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# Reaction kinetics in liquid ammonia up to 120°C: techniques and some solvolysis and substitution reactions<sup>†</sup>

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Liquid ammonia is known to be a useful solvent for aromatic nucleophilic substitution reactions of reactive aromatics. Most of the prior work has been carried out at atmospheric pressure and low temperatures. The purpose of this work is to extend the scope of these studies to less reactive haloaromatic substrates that require elevated temperatures to give useful reaction rates. Equipment has been developed to permit the safe study of reactions in liquid ammonia in small (5 mL) stainless steel tube reactors at temperatures up to 120°C (90 bar). Experimental techniques have been developed to permit meaningful sampling of solutions at high temperature and pressure. Sample capture into closed systems, either into a syringe containing quench solution, or directly into an HPLC sample loop, has been used to overcome problems due to flash precipitation and aerosol formation when sampling from high pressure. Activation parameters for the solvolysis of 4-fluoronitrobenzene have been determined over the temperature range 20° – 120°C, and the rates of solvolysis of 2-chloropyrimidine, 4,6-dichloropyrimidine and 2-chloro-5-trifluoromethylpyridine have been determined at appropriate temperatures. 2-Fluoropyridine is inert to solvolysis even at 120°C. Rates of some nucleophilic substitutions with sodium triazolate and sodium phenoxide have been measured. Useful selectivities towards nucleophilic substitution can be obtained for the reactions examined, and further work is planned to examine the wider scope of these reactions. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: ammonia solvent; aromatic nucleophilic substitution; kinetics

## **INTRODUCTION**

The use of liquid ammonia as a solvent for organic reactions has a long history. Herschel Smith's review, published in 1962,<sup>[1]</sup> cited 1388 references, and work has continued apace since then. There is an extensive bibliography of the physical and solution properties of liquid ammonia.<sup>[2,3]</sup> Ammonia strongly solvates cations,<sup>[4]</sup> and many ammonium and metal salts of mono-anions have high solubilities in the solvent, whereas salts of dianions are generally insoluble.<sup>[5]</sup> For example, the solubility of sodium thiocyanate is 2.06 kg/kg LNH<sub>3</sub>, whereas that of sodium sulphite is 0.9 g/kg LNH<sub>3</sub> (both at 25°C).

Some of the more interesting developments are the use of liquid ammonia as a solvent for aromatic nucleophilic substitution reactions, either via the vicarious nucleophilic substitution route exemplified in Scheme 1,<sup>[6]</sup> or by oxidative nucleophilic substitution of hydrogen, exemplified in Scheme 2.<sup>[7]</sup>

These chemistries have been reviewed.<sup>[8,9]</sup> A more mundane but nonetheless important area is that of S<sub>N</sub>2 substitution reactions, which are of considerable importance industrially. Working at atmospheric pressure in the range  $-40^{\circ}$ C to  $-70^{\circ}$ C, Russian workers have shown that nucleophilic aromatic substitutions reactions with a variety of nucleophiles can be carried out in high yield.<sup>[10–12]</sup> One example is shown in Scheme 3:<sup>[13]</sup>

Our interest in ammonia as a reaction solvent has been driven primarily by the potential to use it as an alternative to dipolar aprotic solvents that are expensive and difficult to recover.<sup>[14]</sup> Work in our group<sup>[15]</sup> has shown that, at 25°C, nucleophilic substitution of fluorine by oxy- and nitrogen anions on 4-fluoronitrobenzene (4-FNB) is much faster than solvolysis. For example, at 25°C, the rate constant for the reaction of sodium phenoxide with 4-FNB in liquid ammonia is  $5.28 \times 10^{-2}$  M<sup>-1</sup> s<sup>-1</sup>, compared with the solvolysis rate of  $2.18 \times 10^{-7}$  M<sup>-1</sup> s<sup>-1</sup>. The purpose of the work reported here was to develop methods to explore the reactivity and selectivity with less reactive aromatic substrates that require higher reaction temperatures.

Some relevant properties of liquid ammonia are shown in Table 1 Liquid ammonia has a very high liquid cubical coefficient of expansion that increases with temperature, and this has to be taken into account, in the first instance, to avoid overfilling our sealed pressure reactors, and second, in order to be able to calculate the true reactant concentrations at the reaction temperature. Figure 1(a) shows the variation in vapour pressure with temperature over the range 0°C to 120°C, and Fig. 1(b) shows the variation in density for liquid in equilibrium with the vapour over the same temperature range.

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Scheme 1. Vicarious nucleophilic substitution in a 1,2-pyrimidine



**Scheme 2.** Oxidative nucleophilic substitution of hydrogen by ammonia in a 1,3-pyrimidine



Scheme 3. Nucleophilic substitution in a fluoroquinoline

Table 1. Some physical properties of liquid ammonia <sup>[2,3,16]</sup>					
Parameter	Values				
Critical temperature/°C Critical pressure/bar Vapour pressure of liquid/bar Dielectric constant	132.4 112.3 8.45 (20°C); 90.6 (120°C) 16.90 (25°C); 9.25 (120°C)				

The liquid density is also pressure sensitive, increasing from 0.405 g cm<sup>-3</sup> when in equilibrium with the vapour at 120°C/90 bar to 0.445 g cm<sup>-3</sup> at 120°C/150 bar.<sup>[16]</sup> The unit "bar" throughout refers to bar (absolute).

# EQUIPMENT AND EXPERIMENTAL PROCEDURES

### Materials

Liquid ammonia was purchased from BOC, 99.98% purity with minimal levels of moisture (<200 ppm) and other impurities (<5 ppm oil). The ammonia was distilled from the cylinder to a burette; no further purification procedure was made before using as reaction solvent. All chemicals and solvents were



**Figure 2.** Diagram of improved setup for handling liquid ammonia in glass vessel. **1**: Ammonia supply cylinder; **2**, **3**, **4**, **5**, **6**, **8**: two-way valves; **7**: glass condenser (dip tubing in and out); **9**: glass burette; **10**: reactor (dip tubing in and head space tubing out)

purchased from commercial suppliers and used directly without further purification except where otherwise noted.

Preparation of reactant solutions in liquid ammonia uses a procedure slightly modified from that described earlier.<sup>[17]</sup> The equipment is shown schematically in Fig. 2.

All the apparatus is purged briefly with ammonia gas prior to the experiment, and then all the valves except **2** are shut. Ice water cooling is applied to the condensing vessel **7**, causing ammonia to condense in vessel **7**. When vessel **7** is 80% full, the ice water mixture is removed and ammonia continues to condense until the vapour pressure inside vessel **7** reaches the same as that in cylinder **1**. (This method is safer than the former one using liquid nitrogen, as using ice to condense ammonia avoids overcool and puts much less temperature stress on the vessel.) Valve **2** is shut, and valves **3** and **4** are opened to connect vessels **7** and **9**. After liquid ammonia has transferred to vessel **9**, solid reactant and internal standard are charged to vessel **10** which is then sealed. Valve **3** is then shut, and valve **5** is opened to transfer ammonia into reactor **10**. An accurate amount of liquid ammonia can be added by use of the glass burette **9**.

The solution thus prepared is then transferred to a small batch reactor consisting of an emptied 4.6 mm i.d stainless steel HPLC column which is placed tilted inside the GC oven as shown in Fig. 3. The lower end allows a liquid sample to be taken while the higher end can be used as vapour venting port. These tubes and fittings have a safe working pressure of 364 bar.<sup>[18]</sup>

The reaction of 4-FNB with ammonia will be used to exemplify the procedure. The internal standard biphenyl and reactant 4-FNB





Figure 3. Setup of batch reactor for high-pressure liquid ammonia reactions 1: reactor (stainless steel column) 2, 3, 4, 5: two-way valves

are added to reactor vessel **10** in Fig. 2. A measured quantity of liquid ammonia is then charged into the vessel. After all solids have dissolved, the solution is then charged into reactor column **1** in Fig. 3. To do this the reactor is first flushed with liquid ammonia then vented via purge valve **2**. The vaporization of liquid ammonia cools the vessel. As soon as venting is finished and the vessel is empty, the valve **5** (Fig. 3) is connected to the vessel **10** (in Fig. 2 via valve **5**). The pre-mixed solution transfers to the reactor because high vapour pressure difference. Before increasing the temperature, a fraction of the solution in column **1** is discarded to prevent "hydrostatic pressure" caused by the thermo expansion of liquid ammonia. It is achieved by repeated alternate opening and closing of valves **3** and **4**.

Reaction samples were initially taken via valves **3** and **4** into a sample vial, and liquid ammonia was allowed to boil off and then the sample was dissolved in organic solvent (DCM for GC, GCMS), or methanol for LC analysis. This workup method had worked better on substrates having a low vapour pressure, such as 4-FNB, when sampled at room temperature. But with compounds having a higher vapour pressure such as 2-fluoropyridine, or when sampling reactions at high temperature, the method produces errors due to selective loss of the reactant versus internal standard. Two different methods were devised to overcome this problem. In the first, referred to as the syringe sampling method, a small liquid sample is vented from the reactor into a horizontal 50 mL syringe containing some water and dichloromethane (Fig. 4).

The plunger is initially driven back by the ammonia gas, but on shaking the syringe, it retracts as ammonia dissolves in the water. This method overcomes the problem of selective volatilization of one component and permits the use of either GC or HPLC for analysis.

The second method developed captures a small (2  $\mu$ L) sample in an HPLC Rheodyne<sup>®</sup> valve and then injects this directly into the HPLC column. The lower end of the reactor in the oven is connected to the Rheodyne<sup>®</sup> injection valve in a modified HPLC autosampler compartment. The action of the Rheodyne<sup>®</sup> valve is controlled by software to perform direct injection of reaction sample onto the analysis column. The result is collected via



Figure 4. Syringe method for sample acquisition

software and analysed at the end of the experiment. In this application, an Agilent HP1050 pump is used. The configuration is shown in Fig. 5.

The Rheodyne® seal (Vespel®) is replaced by PEEK® seal. The pump delivers a single mobile phase which passes through the modified auto sampler into the analytical column, after which it is analysed by UV-vis detector and Chemstation. The needle and tray are disconnected from the auto sampler by still functions. The dotted line is the seat groove which connects each port under the face plate. With the Rheodyne® valve at position A, the HPLC solvent flows into port P2, short cuts through the under channel and exits from P3. To take a sample for analysis, valve 3 is closed and valve 5 is opened. Because the pressure inside the reaction column (~120 bar) is higher than sampling loop (1 bar), the liquid ammonia reaction solution charges the sampling loop P1-P4 near instantaneously, entering via P6 and exiting via P5. After that, valve 5 is shut, and the position of the Rheodyne<sup>®</sup> valve is changed to the position **B** shown on the Fig. 4 to allow the sample to inject into the analysis column. Then, the value **3** is opened to purge out the residue liquid ammonia in the line, and an eluent flush is applied to clear the line. When fine-tuned, this analysis method can perform a complete injection and analysis in 2 min. The consistent sample volume greatly improves the data precision, and the fast injection allows faster reaction kinetics to be researched. Although the valves 3 and 5 still require manual control, all other actions are performed by software. The direct injection method provides much improved results over the open sampling method used initially.

#### **Kinetics of solvolysis of 4-FNB**

4-FNB (106  $\mu$ L) is charged to a glass vessel, and liquid ammonia (10 mL) is added to dissolve the contents. This solution is fed to the stainless steel reactor (6.5 mL), which is vented (liquid phase) to ensure sufficient void volume before heating to reaction temperature. Before raising to reaction temperature, the analysing HPLC is set running and equilibrated. Then, a thermocouple is attached to the stainless steel reactor body to monitor



Figure 5. Setup for online HPLC direct injection system

the temperature. The oven temperature is then set to 200°C to give a rapid temperature rise; after the reactor reaches within 5°C of the target value, the oven set point is readjusted to the required temperature. Usually, this process takes 1–2 min. Samples are taken at appropriate intervals via the Rheodyne<sup>®</sup> valve and injected thence directly into the HPLC column. A typical HPLC trace, with example peak identities, is shown in Fig. 6, in which the decline in the 4-FNB peak and the rise of the product peak can be seen.

Plotted results from a typical run are shown in Fig. 7. Sample size was very reproducible, and use of an internal standard was found not to be necessary.

## **RESULTS AND DISCUSSION**

An earlier project had provided data on the reactivity of 4-FNB close to room temperature,<sup>[19]</sup> and further experiments were



**Figure 6.** Typical reaction analysis for 4-fluoronitrobenzene ammonolysis using the direct injection method. Peaks with odd number: 4-fluoronitrobenzene; peaks with even number: 4-nitroaniline



**Figure 7.** First-order In plot of reaction of ammonolysis of 4-FNB at 120° C. The vertical axis is the natural log of the ratio of the GC areas of 4-FNB and biphenyl

carried out to provide information on solvolysis at higher temperatures. The direct injection method gave extremely reproducible results, of which those shown in Fig. 7 are one example.

Results of rate measurements are shown in Table 2. In order to correctly calculate  $k_2$ , the concentration of liquid ammonia solvent had to be calculated at each temperature based on the density at that temperature.<sup>[16]</sup>

The derived Arrhenius plot is shown in Fig. 8.

These data lead to  $\Delta H^{\ddagger} = 48.8 \text{ kJ mol}^{-1}$  and  $\Delta S^{\ddagger} = -205 \text{ J K}^{-1}$  mole<sup>-1</sup>, and are slightly different from those reported earlier,<sup>[15]</sup> which were measured over a smaller temperature range.

The negative  $\Delta S^{\ddagger}$  is consistent with a highly ordered transition state, expected for this low polarity solvent, and is typical for nucleophilic substitution of halogen by amines in nitro aromatics.<sup>[20]</sup> The dielectric constant  $\epsilon$  of liquid ammonia falls from 16.5 at 20°C to 9.25 at 120°C. Closely analogous reactions of 4-nitrofluorobenzene with piperidine and morpholine in ethanol solvent ( $\epsilon = 24.3$ ) at 80°C show  $\Delta S^{\ddagger}$  of -153 and  $-178 \text{ J K}^{-1}$  mole<sup>-1</sup>, respectively<sup>[21]</sup>; for the reaction of 4-chloro-3-nitrotrifluoromethylbenzene with n-butylamine in hexane, ( $\epsilon = 1.89$ )  $\Delta S^{\ddagger}$  is  $-267 \text{ J K}^{-1}$  mole<sup>-1</sup>.<sup>[22]</sup>

A limited study has been made of the solvolysis of some haloheterocyclic compounds. Results are shown in Table 3.

2-Fluoropyridine is remarkably unreactive, with no detectable reaction after 24 h at 120°C, and perhaps 2% reaction after 72 h. We attribute this to the lack of stabilization in the putative intermediate or transition state, as shown in Scheme 4.

Solvolysis of 4,6-dichloropyrimidine stops cleanly after the first substitution.



Figure 8. Arrhenius plot for ammonolysis of 4-fluoronitrobenzene at 20° – 120°C

Table 2. Summary of 4-fluoronitrobenzene ammonolysis rates							
T/℃	20	60	80	100	120		
T/K	293	333	353	373	393		
1000/T(K)	3.413	3.003	2.833	2.681	2.545		
$k_{obs}/s^{-1}$	7.86E-06 <sup>a</sup>	1.00E-04	2.97E-04	6.37E-04	9.97E-04		
Density LNH <sub>3</sub> /g cm <sup><math>-3</math></sup>	0.6104	0.5452	0.5057	0.457	0.3862		
[NH <sub>3</sub> ]	35.84	32.01	29.69	26.83	22.68		
$k_2/M^{-1} s^{-1}$	2.19E-07	3.11E-06	1.00E-05	2.37E-05	4.40E-05		
ln(k <sub>2</sub> )	-15.33	-12.68	-11.51	-10.65	-10.03		
<sup>a</sup> Taken from ref. 19							

Table 3.         Solvolysis of some chloro- and fluoro-heterocycles in liquid ammonia							
Compound	T/°C	$k_{obs}/s^{-1}$	t <sub>1/2</sub>	[NH <sub>3</sub> ]	$k_2/M^{-1} s^{-1}$		
2-Fluoropyridine	120	no reaction <sup>#</sup>	N.A.	22.7	N.A.		
2-Chloro-5-trifluoromethylpyridine	100	8.83E-05	2.2 h	26.8	3.29E-06		
2-Chloropyrimidine	80	9.31E-04	12.4 min	29.7	3.13E-05		
4,6-Dichloropyrimidine	30	4.60E-03	2.5 min	35.8	1.29E-04		
<sup>#</sup> At 120°C							



Scheme 4. Unreactivity of 2-fluoropyridine due to the lack of stabilization in the putative intermediate or transition state

**Table 4.** Reaction conditions and derived second-order rate constants for some aromatic nucleophilic substitutions.\*D = direct injection method; S = syringe capture method. Product identification by GC/MS and by comparison with GC retention times for products isolated and characterised in this Department<sup>[19]</sup>

Electrophile			Nucleophile			T/°C	Method*
		NaTr		NaOPh			
	Concn.#/M	Concn. <sup>#</sup> /M	$k_2/M^{-1} s^{-1}$	Concn.#/M	$k_2/M^{-1} s^{-1}$		
4-FNB	0.00893	0.0893	5.28E-04			60	D
2-CI-5-TFP	0.1279			0.11	4.45E-03	60	S
2-FP	0.094			0.35	2.02E-04	100	S
<sup>#</sup> calculated for 120°C							

### Some nucleophilic substitution reactions

Both the direct injection and syringe capture methods were evaluated for nucleophilic substitution reactions using sodium triazolate and sodium phenoxide, at temperature where conveniently measured reaction rates occurred. For the reaction of with 4-FNB, solvolvsis significantly competed at the concentration sodium triazolate used, and the solvolysis rate (see Table 2) was subtracted from the measured first-order rate constant of  $6.36 \times 10^{-4} \text{ s}^{-1}$  in order to derive the rate constant given in Table 4. There is no solvolysis of 2-fluoropyridine on the timescale of its reaction with sodium phenoxide, and so the second-order rate constant was directly derived from the observed order rate constant of 7.12  $\times$  10 $^{-5}\,s^{-1}.$  In the reaction of 2-chloro-5-trifluoromethylpyridine with sodium phenoxide, a small excess of the chloropyridine was used, and some solvolysis was seen. Rate constants at 60°C for both solvolysis  $(4.7 \times 10^{-6} \text{ s}^{-1})$  and substitution by phenoxide ion (Table 4) were obtained by fitting the concentration profiles, corrected for ammonia density, using the numerical modelling package Berkeley Madonna®. Reaction conditions and derived second-order rate constants are given in Table 4.

## CONCLUSIONS

Equipment has been developed for the study at small scale (ca. 5 mL reaction volume) of reactions in liquid ammonia solvent at temperatures up to 120°C, at which the vapour pressure of

liquid ammonia is 90 bar. 4.6 mm i.d. stainless steel tubing with a safe working pressure up to 364 barg is used to construct the reactors. Sampling/analysis methods have been developed to overcome problems in taking reaction samples at high pressure and temperature. The successful application of these techniques to a study of the high-temperature solvolysis and nucleophilic substitution of several haloaromatics has been demonstrated. For the reactant combinations investigated, the rate constants for the solvolysis were orders of magnitude smaller than the nucleophilic substitution rates. 2-Fluoropyridine is remarkably resistant to solvolysis, showing no solvolysis whatsoever after 24 h at 120°C in liquid ammonia. These results support our view that liquid ammonia is a potential "green" replacement for dipolar aprotic solvents in this class of reaction.

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