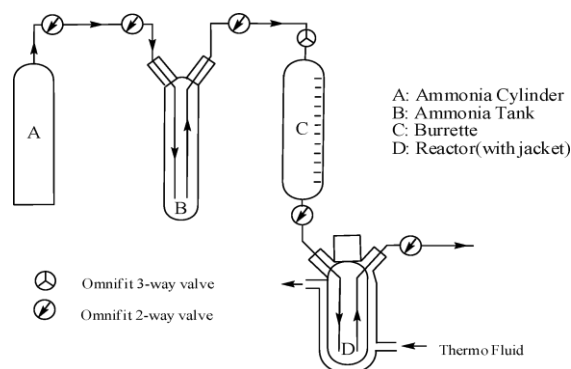
Although there has been much synthetic work done in liquid ammonia, little is known about the kinetics and mechanisms of reactions in this solvent. The early work covered the physical and chemical properties of liquid ammonia<sup>11</sup> and much of the literature of reactions concerns the reduction of organic compounds in alkali metal/ammonia solution,<sup>12</sup> or the application of alkali metal amides in liquid ammonia as strong bases in synthesis, which has been reviewed.<sup>5</sup> The formation of carbanions using alkali metal amides in liquid ammonia as a base and their subsequent reaction for inter- or intramolecular nucleophilic substitution or elimination has been well studied,<sup>13</sup> including arena formation.<sup>14</sup> Presumably due to the inconvenience of using pressure equipment at room temperature, the majority of the studies of the reactions in liquid ammonia were performed below its boiling point.

We are currently investigating the scope of this solvent in synthesis and aim to provide some of the physical organic chemistry required to support the synthesis programme.

## Experimental

A diagrammatic picture of the apparatus used is given in Fig. 1. Ammonia gas is condensed from liquid ammonia cylinder A into a glass ammonia tank B by liquid nitrogen or dry-ice, then the liquid ammonia in B is transferred into a glass graduated burette C (maximum volume 30 ml). The burette is connected to a glass reactor D (15 ml) 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. Generally, one of the reactants is pre-charged into D and the system is maintained at the required temperature accurately by thermostat. An amount of liquid ammonia (normally 10 ml) is released into D and is equilibrated with the surrounding temperature for an hour before another reactant is injected by a pressure syringe through an Omnifit septum into D.<sup>15</sup>

A pressure UV cell was a gift from Syngenta and was based on a design by Gill *et al.*<sup>16</sup> 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<sub>2</sub>, the path length between two windows is 10 mm. The top of the UV cell has



**Fig. 1 Diagram of the pressure equipment used for studies in liquid ammonia. B, C and D are glass, are pressure tested up to 35 bar. 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 front window and a protection sheet is placed in front of D when A is charged with liquid ammonia. The maximum working temperature allowed in the system is 35 °C.**

a standard Swagelock which can be connected to the Omnifit valves, thus the cell can be connected with D and allows the reaction mixture transferred from D to the cell. For the determination of extinction coefficients and the rates of relatively slow reactions in liquid ammonia, the reactants were normally pre-mixed in D and the reaction mixture quickly transferred from D to the chamber between the windows of the cell.

The aliquot from the reaction was carefully released into a 3 ml sample vial by controlling the Omnifit 2-way valves which connected to an ID 0.8 mm PTFE tube that dips into the bottom of D. After rapid evaporation of ammonia, the quenching agent, normally saturated ammonium chloride solution, 1M HCl or 1M NaOH, was added into the vial, and extracted by dichloromethane or toluene. The kinetics of some reactions were measured by a competition method, so that the rate constants were obtained from the molar ratio of products. Biphenyl or phenetole were used as internal standards. The samples from the reaction were analysed by Agilent 7980 GC equipment, and the data were processed using the commercial data-fitting software Scientist 3.0 or Berkeley Madonna.<sup>17</sup>

Generally, a pseudo first order rate constant  $k_{obs}$  was obtained from both decay of the reactants and appearance of products and, where relevant, converted to the corresponding second order rate constant using the concentration of the nucleophile. The second order rate constant for solvolysis was obtained using a concentration

of ammonia in liquid ammonia of 35.5 M at 25 °C and 35.9 M at 20 °C.<sup>18</sup> Some rate

constants were based on both GC and UV analysis. For slow rates of solvolysis, the rate constants were obtained from initial rate measurements. Normally, the initial concentration of the substrates was 0.01 M to 0.02 M for GC method and  $10^{-5}$  to  $10^{-4}$  M for UV method. Product analysis was confirmed by comparison with authentic samples and GC-MS.

Ammonia was from BOC and distilled from the cylinder A into the ammonia tank B, no other further purification was made before used as reaction solvent. All the chemicals and solvents were purchased from Sigma-Aldrich or Fisher Scientific with high purity and used directly without further purification except otherwise noted. 4-Nitrophenyl azide,<sup>19</sup> benzyl azide,<sup>20</sup> *N*-benzylpyrrolidine, *N*-benzylpiperidine and *N*-benzylmorpholine,<sup>21</sup> 2-benzylphenol and benzyloxybenzene,<sup>22</sup> 1-benzyl-1,2,4-triazole and 4-benzyl-1,2,4-triazole<sup>23</sup> were prepared and purified by general flash column chromatography methods. The structures of those compounds were confirmed by DSC analysis, GC-MS and <sup>1</sup>H NMR.

## Results and discussion

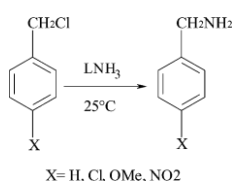
### 1. Solvolysis

The ammonolysis of substrates in liquid ammonia represents the background solvolysis for other reactions and the rate of this process is a guide to the viability of these other reactions in this solvent. The rate constants for the solvolysis of a variety of substrates (Table 1) show a large range of reactivities. The solvolysis rates of some aromatic halides are relatively slow compared with those for aliphatic halides. The solvolysis of 4-fluoronitrobenzene has a half life of about 1 day, but under the same conditions, 4-chloronitrobenzene is quite stable in liquid ammonia, and forcing conditions are required for the reaction.<sup>24</sup>

The solvolysis of substituted benzyl chlorides in liquid ammonia gives the corresponding benzylamines (Scheme 1). In liquid ammonia, there is little or no dependence of the rates of solvolysis of those compounds on the substituent, which is in stark contrast to those in water (Table 2), where the hydrolysis rates increase by about 4 orders of magnitude on going from 4-nitrobenzyl chloride to

Table 1 Solvolysis rate constants of substrates in liquid ammonia (LNH<sub>3</sub>)<sup>a</sup>

Substrates	$k_0/10^6 \text{ s}^{-1}$	$t_{1/2}$
4-Fluoronitrobenzene <sup>b</sup>	7.86	24.4 h
Benzyl chloride	889	13.0 min
2-Chloropyrimidine	14.2	13.3 h
2,4-Dinitrochlorobenzene	6177	1.85 min
4-Nitrophenyl azide <sup>b</sup>	5.11	37.7 h
Styrene oxide <sup>b</sup>	3.06	62.9 h
Styrene oxide-1M NH <sub>4</sub> Cl <sup>b</sup>	6.89	27.9 h
Phenylbenzoate	7704	1.50 min
Methyl-4-nitrobenzoate	14.2	13.3 h
4-Nitrophenylacetate	>70 000	<10 s
<sup>a</sup> At 25 °C. <sup>b</sup> At 20 °C.		



Scheme 1

Table 2 Solvolysis rate constants of substituted benzyl chlorides in LNH<sub>3</sub> and water at 25 °C

	$k_{2,LNH3}/M^{-1} \text{ s}^{-1}$	$k_{2,Water}/M^{-1} \text{ s}^{-1}$ <sup>a</sup>
Benzyl chloride	$2.48 \times 10^{-5}$	$2.40 \times 10^{-7}$
4-Chlorobenzyl chloride	$2.74 \times 10^{-5}$	$1.36 \times 10^{-7}$
4-Nitrobenzyl chloride	$4.27 \times 10^{-5}$	$6.08 \times 10^{-9}$
4-Methoxybenzyl chloride	$5.33 \times 10^{-5}$	$6.66 \times 10^{-2}$

<sup>a</sup> The solvolysis rates were extrapolated data from ref. 25 and ref. 37a.

Table 3 Activation parameters<sup>a</sup> for solvolysis of substituted benzyl chlorides in LNH<sub>3</sub> and water at 25 °C

4-Chlorobenzyl chloride	40.22	—197.2	85.95	—37.2
4-Nitrobenzyl chloride	37.77	—202.3	87.62	—50.1
4-Methoxybenzyl chloride	41.33	<sup>c</sup> —188.0	70.60	—5.10

<sup>a</sup> Activation parameters' units:  $DH^\ddagger$  in  $\text{kJ mol}^{-1}$ ;  $DS^\ddagger$  in  $\text{J K}^{-1} \text{mol}^{-1}$ . <sup>b</sup> Activation parameters were extrapolated to the values at 25 °C from ref. 25, ref. 31 and ref. 37a. <sup>c</sup> There is conflicting data in the literature (ref. 25c with ref. 37a); we have chosen to use the data of ref. 37a, which is corroborated by ref. 36b. The activation parameters shown for 4-methoxybenzyl chloride are for 20% methanol in water.

#### **4-methoxybenzyl chloride. The solvolysis rates in liquid ammonia are generally**

faster than those in water, but the difference decreases with electron-donating substituents so that 4-methoxybenzyl chloride is actually more reactive in water than in liquid ammonia. The mechanism of hydrolysis of benzyl halides in water and aqueous ~ binary solvents remains ambiguous, although that for 4-methoxybenzyl halides is certainly an S<sub>N</sub>1 mechanism with the intermediate formation of a carbocation and that for the 4-nitro derivative is claimed to be S<sub>N</sub>2. Shatenshtein *et al.*<sup>26</sup> showed that the rate of solvolysis of *t*-butyl chloride in liquid ammonia is very slow ( $t_{1/2}$  20 weeks) which is about 6 orders of magnitude slower than that in water.<sup>27</sup>

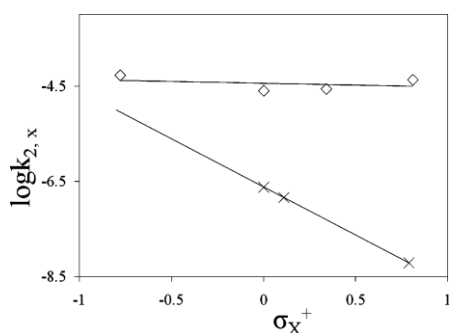
Activation parameters were obtained for the solvolysis of substituted benzyl halides in liquid ammonia (Table 3) and compared with those in water. Enthalpies of activation

( $DH^\ddagger$ ) in liquid ammonia are about half of those in water, that for the hydrolysis of 4-methoxybenzyl chloride is less than that of 4-nitrobenzyl chloride in water, while the opposite is observed in liquid ammonia. For these compounds, the differences between the energies of activation in liquid ammonia are not as great as that in water. The C–Cl bond of benzyl halide has a dipole moment of 1.85 D,<sup>28</sup> and the bond is presumably more polarized in water than in liquid ammonia due to the former having a greater hydrogen bond donating ability. It has generally been accepted that liquid ammonia behaves as a typical hydrogen bond donor solvent and this is extensively stated in the literature.<sup>1</sup> However, there is very

little evidence to support this assertion. Although liquid ammonia is generally accepted as a protic solvent, like water, with good hydrogen bond donator (HBD) and acceptor (HBA) ability, liquid ammonia actually has a very limited HBD ability, not only in gas phase, but also in condensed phase.<sup>7</sup> There is probably a weaker interaction between C–Cl bond and liquid ammonia solvent than in water. Finally, anions are less stable in liquid ammonia for similar reasons, so expulsion of the chloride anion is expected to be more difficult than in water.

Large negative entropies of activation ( $DS^\ddagger$ ) are observed for the solvolysis of benzyl chlorides in liquid ammonia (Table 3), indicative of a restricted activated complex relative to the reactant, which probably suggests a bimolecular concerted  $S_N2$  mechanism. This conclusion is supported by the small dependence of the rate of solvolysis on substituents described below. The variation of  $DS^\ddagger$  with substituent for these solvolytic reactions in liquid ammonia is only about  $12 \text{ J K}^{-1} \text{ mol}^{-1}$ , suggesting all the substrates react by a similar mechanism.

Generally, in bimolecular nucleophilic substitution processes, a large negative entropy of activation between  $90$  and  $120 \text{ J K}^{-1} \text{ mol}^{-1}$  is observed 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.<sup>29</sup> By contrast the



	$\text{LNH}_3$		Water <sup>b</sup>	
	$DH^\ddagger$	$DS^\ddagger$	$DH^\ddagger$	$DS^\ddagger$
Benzyl chloride	39.95	-199.8	83.06	-38.0



Fig. 2 Hammett plot for the solvolysis of benzyl chlorides in  $\text{LNH}_3$  ( $\triangleright$ ) and water ( $\square$ ) at  $25^\circ\text{C}$ . The rate constant for the hydrolysis of 4-methoxybenzyl chloride shows an enormous positive deviation from the extrapolated line, indicative of a change in mechanism, but is not shown.

$DS^\ddagger$  for a typical hydrolytic reaction which follows the  $\text{S}_{\text{N}}1$  mechanism is often positive, e.g. the  $DS^\ddagger$  of the hydrolysis of *t*-butyl chloride<sup>30</sup> is about  $50 \text{ J K}^{-1} \text{ mol}^{-1}$ . There is a significant difference in  $DS^\ddagger$  for the hydrolysis of 4-nitrobenzyl chloride and 4-methoxybenzyl chloride of  $45 \text{ J K}^{-1} \text{ mol}^{-1}$ . Interestingly, the enthalpy of activation for the hydrolysis of benzyl chlorides in DMSO–water mixtures decreases with the increasing ratio of dipolar aprotic DMSO in the mixtures, whereas  $DS^\ddagger$  becomes significantly more negative ( $DS^\ddagger$  being about  $120 \text{ J K}^{-1} \text{ mol}^{-1}$  in 90% v/v DMSO–water mixture), possibly indicative of a change in mechanism to  $\text{S}_{\text{N}}2$ .<sup>25b</sup> Contrary to commonly accepted views, it appears that liquid ammonia behaves like a dipolar aprotic solvent in nucleophilic substitution reactions.

A common method of elucidating reaction mechanisms is the use of linear free energy relationships by measuring the dependence of the rate of reaction upon the nature of substituents. There is surprisingly little or no dependence of the rate of solvolysis of benzyl chlorides in liquid ammonia upon the ring substituent. Unfortunately, there is conflicting data on the corresponding hydrolysis reaction, the reported rate constants in water varying 300-fold for the 4-methoxy derivative.<sup>37a</sup> Nonetheless, a plot of  $\log k_{2,X}$  against  $s_x$  for the substituent is noticeably different in water from that in liquid ammonia (Fig. 2). The  $\rho$  value for the reaction in liquid ammonia is approximately zero, while that in water is  $\rho = 2.01$ ; the point for the hydrolysis of 4-methoxybenzyl chloride shows a positive deviation of nearly four orders of magnitude, indicative of a change in mechanism from  $\text{S}_{\text{N}}2$  for electron-withdrawing substituents to carbocation formation *via* an  $\text{S}_{\text{N}}1$  process for the 4-methoxy derivative. These observations suggest that in liquid ammonia there is little or no charge developed on the central carbon atom in the transition state, whereas there is a large amount of positive charge formed in the hydrolysis reaction in water. However, as noted above, liquid ammonia does not significantly solvate anions, as shown by the high single ion transfer energies from water which would hinder an  $\text{S}_{\text{N}}1$  process. Based on these observations, the mechanism of solvolysis of benzyl halides in liquid ammonia appears to proceed by a concerted  $\text{S}_{\text{N}}2$  mechanism through a transition state structure with complementary charge development on the entering and leaving groups

so that there is little or no change in charge on the central benzylic carbon, *i.e.* the amount of charge development on the incoming nucleophile is counterbalanced by that on the departing nucleofuge. Due to the poorer solvation of the leaving group anion in liquid ammonia, compared with that in water, the unimolecular S<sub>N</sub>1 mechanism is unfavourable.

A typical S<sub>N</sub>1 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.<sup>32</sup> However, whether the common ion effect increases or

Table 4 The solvolysis rates of 4-methoxybenzyl chloride in presence of KClO<sub>4</sub> in LNH<sub>3</sub> at 25 °C

Concentration of KClO <sub>4</sub> /M	0	0.5	1.0	1.5
Solvolysis rate/M <sup>-1</sup> s <sup>-1</sup>	5.33 × 10 <sup>-5</sup>	7.50 × 10 <sup>-5</sup>	1.10 × 10 <sup>-4</sup>	1.31 × 10 <sup>-4</sup>

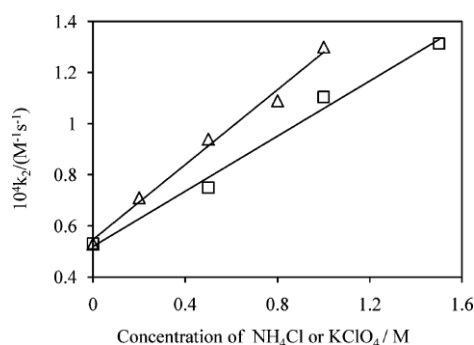


Fig. 3 Changes in the solvolysis rate constants of 4-methoxybenzyl chloride with the addition of various salts in LNH<sub>3</sub> at 25 °C: (O) NH<sub>4</sub>Cl; (Δ) KClO<sub>4</sub>.

Table 5 The solvolysis rates of 4-methoxybenzyl chloride in presence of NH<sub>4</sub>Cl and NaCl<sup>a</sup> in LNH<sub>3</sub> at 25 °C

Concentration of NH <sub>4</sub> Cl/M	0	0.2	0.5	0.8	1.0
Solvolysis rate/M <sup>-1</sup> s <sup>-1</sup>	5.33 × 10 <sup>-5</sup>	7.09 × 10 <sup>-5</sup>	9.39 × 10 <sup>-5</sup>	1.09 × 10 <sup>-4</sup>	1.30 × 10 <sup>-4</sup>

Solvolysis rate of 4-methoxybenzyl chloride in liquid ammonia at 25 °C in presence of 0.2M NaCl is 7.08 × 10<sup>-5</sup> M<sup>-1</sup> s<sup>-1</sup>; the poor solubility of NaCl in liquid ammonia at 25 °C (3.02 g per 100 g)<sup>2</sup> prevents the measurement at higher concentrations.

decreases the rate of the solvolysis reaction depends on the substrate structure. For example, addition of halide ions decreases the rate for diphenylmethyl but not for *t*-butyl halides.<sup>33</sup> Normally, the more stable the intermediate formed in an S<sub>N</sub>1 process, the greater the selectivity towards nucleophilicity but the lower the sensitivity towards the solvent polarity.<sup>34</sup> The salt effect normally has a positive effect on the S<sub>N</sub>2 process when a neutral nucleophile attacks a neutral substrate,<sup>35</sup> 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<sub>N</sub>1 and S<sub>N</sub>2 processes.<sup>36</sup>

An S<sub>N</sub>1 mechanism for the solvolysis of 4-methoxybenzyl chloride was proposed from study of the reactivity and product selectivity in a number of aqueous binary solvents was generally accepted,<sup>37</sup> while extensive research shows that the solvolysis of 4-nitrobenzyl chloride and 4-nitrobenzyl sulfonates follows an S<sub>N</sub>2 mechanism in aqueous binary solvents.<sup>38</sup> Amyes and Richard<sup>39</sup> found that there is a strong common chloride ion inhibition on the solvolysis of 4-methoxybenzyl chloride in 50 : 50 (v/v) trifluoroethanol–water and suggested that the solvolysis occurs through a carbocation intermediate.

The rate of the solvolysis of 4-methoxybenzyl chloride in liquid ammonia increases linearly with increasing concentration of KClO<sub>4</sub> (Table 4, Fig. 3), but the positive effect is not as marked as that for a typical S<sub>N</sub>1 reaction, for which the rate often increases exponentially. The solvolysis rate of 4-methoxybenzyl

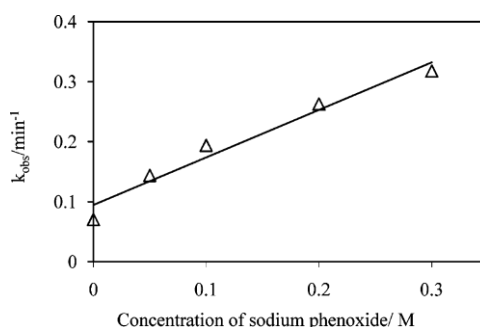


Fig. 4 Changes of the pseudo first order rate constants in the nucleophilic substitution reaction between benzyl chloride and various concentration of sodium phenoxide in LNH<sub>3</sub> (I ¼ 0.3 M, KClO<sub>4</sub>) at 25 °C.

chloride is also increased both by adding sodium chloride and ammonium chloride in liquid ammonia (Table 5, Fig. 3). Probably the increasing solvent ionising power stabilises the transition state of the reaction in liquid ammonia, and helps the expulsion of the leaving group by increasing its solubility in liquid ammonia.

## 2. Nucleophilic substitution of benzyl chloride

A variety of nucleophiles react with benzyl chloride in liquid ammonia to give the corresponding substitution products. 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 these rate constants against the concentration of the nucleophile shows an intercept corresponding to the rate constant for solvolysis (Fig. 4).

There is a first order dependence of the pseudo-first order constants on the concentration of the nucleophile supporting the conclusion from solvolysis kinetic data that these reactions follow a bimolecular  $S_N2$  type mechanism. The slope of these plots gives the corresponding second order rate constants and these are shown in Table 6 for a variety of oxygen and nitrogen nucleophiles. There is a surprisingly small variation in the rate constants for various nucleophiles, but those for morpholine, piperidine and pyrrolidine increase with increasing basicity of the nucleophile. A Brønsted plot (Fig. 5) for these three bases using their aqueous  $pK_a$  gives an apparent  $b_{nuc}$  value of 0.33, which is compatible with the conclusion that nucleophilic substitution occurs *via* a transition state structure with little positive charge development on the incoming nucleophile (Scheme 2).

Table 6 Second order rate constants for the reaction of benzyl chloride with nucleophiles in  $\text{LNH}_3$  at  $25^\circ\text{C}$

Nucleophile	$k_{\text{Nu}}/\times 10^2 \text{ M}^{-1} \text{ s}^{-1}$
Sodium phenoxide	2.01
Sodium triazolate	0.942
Sodium azide	0.773
Sodium cyanide	0.214
Pyrrolidine	2.67
Piperidine	1.70
Morpholine	0.324

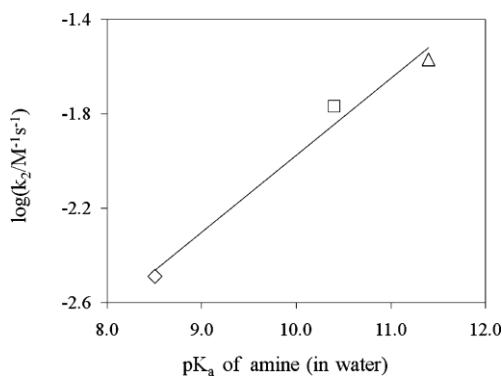
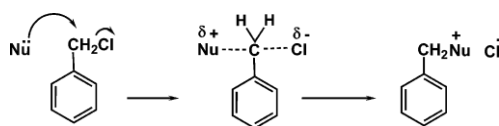
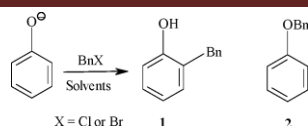


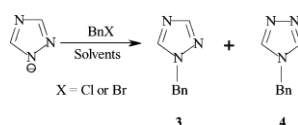
Fig. 5 Brønsted plot for the nucleophilic substitution reaction between benzyl chloride and various secondary amines in  $\text{LNH}_3$  at  $25^\circ\text{C}$ : (>) morpholine; (,) piperidine; (O) pyrrolidine.



Scheme 2



Scheme 3



Scheme 4

Although cyanide anion is a more reactive nucleophile towards methyl iodide than are phenoxide and azide anions in methanol,<sup>40</sup> in liquid ammonia cyanide anion is a weaker nucleophile towards benzyl chloride than both phenoxide and azide. With 0.3 M sodium phenoxide and 0.1 M benzyl chloride (Scheme 3) there is less than 0.5% solvolysis product and no C-alkylation (1) product formed, giving a selectivity for O-alkylation (2) of almost 100% within half an hour. In diethyl ether as solvent but under heterogeneous conditions, the major product (75%) was the C-alkylated one in the reaction between benzyl bromide and phenoxide ion after 3 days at 35 °C.<sup>22</sup> The major product of equimolar reaction between benzyl chloride and sodium triazol-5-olate (Scheme 4) is 1-benzyl-1,2,4-triazole (3) rather than 4-benzyl-1,2,4-triazole (4) in a ratio of 12 : 1 within hours. Previous studies of this reaction in other solvents, again often under heterogeneous conditions, preferentially also give the 1-substituted triazole derivatives, but with much lower selectivity and longer reaction time.<sup>41</sup>

## Conclusion


Liquid ammonia acts like a typical dipolar aprotic solvent in its effect on nucleophilic substitution reactions. The activation parameters, substituent and salt effects indicate that the solvolysis mechanism of benzyl halides in liquid ammonia is forced to be a concerted S<sub>N</sub>2 process through a transition state structure that has little charge development on the incoming nucleophile and the departing nucleofuge and little or no change in charge on the central benzylic carbon compared with that in the reactant state. This is probably largely due to the difficulty of expelling a leaving group anion in liquid ammonia.

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