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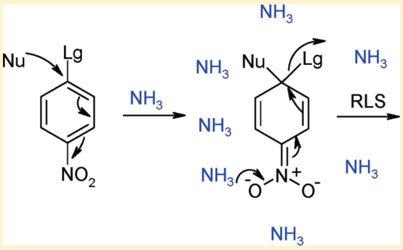
The Kinetics and Mechanisms of Aromatic Nucleophilic Substitution Reactions in Liquid Ammonia

Pengju Ji, John H. Atherton, and Michael I. Page*

IPOS, The Page Laboratories, Department of Chemical and Biological Sciences, The University of Huddersfield, Queensgate, Huddersfield, HD1 3DH, United Kingdom

S Supporting Information



ABSTRACT: 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-nitrofluorobenzene 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 the 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 then give diazene or be trapped by ammonia to give the unstable hydrazine which then yields nitrobenzene.

INTRODUCTION

A significant proportion of reactions carried out by the pharmaceutical and agrochemical industries involve aromatic nucleophilic substitution. 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. Ever increasing cost, health, and environmental concerns have resulted in some previously common solvents, for example chloroform, being prohibited. Although a particular solvent may be used in research syntheses, they are often avoided on the manufacturing scale. Dipolar aprotic solvents (e.g., DMSO and DMF) 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.[2]

Liquid ammonia (LNH$_3$) is cheap[3] and is a promising candidate to replace dipolar aprotic solvents in a number of industrial processes, although at present its use as a solvent is uncommon. Ammonia is relatively weakly associated in the liquid state as it has only one lone pair for three potential N−H hydrogen bonds leading to a boiling point of −33 °C and a vapor pressure of 10 bar at 25 °C.[4] Although liquid ammonia has a low dielectric constant (16.7 at 25 °C),[5] many salts and organic compounds are highly soluble. Cations are strongly solvated in liquid ammonia by the nitrogen lone pair but liquid ammonia does not significantly solvate anions as it is not a good hydrogen donor.[6] We have recently shown that, contrary to common understanding, liquid ammonia behaves similarly to dipolar aprotic solvents and is potentially useful as a solvent for organic synthesis.[7] Thus, the poor solvation of anions in liquid ammonia makes them good nucleophiles but poor leaving groups compared with similar reactions in water, which leads to a significant impact on the kinetics and mechanisms of aliphatic nucleophilic substitution.[8] Liquid ammonia is much easier to recover than many conventional solvents and it is easily handled in small scale laboratory glassware over a useful temperature range.

Herein, we report on the kinetics and mechanisms of aromatic nucleophilic substitution, using nitrofluorobenzenes as substrates.

RESULTS AND DISCUSSION

i. Meisenheimer Complexes and UV−Vis Spectra of Aromatic Compounds in Liquid Ammonia. The UV−vis extinction coefficients of compounds are generally greater in liquid ammonia compared with those in water or ether under similar conditions, although the maximum wavelength of absorption of some nitrobenzene derivatives changes little on going from water to liquid ammonia (Supporting Information, Table S1). The wavelength of maximum absorption of 4-nitrofluorobenzene,

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Scheme 1

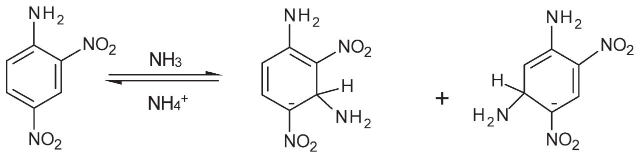


Table 1. Solvolysis Rate Constants and Half-Lives of Some Aromatic Compounds in LNH_3[a]

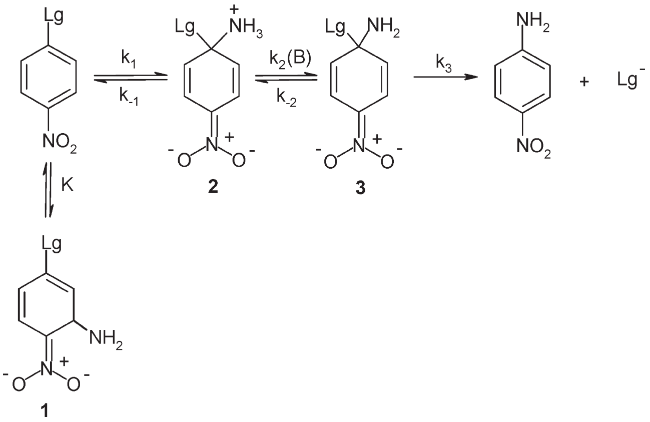
substrate	temp (°C)	$10^6 k_0$ (s^{-1})	$t_{1/2}$
2-nitrofluorobenzene (2-NFB)	25	2.15×10^2	54 min
3-nitrofluorobenzene	100	no reaction	
4-nitrofluorobenzene (4-NFB)[b]	20	7.86	24.4 h
2,4-difluoronitrobenzene (2,4-DFNB)	25	6.72×10^3	1.7 min
2,4-dinitrofluorobenzene (2,4-DNFB)	25	$>1.4 \times 10^5$	<5 s
4-nitrochlorobenzene	25	no reaction	
2,4-dinitrochlorobenzene	25	6.18×10^3	1.9 min
3-nitroiodobenzene	25	no reaction	
2-nitroazidobenzene (2-NAB)	20	5.81	33.1 h
4-nitroazidobenzene (4-NAB)[b]	25	5.11	37.7 h
2,4-dinitroazidobenzene	25	$>1.4 \times 10^5$	<5 s
2-chloropyrimidine	20	14.2	13.3 h
2-chlorobenzthiazole	20	5.33	36.1 h
2-fluoropyridine	25	no reaction	

[a] The kinetics were measured by GC unless otherwise noted. [b] Measured by GC and UV, both methods gave similar pseudo-first-order rate constants.

4-nitroaniline, and 4-nitroazidobenzene is significantly smaller than those of the corresponding ortho analogues and may indicate a stronger resonance effect from the ortho nitro group, which considerably decreases the energy gaps between ground and excited states. The absorption spectrum of 2,4-dinitroaniline in liquid ammonia shows several absorptions (257, 353, 387, 537 nm) which are more complicated than those in ether or water (220 and 330 nm). A likely interpretation is that 2,4-dinitroaniline is attacked by a solvent molecule to form stable Meisenheimer complexes (Scheme 1),[9] which are written as anions rather than zwitterions, as we have shown that aminium ions exist as free bases in liquid ammonia.[8] The formation of Meisenheimer complexes between highly activated benzenes and nucleophiles is well-known, and has been shown spectroscopically,[10] including NMR.[11] The UV−vis absorption of a typical Meisenheimer complex is in the range 450−600 nm,[12] and therefore often color is observed with the formation of the σ-adducts. The absorption of 2,4-dinitroaniline in liquid ammonia at 537 nm can be assigned to one or both of the intermediates shown in Scheme 1. There is no new product formed after vaporization of liquid ammonia from a solution of either 2,4-dinitroaniline or 1,3-dinitrobenzene and it appears that the Meisenheimer complex is formed rapidly but reversibly and removal of the ammonia solvent results in its reversion to starting material.

ii. Solvolysis of Aromatic Compounds in Liquid Ammonia. 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 normalized areas from GC or HPLC analysis 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 1). There 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.[13] The introduction of additional fluoro- or nitro-groups increases the solvolysis rates by more than 4 orders of magnitude.

Scheme 2



Given the demonstration that nitro-substituted aromatic compounds without a leaving group reversibly form Meisenheimer complexes in liquid ammonia (Scheme 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).[9] However, an unproductive intermediate **1** may also be formed by nucleophilic attack on the C-3 unsubstituted position[9,14] and in the case of dinitro-substituted derivatives these complexes may actually be the effective starting material as they are formed rapidly and are often more stable than the reactants.[9] Attack at the *ipso* C-1-fluoro-subtituted position generates the reactive intermediate **2** with a charged ammonium ion but product formation probably requires deprotonation to form the anionic intermediate **3** 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.[8] It is therefore likely that the zwitterionic intermediate **2** is rapidly converted to the thermodynamically more stable anionic intermediate **3** by proton transfer to the solvent (k_2 step in Scheme 2 where B = NH_3). In fact the intermediate **3** 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 **3**, step k_3 (Scheme 2), which is also compatible with the observations for other aromatic nucleophilic substitutions in liquid ammonia (vide infra).

The solvolysis rates of 4-nitrofluorobenzene and 2-nitrofluorobenzene (4-NFB and 2-NFB, respectively) show relatively small salt effects (Figures 1 and 2); however, it is worth noting that 2 M salt increases the rate for the 4-isomer nearly 3-fold but by only 28% for the 2- isomer (Supporting Information, Table S2).

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

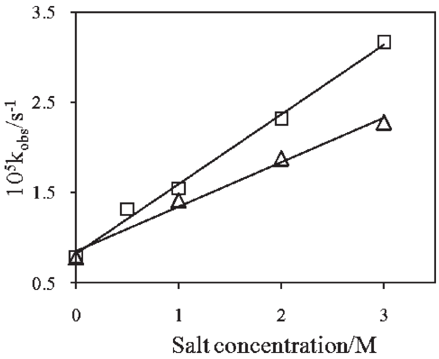


Figure 1. The dependence of the solvolysis rate of 4-NFB on the salt concentration in LNH_3 at 25 °C: (Δ) NH_4Cl and (☐) $NaNO_3$.

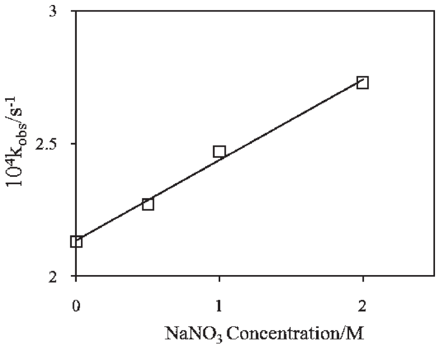


Figure 2. The dependence of the solvolysis rate of 2-NFB on the salt concentration in LNH_3.

Scheme 3

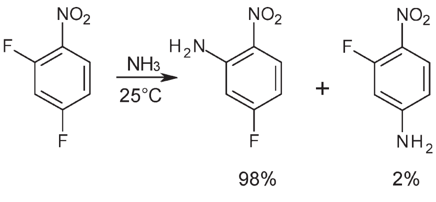


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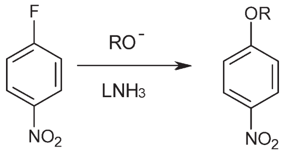
Table 2. The Rates and Activation Parameters for the Solvolysis of 2-NFB, 4-NFB, and 2,4-DFNB in LNH_3 at 25 °C

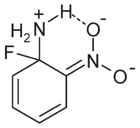
substrate	$10^6k_{obs}/s^{-1}$	$k_{rel.}$	$\Delta G^{\ddagger}$/ kJ mol^{-1}	$\Delta H^{\ddagger}$/ kJ mol^{-1}	$\Delta S^{\ddagger}$/ J K^{-1}mol^{-1}
4-NFB	7.86	1	101.1	53.0	−161.3
2-NFB	215	27	94.1	51.3	−143.4
2,4-DFNB	6717	852	87.7	40.0	−151.6

Scheme 4



nearly 2 orders of magnitude greater than that for 2-NAB (Table 1). As well as a significant difference in salt effects, 2-NFB is nearly 30 times more reactive toward 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 disubstituted 2,4-DFNB, which gives almost exclusively the ortho-substituted derivative **4** as product in liquid ammonia at 25 °C (Scheme 3). The product ratio of ortho to para isomers is compatible with the rate differences observed between 2-NFB and 4-NFB (Table 1).

Preferential substitution ortho to the nitro group is sometimes observed in the reactions of nitrohalobenzenes with neutral nucleophiles,[15] and even with sterically hindered nucleophiles.[15f,g] However, some calculations indicate that the Meisenheimer σ-complex formed by nucleophilic addition of anionic nucleophiles to the para position is generally about 10−20 kJ mol^{-1} *more* stable than the ortho one.[16] Furthermore, the ground state of 2-NFB is better solvated than 4-NFB in both aprotic and dipolar aprotic solvents according to DFT calculations,[17] probably due to the relatively larger molecular dipole of 2-NFB than 4-NFB. It is therefore likely that the enhanced reactivity of 2-NFB over 4-NFB is due to a transition state effect. The entropy of activation for the ortho-isomer is less negative than that for the para-isomer (Table 2, and in the Supporting Information Tables S4−S6 and Figures S1−S3). 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 stabilize the intermediate **5**,[18] it would not explain why this favorable interaction cannot occur with 2-NAB. The generation of negative charge on the nitro group oxygens in the Meisenheimer σ-adduct formed from 4-NFB requires solvation and restriction of solvent molecules giving rise to a slightly more negative entropy of activation.



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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.[19] 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.

iii. Aromatic Nucleophilic Substitution by Oxygen Nucleophiles. Oxygen nucleophiles, such as alkoxide and phenoxide ions, react readily with 4-NFB in liquid ammonia to give the corresponding substitution product (Scheme 4). There is little solvolysis product formed as the background rate of reaction of 4-NFB with ammonia is too slow to compete with the rates of substitution by anionic O-nucleophiles. The rate of the latter reaction shows a first-order dependence on the concentration of the anion and the associated second-order rate constants (Table 3) were obtained from the slope of these plots (Figure 3). The rate of the reaction between 4-NFB and phenoxide is reduced by about 2-fold as the concentration of

Table 3. The Second-Order Rate Constants for the Nucleophilic Substitution of 4-NFB by Oxygen Anions in Different Solvents at 25 °C

O-nucleophile	solvent	k_2/M^{-1} s^{-1}	$k_{rel.}$	ref
MeO^-	LNH_3	>3.5[a]	>20 000	present work
MeO^-	DMSO-MeOH[b]	3.77×10^{-1}	2 100	21
MeO^-	MeOH	1.79×10^{-4}	1	22
PhO^-	LNH_3	0.0528	41 000	present work
PhO^-	DMSO[c]	0.52	400 000	23
PhO^-	MeOH	1.29×10^{-6}	1	15e, 15f, 24

[a] Rate is too fast to be measured accurately. [b] 80% (% v/v) DMSO–MeOH solution. [c] 20 °C.

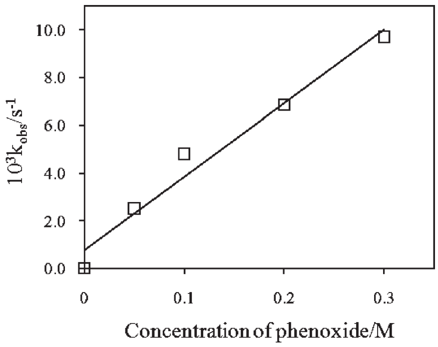


Figure 3. The dependence of the observed pseudo-first-order rate constants for the reaction between 4-NFB and sodium phenoxide on the concentration of phenoxide ion (I = 0.3 M, $KClO_4$) in LNH_3 at 25 °C (Supporting Information, Table S7).

the salt is changed from 0 to 1.5 M (Supporting Information, Table S10 and Figure S5) in common with the general observation that salt effects have very limited influence on the rate of aromatic nucleophilic substitutions.[20]

The rates of reactions of 4-NFB with O-nucleophiles are 4–5 orders of magnitude faster in liquid ammonia than in methanol and are similar to those in DMSO. This large rate enhancement is probably due to the differences in solvation of the nucleophilic anions in dipolar aprotic and protic solvents, giving rise to enhanced nucleophilicity of anions in liquid ammonia. The second-order rate constant for the reaction of phenoxide with 4-nitrochlorobenzene, 2.51×10^{-7} M^{-1} s^{-1} at 25 °C, is 5 orders of magnitude smaller than that of 4-NFB (Table 3), which probably reflects the less favorable formation of the σ-complex. It is usually assumed that the mechanism of S_NAr reactions involves a charge delocalized Meisenheimer intermediate, the σ-complex (Scheme 2), in which negative charge of an incoming nucleophile is spread into the aromatic ring and substituents through the resonance, and so any stabilizing influence of the solvent is expected to be less in the transition state than in the relatively localized reactant anion. Liquid ammonia, in common with dipolar aprotic solvents and unlike protic ones,[25,39] 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 unfavorable large negative entropies of activation compared with those in the protic solvent methanol (Table 4, and in the Supporting Information Table S8 and Figure S4).

Table 4. 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}	ref
PhO^-	LNH_3	38.1	−141.3	present work
PhO^-	MeOH	102.9	−19.7	15e, 15f
MeO^-	MeOH	88.6	−27.6	15a, 26

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[27] 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. The good solvation of metal cations in liquid ammonia through electron donation from ammonia presumably also increases the nucleophilicity and reactivity of the counteranion 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. We have previously reported the ionization constants for substituted phenols in liquid ammonia and that these show a linear relationship with the corresponding values in water.[8] 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 (Figure 4). These values are much larger than those for the reaction of 4-NFB with phenoxides or thiophenoxides in protic solvents which are around 0.5.[28] 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 the σ-complex is the rate limiting step or possibly formation with a very late transition state. This is probably due to the difficulty of expelling and solvating the leaving fluoride anion from the Meisenheimer σ-complex (Scheme 2) in liquid ammonia.

iv. Aromatic Nucleophilic Substitution by Nitrogen Nucleophiles. The kinetics and mechanisms of secondary amines reacting with activated aryl halides have been extensively studied.[16a,29] Solvent effects on those reactions are often complicated by base catalysis, which depends on the reaction medium and substrate structure. Normally, general base catalysis occurs in nonpolar 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.[30] However, in dipolar aprotic solvents the general base catalysis is generally not observed.[29e−g] The observed pseudo-first-order rate constants for the reaction of secondary amines with 4-NFB in liquid ammonia (Scheme 5) are first order in amine concentration (Figure 5), indicating the

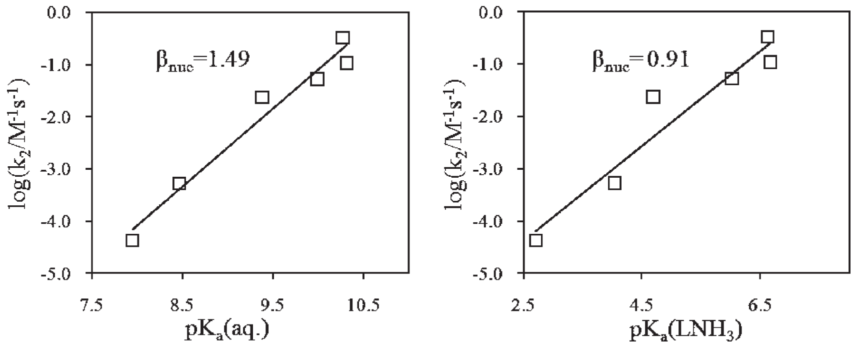
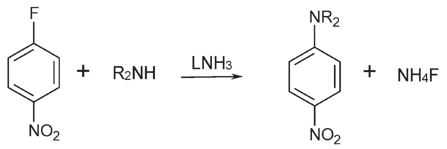


Figure 4. Brønsted type plot for the reactions between para-substituted phenoxides and 4-NFB in LNH_3 (Supporting Information, Table S9).

Scheme 5



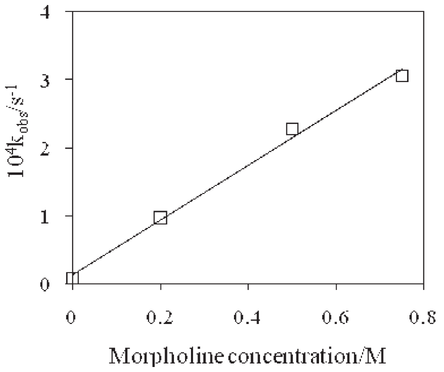


Figure 5. The dependence of the pseudo-first-order reaction between 4-NFB and morpholine on the concentration of morpholine in LNH_3 at 25 °C (Supporting Information, Table S11).

Table 5. The Second-Order Rate Constants for the Substitution of 4-NFB by Nitrogen Nucleophiles in LNH_3 at 25 °C

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: 0.1 M 4-NFB with 0.01 M sodium azide.

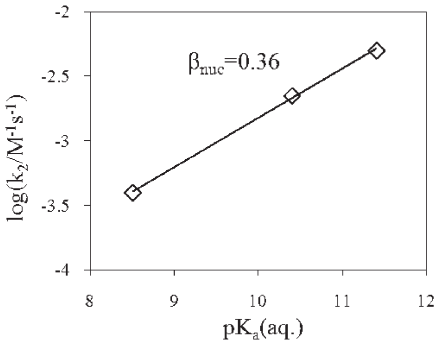
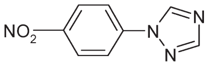


Figure 6. Brønsted type plot for the substitution of 4-NFB by nitrogen nucleophiles in LNH_3 using the corresponding aqueous pK_a of the aminium ion.

absence of general base catalysis by a second molecule of amine. The corresponding second-order rate constants for secondary amines and other nitrogen nucleophiles reacting with 4-NFB are shown in Table 5. 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 **3** (Scheme 2) therefore is thermodynamically more stable than its conjugate acid **2** in liquid ammonia and other amines are unlikely to be able to compete with solvent ammonia in converting **2** to **3** and so the absence of general base catalysis by amines is not surprising.

There is no nucleophilic substitution of 4-NFB with aniline, 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 was 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, and DMF.[31] The reaction between 1,2,4- triazolate and 4-NFB in liquid ammonia gives only the 1-substituted product **6**.



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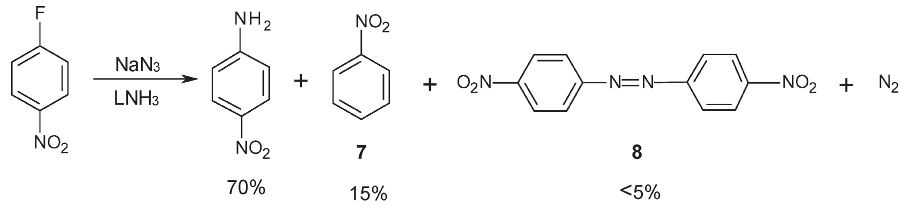
As already stated, all amines exist in their free base unprotonated form in liquid ammonia[8] and so it has not been possible to evaluate the pK_a of aminium ions in this solvent. Nonetheless, the second-order rate constants (Table 5) do increase with increasing aqueous basicity of the amine, and there 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 6). A plot of the pK_a values of aminium ions in acetonitrile against those in water is a linear slope of 1.0[32] and so using the pK_a values in this aprotic solvent would generate the

Scheme 6



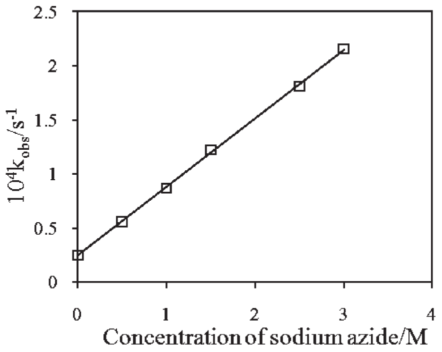


Figure 7. The dependence of the observed pseudo-first-order rate constant for the reaction of 4-NFB on sodium azide concentration in LNH_3 at 25 °C (I = 3 M, $NaNO_3$).

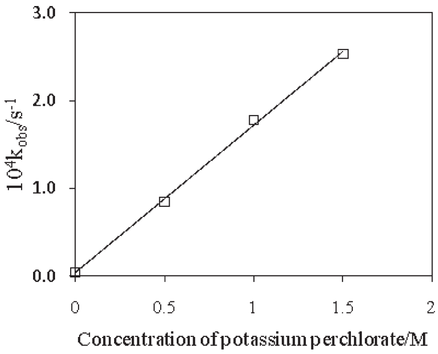


Figure 9. The dependence of the observed pseudo-first-order rate constant for the reaction of 4-NAB on potassium perchlorate concentration in LNH_3 at 25 °C.

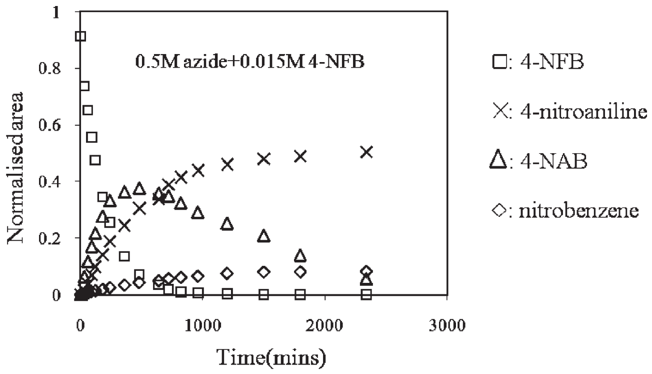


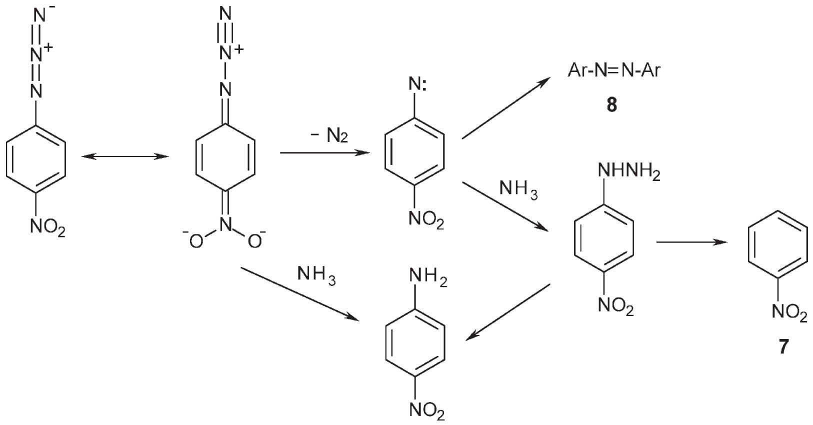
Figure 8. Reaction profile for 4-FBN reacts with sodium azide in LNH_3 at 25 °C.

same Brønsted β_{nuc}. The small Brønsted β_{nuc} contrasts with the β_{nuc} of 0.91 observed with phenoxide anions, which was obtained by using pK_a values for phenols determined in ammonia. Without the knowledge of the relative pK_a values in liquid ammonia it is not possible to interpret the small values of Brønsted β_{nuc} for amines reacting with 4-NFB with any certainty, but it is indicative of only a small amount of positive charge development on the amine nitrogen nucleophile in the transition state. This small value is compatible with the rate limiting breakdown of the σ-complex **3**, following the deprotonation of the aminium ion in the Meisenheimer intermediate **2** (Scheme 2). This proton transfer step to the solvent ammonia is probably thermodynamically favorable 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, 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.

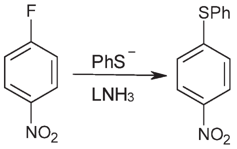
In addition to the enhanced reactivity of azide ion compared with its aqueous basicity (Table 5) there are some unusual observations with the reactions of this nucleophile with 4-NFB in liquid ammonia. The reaction between sodium azide and 4-NFB in other solvents affords, as expected, the corresponding 4-nitroazidobenzene (4-NAB). However, in liquid ammonia the reaction gives no 4-NAB after 4-NFB has completely reacted. The final reaction products are 4-nitroaniline, nitrobenzene (**7**), diazene (**8**), and nitrogen (Scheme 6). The molar ratio of **7** and **8** in the products is independent of whether the reaction vessel is covered in aluminum foil or not. In the absence of air, with control of ionic strength (I = 3 M, $NaNO_3$), the apparent first-order rate constant, based on the disappearance of 4-NFB in liquid ammonia, is proportional to the azide concentration at 25 °C (Figure 7, and Table S12 in the Supporting Information).

An 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 8). 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 h and yields the same products as does 4-NFB with azide anion (Scheme 6). 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 9, and Table S13 in the Supporting Information). The rate of

Scheme 7



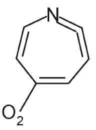
Scheme 8



reaction of 4-NAB is independent of the nature of salt, whether sodium nitrate, sodium azide, or potassium perchlorate.

The unusual products nitrobenzene **7** and diazene **8** formed from 4-NFB and azide ion (Scheme 6) could be explained by the formation of an intermediate nitrene that is trapped by ammonia to form 4-nitrophenyl hydrazine. Interestingly, the reaction of hydrazine with 4-NFB in liquid ammonia gives, after workup with sodium hydroxide and extraction with dichloromethane, a mixture of nitrobenzene, 4-nitroaniline, and aniline in a molar ratio of 12:5:1.[33] 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. This is further substantiated by the observation that 4-nitrophenyl hydrazine in liquid ammonia does indeed give nitrobenzene and aniline, but no diazene **8** is formed. It is also worth noting that there is no cross-coupling reactions between phenyl azide or benzyl azide with 4-NAB in the presence of $KClO_4$ or NaN_3 in liquid ammonia at room temperature, and only the self-coupling diazene product of 4-NAB (**8**) is formed.

So a possible origin of nitrobenzene **7** and diazene **8** 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, photolytic conditions and electrochemically,[34] and singlet aromatic nitrenes with electro-withdrawing groups are known to undergo insertion into the N—H bonds of amines to give the corresponding hydrazines.[35] The major product of 4-nitrophenyl nitrene trapped by diethylamine is 4-nitroaniline, with the minor product being 4-nitrophenyl hydrazine under photoirradiation. However, photolysis of 4-NAB in acetonitrile in the presence of a 3-fold excess of phenyl azide, under conditions where only the 4-NAB absorbs, gives only the diazene **8**, with no crossover product formed, which was seen as evidence for dimerization of the triplet nitrene in preference to nitrene attack on the azide.[35b]



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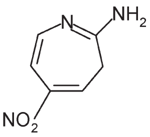

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No ring enlargement products, such as 5-nitro-1,2-didehydroazepine (**9**) or its amination derivative **10**, were found from the solvolysis of 4-NAB in liquid ammonia, and the molar ratio between 4-nitroaniline and nitrobenzene is about 5:1 in the product mixture. The diazene compound **8** is quite stable in liquid ammonia at room temperature. The possible routes for the decomposition of 4-NAB in liquid ammonia are therefore summarized as in Scheme 7.

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. Given the expected low concentration of the nitrene, it is unlikely to dimerize to form the diazene **8**, but the latter could be formed from the nitrene reacting with 4-NAB and releasing nitrogen. Most of the 4-nitroaniline formed may come from the direct solvolysis of 4-NAB by displacement of azide ion. Interestingly, similar results were observed when 4-NAB was dissolved in DMSO together with an excess of tetraethylammonium azide, followed by passing ammonia gas into the solution for several hours; however, no reaction was observed in methanol.

v. Nucleophilic Substitution by Sulfur Nucleophiles. 4-NFB reacts rapidly with thiophenoxide anion in liquid ammonia to give 4-nitrophenyl sulfide (Scheme 8) and a trace amount of diphenyl thioether, probably due to the oxidation of thiophenoxide by air during the sample processing stage. The rate of reaction between thiophenoxide and 4-NFB in liquid ammonia is significantly greater than that in methanol, and is similar to that in DMSO (Table 6). The rate difference of this reaction in liquid ammonia and in methanol is more pronounced in aromatic than in aliphatic nucleophilic substitution, which suggests the potential benefit of using liquid ammonia as solvent in aromatic substitution reactions.

Table 6. The Second-Order Rate Constants for the Reaction of Thiophenoxide Ion with 4-NFB in Various Solvents at 25 °C

nucleophile	solvent	$k_2/\mathrm{M^{-1}\ s^{-1}}$	$k_{\mathrm{rel.}}$	ref
PhSNa	MeOH	2.1×10^{-4}	1	36
$PhSNH_4$[a]	LNH_3	3.1	1.5×10^4	present work
PhSNa	DMSO	10.4	5×10^4	37

[a] Thiophenol (aqueous pK_a = 6.5) is completely self-ionized in liquid ammonia at room temperature, for detail, see ref 38.

CONCLUSION

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.

EXPERIMENTAL SECTION

Materials. Liquid ammonia was 99.98% pure with moisture levels <200 ppm and other impurities <5 ppm. It was used directly as reaction medium without further purification. All the organic chemicals were purchased from commercial source with at least 98% purity; all the inorganic salts were either analytical or laboratory grade. They were used without further purification unless otherwise noted. Sodium phenoxide salts were prepared from sodium metal and the corresponding phenols;[39] sodium triazolate and imidazolate were prepared as previously reported;[40] 4-nitroazidobenzene, 2-nitroazidobenzene, and 2,4-dinitroazidobenzene were prepared in DMF[41,42] and recrystallized in water−ethanol twice. *N*-(4-Nitrophenyl)pyrrolidine, piperidine, and morpholine;[43] 1-substituted-4-(4-nitrophenoxy)benzene;[44] 1-(4-nitrophenyl)-1*H*-imidazole,[45] and 1-(4-nitrophenyl)-1*H*-1,2,4-triazole[46] were prepared and purified by recrystallization or general flash column methods; the structures of those compounds were confirmed by DSC, GC-MS, and NMR analysis. The general solvents were laboratory grade and were used without further purification. For HPLC analysis, HPLC grade acetonitrile, methanol, and toluene were used as eluent.

Kinetics. Ammonia gas was condensed from a liquid ammonia cylinder into a glass ammonia tank cooled by liquid nitrogen or dry ice, then transferred into a glass graduated buret (maximum volume 30 mL). The buret was connected to a glass reactor (15 mL) through several Omnifit 3-way and 2-way valves in order to keep the pressure balanced between the reactor and the buret during the liquid ammonia transfer. Generally, one of the reactants was precharged into the reactor and the system maintained at the required temperature by a thermostat. Liquid ammonia (normally 10 mL) was released into the reactor and equilibrated for an hour, before another reactant was injected by a pressure syringe through an Omnifit septum.[47]

The pressure UV cell was based on a design by Gill.[48] 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, with the path length between two windows being 10 mm. The top of the UV cell has a standard Swagelok that can be connected to the Omnifit valves, thus the cell can be connected with the reactor and allows the reaction mixture to be transferred from it to the cell. For the determination of extinction coefficients and the rates of relatively slow reactions, the reactants were normally premixed in the reactor and the reaction mixture was quickly transferred from it to the chamber between the windows of the cell for the measurement of maximum absorbance wavelength ($\lambda_{\max}$) and extinction coefficient ($\varepsilon_{\max}$). The concentration of the compounds in liquid ammonia normally varied from 10^{-5} to 10^{-4} M. Generally, a standard ether solution of solute (0.02 M) was prepared, 0.05 to 0.1 mL of this standard solution was injected though a syringe into the reactor, then 10 mL of liquid ammonia was released into the vessel, and liquid ammonia solution was transferred into the pressure UV cell.

For kinetic studies, the nucleophile was precharged in the reaction vessel and dissolved in 10 mL of liquid ammonia. The concentration of nucleophile varied from 0.1 to 1 M depending on the nature of the reaction. Normally the substrate concentration was 0.01−0.015 M and the internal standard was biphenyl or phenetole. The substrate standard ether solution was injected into the vessel through an Omnifit septum after the precharged nucleophile in liquid ammonia had been equilibrated at the required temperature. At suitable time intervals, a reaction aliquot 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 the reaction vessel. After rapid evaporation of ammonia, saturated ammonium chloride solution, 1 M HCl or 1 M NaOH, was added as a quenching agent, then the sample was extracted with dichloromethane or toluene and dried over anhydrous Na_2SO_4. The kinetics of some reactions were measured by a competition method, so that the rate constants were obtained from the molar ratio of products. The samples from the reaction were analyzed by GC or HPLC and the data were processed with commercial data-fitting software.

The pseudo-first-order rate constants for the reactions of NFBs with anionic oxygen and nitrogen nucleophiles and for the reaction between 4-NFB and azide, under constant ionic strength, and the solvolysis of 4-NAB under different salt concentration were obtained by a general sampling method measuring the formation of the product and the disappearance of the reactant by GC analysis. The kinetics for the reactions of 4-NFB with sulfur nucleophiles were too fast to be measured by this method, and the rate constants for these reactions were measured by a competition method.

The reactions in liquid ammonia above 45 °C were carried out in a stainless steel tube (ammonia resistant) that had a total volume of 15 mL. Both ends of the tube could be sealed with standard Swagelok caps. Normally the reactants were premixed in a glass pressure vessel, and then transferred into the tube by cooling the tube with liquid nitrogen. The end of the tube was quickly sealed after the reaction mixture was transferred into the tube, and then the reactor was placed in a GC oven where the required temperature can be controlled accurately.

Calculations. The calculation of ground state solvation energy for the nitrofluorobenzenes in different solvents was performed by using Spartan 08 software (Spartan 08, Wave function, Inc., Irvine, CA, USA, 2008). The calculation was carried on the HF and DFT/B3LYP method, both with 6-31+G* as the basis set.

ASSOCIATED CONTENT

S Supporting Information. Tables and figures that containing the UV absorbance and extinction coefficient of aromatic nitro compounds; the rate constants of the individual kinetic experiments in liquid ammonia; calculation of solvation energy for 2-NFB and 4-NFB in typical protic and dipolar aprotic solvents; and ^{19}F NMR spectra for the solvolysis of 2,4-DFNB. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: m.i.page@hud.ac.uk.

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