JOC Article
pubs.acs.org/joc

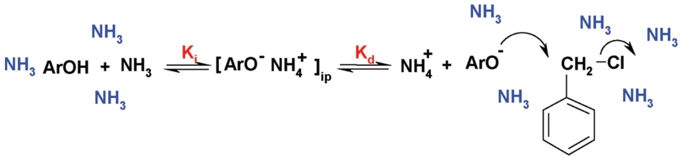
Liquid Ammonia as a Dipolar Aprotic Solvent for Aliphatic Nucleophilic Substitution Reactions

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

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

m.i.page@hud.ac.uk

Received November 10, 2010



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

Introduction

Nucleophilic displacement reactions at saturated carbon centers occur either with simultaneous breaking and forming of the involved bonds (S_N2 or A_ND_N) or by a mechanism where breaking the old bond precedes formation of the new bond (S_N1 or D_N+A_N). It is well-known that the nature of the solvent used for these reactions can influence the mechanism adopted and the transition state structure with, for example, a gradation of transition states between the S_N1 and S_N2 extremes with varying degrees of participation by the solvent.[1] However, some theoretical calculations indicate that changes in solvent should not lead to significant changes in transition state structure.[2] An additional complication, particularly in solvents of low polarity, is the possible intervention of ion pairs. There are many examples of reactions of various nucleophiles with benzyl derivatives that show a mixed rate law compatible with the occurrence of simultaneous S_N1 and S_N2 mechanisms. There have also been attempts to predict when the change from one mechanism to the other occurs by variation in the structure of the reactants or solvent.

---

(1) For examples, see: (a) Westaway, K. C. *Can. J. Chem.* **1978**, *56*, 2691–2699. (b) Westaway, K. C.; Lai, Z. *Can. J. Chem.* **1987**, *67*, 345–349. (c) FangY.; MacMillar, S.; Eriksson, J.; Kolodziejska-Huben, M.; Dybala-Defratyka, A.; Paneth, P.; Matsson, O.; Westaway, K. C. *J. Org. Chem.* **2006**, *71*, 4742–4747.

(2) Acevedo, O.; Jorgensen, W. L. *Acc. Chem. Res.* **2010**, *43*, 145–151.

DOI: 10.1021/jo102173k

For solvolysis reactions, the solvent, in addition to its role as a nucleophile and possibly acting as a general base in a S_N3 type process,[3] can influence the mechanism of substitution by its effects on the stability of the intermediate carbocation and on its solvation of the leaving group. These solvent effects are also present for substitutions by other nucleophiles, especially by solvation of the nucleophile and leaving group in determining the extent of "push and pull".

There is much concern about the solvents used for industrial purposes, both from an efficiency and environmental point of view and when solvents are used in large quantities, such as in the fine-chemical and pharmaceutical production, their selection is a major part of the environmental performance of a process and its impact on cost and safety issues. Some previously used common solvents, for example chloroform, are now proscribed, while others, although still commonly used in research syntheses, are generally avoided on the manufacturing scale. It is estimated that 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.[4]

Although liquid ammonia is among the least expensive bulk chemicals and is a promising candidate to replace dipolar aprotic solvents in a number of industrial processes, its application as a common solvent is relatively unusual. Ammonia has only one lone pair for three potential N−H hydrogen bonds leading to relatively weak association in the liquid state. The internal energy of liquid ammonia is about -21 kJ mol^{-1}, around half the value for water,[5] and it has a boiling point of -33 °C and a vapor pressure of 10 bar at 25 °C.[6] 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 (16.9 at 25 °C),[7] many synthetically useful salts are highly soluble, for example, NH_4N_3, 67.3 g/100 g at -36 °C.[8] Moreover many organic compounds have appreciable solubility in liquid ammonia, e.g. biphenyl has a moderate solubility, while anisole is totally miscible with liquid ammonia.[9] The nitrogen lone pair makes ammonia a good H-bond acceptor and liquid ammonia strongly solvates cations, as evidenced, for example, by ^{23}Na chemical shifts.[10] However, unlike water, it is not a good hydrogen bond donor[11] and does not significantly solvate anions, as shown by the high single ion transfer energies from water.[12] This poor solvation of anions in liquid ammonia is therefore expected to make anionic nucleophiles more reactive but anionic nucleofuges poorer leaving groups compared with similar reactions in water. The normalized donor number (DN^N) of liquid ammonia is 1.52, greater than that of HMPTA (1.0),[13] while its autoprotolysis constant gives a pK_a of 27.6 (25 °C), compared with 14 for water (25 °C).[14]

There is an extensive literature on the physical and chemical properties of liquid ammonia[15] and also on the reduction of organic compounds in alkali metal/ammonia solution[16] and the application of alkali metal amides in liquid ammonia as strong bases in synthesis.[17] However, there is little about the kinetics and mechanisms of aromatic and aliphatic[18] nucleophilic substitution in liquid ammonia. Herein, we report on the latter using substituted benzyl chlorides as the substrate.

Results and Discussion

(i). Ionization of Phenols and Aminium Ions. Liquid ammonia is a basic solvent with a very low self-ionization constant (pK_a = 27.6 at 25 °C)[14] and the ionization of acids in this solvent generates equivalent amounts of the conjugate base and ammonium ion (eq 1).

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

The low dielectric constant of liquid ammonia indicates that most ionic species will be strongly associated in this solvent and conductivity data shows that ion-pairing occurs even at low concentrations and probably larger aggregates form at higher concentrations.[19] There have been several methods used to determine ionization and dissociation constants including spectroscopic, conductivity and NMR,[20] however, to our knowledge, there has been no systematic evaluation of substituent effects on any one class of acids. We are

---

(3) Bentley, T. W.; Jones, R. O.; Kang, D. H.; Koo, I. S. *J. Phys. Org. Chem.* **2009**, *22*, 799–806.

(4) Constable, D. J. C.; Jimenez-Gonzalez, C.; Henderson, R. K. *Org. Process Res. Dev.* **2007**, *11*, 133–137.

(5) (a) Impey, R. W.; Sprik, M.; Klein, M. L. *J. Am. Chem. Soc.* **1987**, *109*, 5900–5904. (b) Goldman, N.; Fellers, R. S.; Brown, M. G.; Braly, L. B.; Keoshin, C. J.; Leforestier, C.; Saykally, R. J. *J. Chem. Phys.* **2002**, *116*, 10148–10163.

(6) Nicholls, D. *Inorganic chemistry in liquid ammonia*; Clark, R. J. H., Ed.; Topic in Inorganic and General Chemistry, Monograph 17; Elsevier Scientific Publishing Company: Amsterdam, 1979.

(7) (a) Billaud, G.; Demortler, A. *J. Phys. Chem.* **1975**, *79*, 3053–3055. (b) Grubb, H. M.; Chittum, J. F.; Hunt, H. *J. Am. Chem. Soc.* **1936**, *58*, 776–776.

(8) Howard, D. H., Jr.; Friedrich, F.; Browne, A. W. *J. Am. Chem. Soc.* **1934**, *56*, 2332–2340.

(9) Smith, H. *Organic Reactions in Liquid Ammonia*; Jander, G., Spandau, H., Addison, C. C., Eds.; Chemistry in Nonaqueous Ionizing Solvents, Vol. 1, Part 2; John Wiley&Sons Inc.: New York, 1963.

(10) Herlem, M.; Popov, A. I. *J. Am. Chem. Soc.* **1972**, *94*, 1431–1434.

(11) For examples, see: (a) Nelson, D. D., Jr.; Fraser, G. T.; Klemperer, W. *Science* **1987**, *238*, 1670–1674. (b) Luehurs, D. C.; Brown, R. E.; Godbole, K. A. *J. Solution Chem.* **1989**, *18*, 463–469. (c) Swift, T. J.; Marks, S. B.; Sayre, W. G. *J. Chem. Phys.* **1966**, *44*, 2797–2801. (d) Tongraar, A.; Kerdcharoen, T.; Hannongbua, S. *J. Phys. Chem. A* **2006**, *110*, 4924–4929.

(12) Marcus, Y. *Pure Appl. Chem.* **1983**, *55*, 977–1021.

(13) Rydberg, J.; Cox, M.; Musikas, C. *Solvent Extraction Principles and Practice*, 2nd ed.; CRC Press: Boca Raton, FL, 2004; Chapter 3, p 101.

(14) Coulter, L. V.; Sinclair, J. R.; Cole, A. G.; Rope, G. C. *J. Am. Chem. Soc.* **1959**, *81*, 2986–2989.

(15) For examples, see: (a) Watt, G. W.; Leslie, W. B.; Moore, T. E. *Chem. Rev.* **1942**, *31*, 525–536. (b) Watt, G. W.; Leslie, W. B.; Moore, T. E. *Chem. Rev.* **1943**, *32*, 219–229. (c) Jorgensen, W. L.; Ibrahim, M. *J. Am. Chem. Soc.* **1980**, *102*, 3309–3315. (d) Kraus, C. A. *Chem. Rev.* **1940**, *26*, 95–104. (d) Schmidt, F. C.; Sottysiak, J.; Kluge, H. D. *J. Am. Chem. Soc.* **1936**, *58*, 2509–2510. (e) Fernelius, W. C.; Bowman, G. B. *Chem. Rev.* **1940**, *26*, 3–48. (f) Jolly, W. A. *Chem. Rev.* **1952**, *50*, 351–361.

(16) For examples, see: (a) Birch, A. J. *Pure Appl. Chem.* **1996**, *68*, 553–556. (b) Schon, I. *Chem. Rev.* **1984**, *84*, 287–297. (c) Fernelius, W. C.; Watt, G. W. *Chem. Rev.* **1937**, *20*, 195–258.

(17) For examples, see: (a) Harris, T. M.; Harris, C. M. *J. Org. Chem.* **1966**, *31*, 1032–1035. (b) Flahaut, J.; Miginiac, P. *Helv. Chim. Acta* **1978**, *61*, 2275–2285. (c) Vaughn, T. H.; Hennion, G. F.; Vogt, R. R.; Nieuwland, J. A. *J. Org. Chem.* **1937**, *2*, 1–22. (d) Baldinger, L. H.; Nieuwland, J. A. *J. Am. Chem. Soc.* **1933**, *55*, 2851–2853.

(18) Ji, P.; Atherton, J. H.; Page, M. I. *J. Chem. Soc., Faraday Discuss.* **2010**, *145*, 15–25.

(19) For details, see: (a) Lagowski, J. J. *Pure Appl. Chem.* **1971**, *25*, 429–456. (b) Cuthrell, R. E.; Fohn, E. C.; Lagowski, J. J. *Inorg. Chem.* **1966**, *5*, 111–114.

(20) For examples: (a) Kraus, C. A.; Bray, W. C. *J. Am. Chem. Soc.* **1913**, *35*, 1315–1434. (b) Badoz-lambling, J.; Herlem, M.; Thiebault, A. *Anal. Lett.* **1969**, *2*, 35–39. (c) Birchall, T.; Jolly, W. L. *J. Am. Chem. Soc.* **1966**, *83*, 5439–5443.

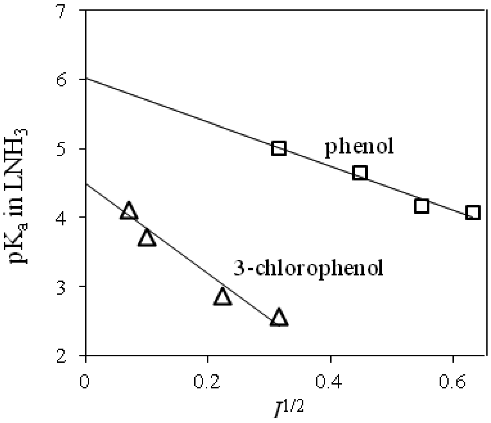


FIGURE 1. Linear relationship between pK_a of phenol and square root of ionic strength in LNH_3 at room temperature.

TABLE 1. pK_a of Phenols in LNH_3 at Room Temperature

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

[a] Aqueous pK_a value is from ref 21.

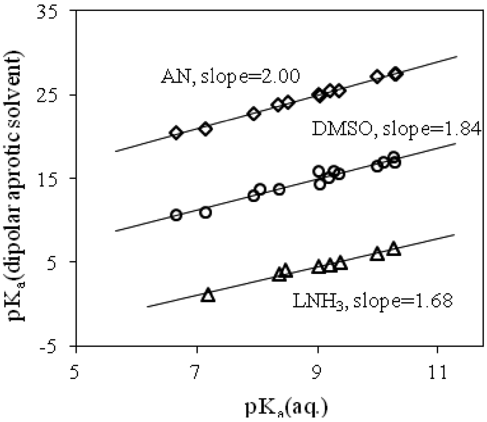


FIGURE 2. pK_a of phenols in liquid ammonia (LNH_3), DMSO and acetonitrile (AN) against their aqueous pK_a.

interested in the relationship between ionization constants in liquid ammonia compared with other solvents and their variation with substituents to aid the interpretation of linear free energy relationships in liquid ammonia.

The ionization of phenols generates anions with a convenient UV absorption and the λ_{max} and ε_{max} of some phenols in liquid ammonia show that that the extinction coefficients of compounds are greater in liquid ammonia compared with those in water and ether under similar conditions. The λ_{max} of phenol, 3-chlorophenol show no difference to those in acidified water, whereas those for 4-cyano, 3,5-dichloro, 2-nitro, 4-nitrophenol exhibit a large bathochromic shift and an intensified absorption, similar to the corresponding spectra in basified water (see Supporting Information Table S1). Therefore, phenols with aqueous $pK_a < 7.0$ are fully ionised in liquid ammonia at room temperature, but not those with $pK_a > 8.5$. Increasing the ionic strength by the addition of salts increases the absorbance at the longer wavelength indicating that the extent of ionization increases. Using this observation and the extinction coefficient of the substituted phenoxide ion and the absorbance at λ_{max} the apparent ionization constant can be calculated. Empirically, we found a reasonable linear relationship between these constants and the square root of the ionic strength (Figure 1) and this allows an estimate of the apparent pK_a (Table 1) for substituted phenols at zero ionic strength (see Supporting Information Table S2−S8, Figure S2−S8). Interestingly, there is a linear relationship between these apparent pK_a values and the corresponding aqueous ones with a slope of 1.68 (Figure 2). This compares with similar plots of the acidity constants in other solvents, for example, those in acetonitrile and DMSO against the corresponding values in water give slopes of 2.00 and 1.84,[22] respectively (Figure 2). This greater dependence of the acidity of phenols on substituents in liquid ammonia compared with water presumably results from the poorer solvation of the phenoxide anions in the nonaqueous solvent so their stability is more dependent on negative charge delocalization through the substituent.

These apparent pK_a's are actually the product of the two constants K_i, for ion pair formation, and K_d, for dissociation to the free ions (eq 1). The degree of dissociation is dependent on the concentration of ammonium ions and the addition of the latter generally decreases the UV absorption of the phenoxide ion which then levels out when only the ion-pair is present. At higher concentrations of ammonium ions, the absorbance then increases again in line with that expected from the ionic strength effect described earlier. The values of K_i and K_d can be approximated from eq 2, where $[ArOH]_t$ is the total amount of phenol present, if it is assumed that the extinction coefficients of the phenoxide-ion are the same in the ion pair and the free ion.

$$\text{Abs.} = \frac{K_i(K_d + [NH_4^+])}{[NH_4^+] + K_i(K_d + [NH_4^+])} \bullet \varepsilon \bullet [ArOH]_t \qquad (2)$$

For example, for 4-carbomethoxy phenol at $I = 0.2$ M (NaCl), $K_i = 0.63\ M^{-1}$ and $K_d = 5.0 \times 10^{-2}$ M. The dissociation constant of the ion-pair to the free ions, K_d, is very dependent on the ionic strength of the medium. For 4-nitrophenol at $I = 0.2$ M (NaCl), $K_i = 1.9\ M^{-1}$ and $K_d = 0.11$ M whereas at low ionic strength (the concentration of ammonium ion added varying from zero to 5×10^{-3} M) $K_i = 5.6\ M^{-1}$ and $K_d = 1.5 \times 10^{-2}$ M. The latter data generates an apparent pK_a for 4-nitrophenol from K_i and K_d of 1.08, in good agreement with the value of 1.10 obtained by extrapolation to zero ionic strength (see Supporting Information Tables S9−12, Figures S9−S12).

Attempts to measure the ionization of aminium ions by examining the effect on the UV absorbance by adding amines to phenols in liquid ammonia were unsuccessful. For example, adding 0.1 M triethylamine to 3-chlorophenol (1 mM) showed an increase of less than 5% in absorption at the λ_{max} of the phenoxide ion, indicating that the pK_a of

---

(21) (a) Jover, J.; Bosque, R.; Sales, J. *QSAR Comb. Sci.* **2007**, *26*, 385–397. (b) Serjeant, E. P.; Dempsey, B. *Ionization Constants of Organic Acids in Aqueous Solution*; Pergamon Press: New York, 1979.

(22) Izutsu, K. *Acid-Base Dissociation Constants in Dipolar Aprotic Solvents*, Blackwell Scientific Publications: Oxford, 1990.

SCHEME 1

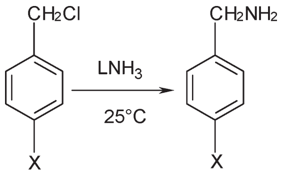


TABLE 2. Pseudo First Order Rate Constants for the Solvolysis of Substituted Benzyl Chlorides in LNH_3 and Water at 25 °C

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

[a] The solvolysis rates were extrapolated data from ref 23. [b] Reference 24. [c] Reference 25. [d] Reference 26; the data is for 80% (v/v) ethanol/water.

triethylammonium ion in liquid ammonia is < -1. The ionization of aminium ions in liquid ammonia were studied using ^{1}H NMR at 25 °C using, as an indicator, the chemical shift differences of the protonated and free base forms of the amine seen in other solvents. Trifluoroethylamine hydrochloride (aqueous pK_a 5.8) is fully deprotonated in liquid ammonia and shows the same ^{1}H NMR spectrum as the free base. Surprisingly, benzylamine hydrochloride (aqueous pK_a 9.33) and piperidine hydrochloride (aqueous pK_a 11.27) also show the same ^{1}H NMR spectrum as their free bases indicating that they also are fully deprotonated in liquid ammonia (see Supporting Information Tables S13−S15). The equilibrium (eq 3) must lie well over to the right, suggesting that ammonia solvent stabilizes the ammonium ion (NH_4^+) more than the aminium ions (RNH_3^+).

$$RNH_3^+ + NH_3 \overset{K}{\rightleftharpoons} RNH_2 + NH_4^+ \qquad (3)$$

Although all amines exist effectively solely in their free base form in liquid ammonia, as will be discussed later their nucleophilic reactivity still varies with their aqueous basicities.

(ii). Solvolysis of 4-Substituted Benzyl Chlorides. The solvolysis of substituted benzyl chlorides in liquid ammonia[18] gives the corresponding benzylamines (Scheme 1) and the pseudo first order rate constants show little or no dependence of on the substituent (Table 2). This is very different from hydrolysis in water where the hydrolysis rates increase by about 7 orders of magnitude on going from 4-nitrobenzyl chloride to 4-methoxybenzyl chloride (Table 2). The rates of solvolysis in liquid ammonia are generally faster than those in water, but the difference decreases with electron-donating substituents so that 4-methoxybenzyl chloride is more reactive in water than in liquid ammonia. There is no clear consensus on the mechanism of hydrolysis of benzyl halides in water and aqueous binary solvents, although that for 4-methoxybenzyl halides is certainly an S_N1 mechanism with the intermediate formation of a carbocation,[24,27] and that for the 4-nitro derivative is claimed to be S_N2.[28] The rate of solvolysis in liquid ammonia is retarded dramatically when the methylene hydrogen of benzyl chloride in the α-position is replaced by a methyl group; α-methyl benzyl chloride is solvolysed about 130 times *slower* than benzyl chloride. This is strong evidence for solvolysis occurring by an S_N2 mechanism due to a more sterically hindered transition state. Furthermore, α-methyl 4-methoxybenzyl chloride, which undergoes solvolysis by the unimolecular mechanism in protic solvents,[29] is solvolysed nearly at the same rate as benzyl chloride in liquid ammonia, but about 1600 and 400 times slower than in 80% (v/v) ethanol/water and 100% methanol at 25 °C, respectively.[26] This indicates that, even with activated benzyl chloride derivatives, the solvolysis of these compounds in liquid ammonia proceeds through a concerted bimolecular mechanism.[18] The activation parameters for the solvolysis of substituted benzyl halides in liquid ammonia are significantly different from those in water (Table 3, Supporting Information Tables S16 to S20, Figures S13 to S17). Very large negative entropies of activation ($\Delta S^{\ddagger}$) are observed for the solvolysis of all substituted benzyl chlorides in liquid ammonia, indicative of a restricted activated complex relative to the reactant and a bimolecular concerted S_N2 mechanism for all derivatives. Bimolecular nucleophilic substitution processes are usually characterized by large negative entropies of activation of -90 and -120 J K^{-1} mol^{-1} due to the loss of translational and rotational entropy of the reactants and the development of charge in the transition state leading to solvent restriction.[31] By contrast the $\Delta S^{\ddagger}$ for a typical hydrolytic reaction which follows the S_N1 mechanism is often positive, e.g. the $\Delta S^{\ddagger}$ of the hydrolysis of *t*-butyl chloride[32] is about 50 J K^{-1} mol^{-1}. The additional methyl group on the α-position of benzyl chloride increases $\Delta H^{\ddagger}$ of the reaction significantly in liquid ammonia (Table 3), as expected from a more sterically hindered reaction in a bimolecular process.

Fission of the C−Cl bond is expected to be easier in water than in liquid ammonia. Compared with liquid ammonia, the C−Cl bond of benzyl chloride is presumably more polarized in water due to the latter's greater hydrogen bond donating ability. Although liquid ammonia is generally described[33] as a protic solvent, like water, with good hydrogen bond donor (HBD) and acceptor (HBA) ability, there is very little evidence to support this assertion. It actually has a very limited HBD ability, not only in the gas phase but also in

---

(23) (a) Hyne, J. B.; Wills, R.; Wonkka, R. E. *J. Am. Chem. Soc.* **1962**, *84*, 2914–2919. (b) Tommila, E. *Acta Chem. Scand.* **1966**, *20*, 923–936. (c) Kwun, O. C.; Kyong, J. B.; Choi, K. J. *J. Korean. Chem. Soc.* **1986**, *30*, 301–306. (d) Kwun, O. C.; Kim, J. R.; Ryu, J. C. *J. Korean. Chem. Soc.* **1981**, *25*, 152–159.

(24) Bentley, T. W.; Koo, I. S.; Norman, S. J. *J. Org. Chem.* **1991**, *56*, 1604–1609.

(25) Fainberg, A. H.; Winstein, S. *J. Am. Chem. Soc.* **1957**, *79*, 1957–1602.

(26) Liu, K. T.; Duan, Y. F.; Hou, S. J. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2181–2185.

(27) For examples, see: (a) Chung, D. S.; Kim, C. K.; Lee, B. S.; Lee, I. *Tetrahedron* **1993**, *49*, 8359–8372. (b) Kevill, D. N.; Ismail, N. H. J.; D'Souza, M. J. *J. Org. Chem.* **1994**, *59*, 6303–6312.

(28) For examples, see: (a) Fujio, M.; Susuki, T.; Goto, M.; Tsuji, Y.; Yatsugi, K.; Kim, S. H.; Ahmed, G. A. W.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 673–682. (b) Dietze, P.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 5880–5886.

(29) For examples, see: (a) Liu, K. T.; Chang, L. W.; Yu, D. G.; Chen, P. S.; Fan, J. T. *J. Phys. Org. Chem.* **1997**, *10*, 879–884. (b) Shiner, V. J., Jr.; Buddenbaum, W. E.; Murr, B. L.; Lamaty, G. *J. Am. Chem. Soc.* **1968**, *90*, 418–426. (c) Traylor, T. G.; Ware, J. C. *J. Am. Chem. Soc.* **1967**, *89*, 2304–2315.

(30) Scott, J. M.; Robertson, R. E. *Can. J. Chem.* **1972**, *50*, 167–175.

(31) Page, M. I. *Chem. Soc. Rev.* **1973**, *2*, 295–323.

(32) Winstein, S.; Fainberg, A. H. *J. Am. Chem. Soc.* **1957**, *79*, 5937–5950.

(33) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH, Verlag GmbH & Co. KGaA: Weinheim, 2003.

TABLE 3. Activation Parameters for Solvolysis of Substituted Benzyl Chlorides in LNH_3 and Water at 25 °C

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

[a] Activation parameters for 4-substituted benzyl chlorides were extrapolated from refs 23, 24, and 30; the data for 4-methyoxybenzyl chloride were for 20% (v/v) methanol in water; the data for α-methyl benzyl chloride were from ref 25.

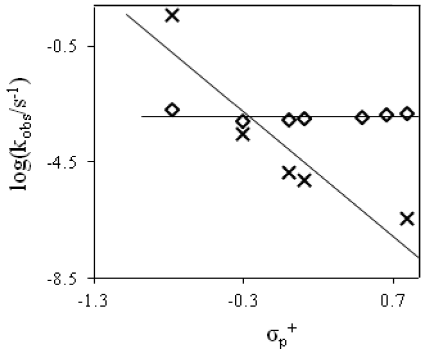


FIGURE 3. Hammett plot for the solvolysis of 4-substituted benzyl chlorides in LNH_3 (◊) and water (×) at 25 °C.

the condensed phase,[11] and anions are poorly solvated in liquid ammonia. Expulsion of the chloride anion is thus expected to be more difficult in liquid ammonia than in water and so the probability of a unimolecular mechanism is less with the necessity of more "push" required from the incoming nucleophile. Contrary to commonly accepted views, it appears that liquid ammonia acts more like a dipolar aprotic solvent in nucleophilic substitution reactions.

As noted earlier, there is surprisingly little or no dependence of the rate of solvolysis of benzyl chlorides in liquid ammonia upon ring substituents, again in contrast to that in water (Table 2). Consequently the Hammett plot for the solvolysis in liquid ammonia is very different from that in water (Figure 3), the ρ value for the reaction in liquid ammonia is zero, while that in water, although not ideally linear, shows $\rho = -4.32$. These different values suggest that for the solvolysis of benzyl chlorides in liquid ammonia there is little or no charge developed on the central carbon atom in the transition state with any charge developed due to partial fission of the bond to the leaving group being counterbalanced by an equal transfer of charge from the incoming nucleophile.

Due to the poorer solvation of the leaving group chloride anion in the solvolysis of benzyl chloride in liquid ammonia, compared with that in water, the unimolecular S_N1 mechanism is unfavorable. Even though chloride ion is not a particularly good hydrogen bond acceptor, it may have been anticipated that ammonium ions may facilitate chloride ion expulsion but added ammonium chloride acts simply as a salt effect. The pseudo first order rate constants for the solvolysis of 4-methoxybenzyl chloride in liquid ammonia do increase linearly with increasing concentration of ammonium chloride but not significantly more than that with potassium perchlorate (Table 4). The effect is not as marked as that for a typical S_N1 reaction, for which the rate often increases exponentially[34]and is probably due to the increased solvent ionizing power which stabilizes the transition state of the reaction in liquid ammonia. The expulsion of the leaving group chloride ion is facilitated by increasing its solubility in liquid ammonia, similar to the effect seen by increasing ionic strength increasing the ionization constants for phenols.

The stereochemical consequences of aliphatic nucleophilic substitutions are classic criteria for mechanisms. Based on a racemised product, Ingold[35] claimed that the solvolysis of α-methyl benzyl chloride in liquid ammonia at room temperature occurs completely through a unimolecular path. However, in our hands the synthesis of enantiomerically pure α-methyl benzyl chloride proved to be difficult; α-methyl benzyl alcohol racemises during the chlorination process and also during the silica gel purification step.[35,36] The best result we achieved was only about 40% ee chloride and enantiomeric synthesis via tosylation, mesylation, phosphorylation of α-methyl benzyl alcohol all proved to be unsuccessful. 1-Phenyl ethyl acetate proved to be very inert toward nucleophilic attack by ammonia and no reaction was observed after 2 h at 45 °C in liquid ammonia, and the lack of formation of acetamide is also consistent with our previous observation[18] that alkyl esters solvolyse slowly in liquid ammonia.

Complete inversion of configuration of 38% ee S-α-methyl benzyl chloride was observed during the solvolysis to give 38% ee R-enriched α-methyl benzylamine (Scheme 2) with almost 100% yield after the reaction reached completion and no elimination product was found. This is another strong indication that the solvolysis of primary and secondary aliphatic halides in liquid ammonia follows an S_N2 mechanism.

It is of interest to determine the degree of inversion not only in liquid ammonia but also in aqueous liquid ammonia solutions to see if any adventitious water would compromise the use of liquid ammonia as a solvent for large scale enantiomeric synthesis. However, there is little indication that significant racemisation occurs with increasing water content. The solvolysis of 41% ee S-α-methyl benzyl chloride gives a slightly reduced ee of R-α-methyl benzylamine in 10, 20 and 30% water−ammonia solution (see Supporting Information

---

(34) Hojo, M.; Ueda, T.; Inoue, S.; Kawahara, Y. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1735–1740.

(35) Hughes, E. D.; Ingold, C. K.; Scott, A. D. *J. Chem. Soc.* **1937**, 1201–1208.

(36) For examples, see: (a) Flores-Parra, A.; Suarez-Moreno, P.; Sanchez-Ruiz, S. A.; Tlahuextl, M.; Jaen-Gaspar, J.; Tlahuext, H.; Salas-Coronado, R.; Cruz, A.; Noth, H.; Contreras, R. *Tetrahedron Asymm.* **1998**, *9*, 1661–1671. [20% ee]. (b) Durrat, F.; Sanchez, M. V.; Couty, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2008**, *19*, 3286–3297. (c) Ashby, E. C.; DePriest, R. N.; Goel, A. B.; Wenderoth, B.; Pham, T. N. *J. Org. Chem.* **1984**, *49*, 3545–3556. [57% ee]. (d) Mangold, J. B.; Abdel-Monem, M. M. *J. Med. Chem.* **1983**, *26*, 66–71. [79.8% ee, but a different synthetic route].

TABLE 4. **Rate Constants for the Solvolysis of 4-Methoxybenzyl Chloride in Presence of $KClO_4$ in LNH_3 at 25 °C**

concentration of salt (M)	0	0.5 M		1.0 M	
		$KClO_4$	NH_4Cl	$KClO_4$	NH_4Cl
solvolysis rate (s^{-1})	1.91×10^{-3}	2.69×10^{-3}	3.37×10^{-3}	3.94×10^{-3}	4.66×10^{-3}

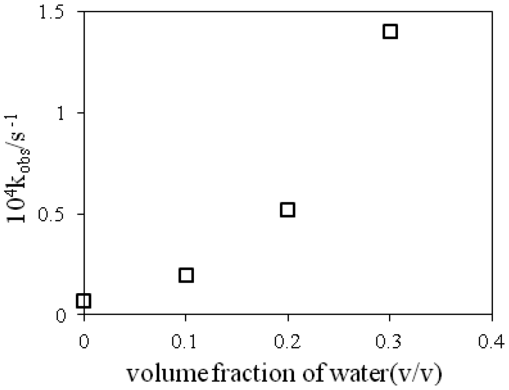
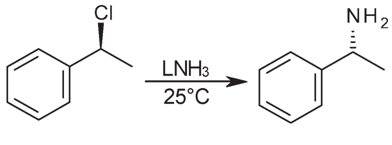


FIGURE 4. Increasing of the solvolysis rate of α-methyl benzyl chloride with increasing volume fraction of water in water–ammonia solution.

SCHEME 2



SCHEME 3

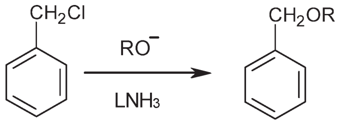


Table S21). The increasing water content could facilitate the expulsion of chloride due to better solvation from water and the rate of solvolysis does increase exponentially with the increasing of water content in the reaction system (Figure 4), the half-life decreases from 29 h in pure liquid ammonia to 3.7 h in 10% water, however, even in 10% water–ammonia there is little or no competing hydrolysis, with less than 1% of alcohol produced (see Supporting Information Table S22). In general, the rate of solvolysis of α-methyl benzyl chloride dramatically increases with increasing content of water in aqueous binary organic solvents,[25,37] presumably with the driving force coming from the solvation difference of leaving chloride anion, as shown by the large positive Gibbs transfer energy of chloride anion from water to ammonia or DMSO.[12,38]

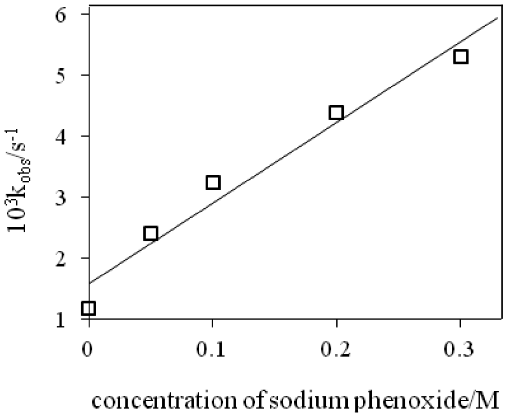


FIGURE 5. First order dependence upon the concentration of sodium phenoxide of the nucleophilic substitution of benzyl chloride with phenoxide anion in LNH_3 (I = 0.3 M, $KClO_4$) at 25 °C.

TABLE 5. **Second Order Rate Constants of the Reactions between 4-Substituted Phenoxide and Alkoxide Ions with Benzyl Chloride in LNH_3 at 25 °C**

phenoxide/alkoxide ion	pK_a (aq.) [a]	pK_a (LNH_3)	$10^2\ k_{2,LNH3}$ ($M^{-1}s^{-1}$)
4-cyanophenoxide	7.95	2.71	0.077
4-carbomethoxyphenoxide	8.47	4.04	0.273
4-chlorophenoxide	9.20	4.69	0.95
phenoxide	9.99	6.02	2.01
4-methoxyphenoxide	10.27	6.62	3.97
4-^{t}butylphenoxide	10.31	6.67	3.19
benzyloxide[b]	15.0	–	45.6
methoxide[b]	15.5	–	20.1

[a] Corresponding aqueous pK_a's of phenols and alcohols are from refs 21 and 42. [b] Solubility of sodium alkoxides in liquid ammonia at room temperature is very poor. The rate for methoxide and benzyloxide with benzyl chloride was measured by adding 2.5 equivalents of the corresponding alcohol (the total alcohol volume added is less than 3.5% v/v) in order to give a homogeneous solution. There is no reaction between the alcohols and benzyl chloride in liquid ammonia at 25 °C.

(iii). Nucleophilic Substitution with Oxygen Nucleophiles. A variety of oxygen nucleophiles react with benzyl chloride in liquid ammonia to give the corresponding substitution products (Scheme 3), although solvolysis is sometimes competitive with these reactions and a mixture of products is obtained. The kinetics of nucleophilic substitution was determined under pseudo first order conditions with an 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 under constant ionic strength (Figure 5, Supporting Information, Table S23). The slope of these plots gives the corresponding second order rate constants. This first order dependence of the pseudo first order constants on the concentration of the nucleophile supports the conclusion from solvolysis kinetic data that these reactions follow a bimolecular S_N2 type mechanism.

---

(37) The rate enhancement with increasing water content in aqueous binary organic solvents is far more pronounced than in aqueous liquid ammonia solution, which indicates a change of reaction mechanism from bimolecular to unimolecular. For details and discussions, see: Anantaraman, R.; Saramma, K. *Can. J. Chem.* **1967**, *4*, 1770–1777.

(38) For examples, see: (a) Marcus, Y.; Kamlet, M. J.; Tafts, R. W. *J. Phys. Chem.* **1988**, *92*, 3613–3622. (b) Parker, A. J. *Quart. Rev. Chem. Soc.* **1962**, *16*, 163–187.

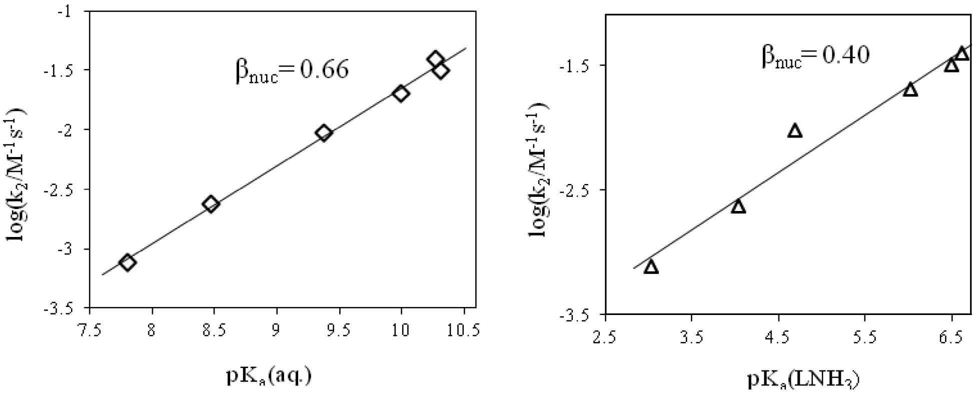


FIGURE 6. Brønsted plots for the para substituted phenoxides react with benzyl chloride in LNH_3 at 25 °C.

There is a large rate enhancement of about 10^4-fold for the reaction of methoxide ion with benzyl chloride in liquid ammonia compared with that in methanol.[39] The second order rate constants for the nucleophilic substitution of benzyl chloride by phenoxide ion are similar in liquid ammonia and DMF, a typical dipolar aprotic solvent, and are about 5000 times greater than that in methanol (Table 5).[40] The rate increase on going from protic to dipolar aprotic solvents is attributable to specific solvation through hydrogen bonding of anionic nucleophiles in protic solvents, which decreases their activity as nucleophiles due to the large desolvation energy required on going from initial state to the transition state.[41] This is also shown by the large positive Gibbs transfer energies of anions from protic solvents to nonpolar and dipolar aprotic solvents.[38] On the other hand, some dipolar aprotic solvents strongly favor the solvation of cations due to the availability of electron donation from a solvent molecule's lone pair, which can lead to the destruction ion pairs and thus an increased nucleophilicity of the counteranion. One of main reasons for dipolar aprotic solvents favoring bimolecular concerted over a unimolecular mechanisms lies in their poor solvation of the leaving anion.

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

The rates of reaction of substituted phenoxides with benzyl chloride in liquid ammonia are generally several thousand-fold greater than those in methanol and water. The second order rate constants for substituted phenoxide ions reacting with benzyl chloride in liquid ammonia vary significantly with substituents (Table 5). The rate difference between 4-cyano and 4-methoxy phenoxide ion reactions is about 40-fold in liquid ammonia, whereas, in methanol or alcoholic solvent, the rate is insensitive to the substituent.[44] The Brønsted plot for the rate constants in liquid ammonia using the aqueous pK_a of the phenol shows a very good linear free energy relationship (Figure 6) with a $\beta_{nuc} = 0.66$.

There is a linear relationship between the ionization of substituted phenols in liquid ammonia and those in water, the slope of a plot of the pK_a of the former against the corresponding aqueous pK_a is 1.68 (Figure 1). Hence a more meaningful Brønsted β_{nuc} for the substituted phenoxides reacting with benzyl chloride in LNH_3 is 0.40. The latter value indicates the transfer of some negative charge from the attacking phenoxide anion to the benzyl group and the leaving chloride ion and partial bond formation between the phenoxide oxygen and the benzylic carbon in the transition state. The β_{nuc} of the analogous reaction in methanol is 0.28,[45] suggesting an earlier type of transition state with a smaller fraction of charge transferred from oxygen to carbon in this solvent. The solvation ability of a solvent is not only a function of its dielectric constant and dipole moment, but also of its ability to donate protons or electrons. Although the dielectric constant and dipole moment of liquid ammonia are much less than those for common dipolar aprotic and protic solvents, the enhanced rate of reaction between anionic O-nucleophiles and alkyl halides in liquid ammonia compared with alcoholic solvents is probably due to the poor solvation of anions in the former compared with the latter and good solvation of the anion's countercation from the ammonia lone pair, thus decreasing ion-pair formation.

In order to obtain a more detailed picture of the transition state structure the rates of reaction of phenoxide ion with substituted benzyl chlorides were measured. A plot of the second order rate constants against the Hammett constant for the substituent (Figure 7, Supporting Information Table 24) is linear apart from the typical deviation for 4-methoxybenzyl chloride.[46] The latter is not due to a change in

---

(39) For details, see: (a) Vlasov, V. M. *Russ. Chem. Rev.* **2006**, *75*, 765–796. (b) Tsai, Y. H. Nucleophilic displacement reactions of benzyl chlorides, Ph.D thesis, University of Ottawa, 1968.

(40) Fang, Y.; Lai, Z.; Westaway, K. C. *Can. J. Chem.* **1998**, *76*, 758–764.

(41) For examples, see: (a) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1–32. (b) Miller, J.; Parker, A. J. *J. Am. Chem. Soc.* **1961**, *83*, 117–123. (c) Cox, B. G. *Morden Liquid Phase Kinetics, in Oxford Chemistry Primers*; Compton, R. G., Ed.; Oxford University Press: New York, 1994.

(42) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795–798.

(43) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1953; pp 346–350.

(44) For details, see: (a) Breslow, R.; Groves, K.; Mayer, M. U. *Org. Lett.* **1999**, *1*, 117–120. (b) Madhavan, K.; Srinivasan, V. S.; Venkatasubramanian, N. *Proc. Indian Aead. Sci.* **1979**, *88*, 329–335.

(45) $\beta_{nuc} = 0.28$ in methanol ($r^2 = 0.9310$) and 0.17 in 2-propanol/water [(%v/v) = 1:1] ($r^2 = 0.9859$) system at 25 °C. For details, see ref 44.

(46) For examples, see: (a) Fuchs, R.; Carlton, D. M. *J. Org. Chem.* **1962**, *27*, 1520–1523. (b) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 3288–3294. (c) Tsuno, Y.; Fujio, M. The Yukawa-Tsuno Relationship in Carbocationic Systems. *Advanced Physics and Organic Chemistry*; Bethell, D., Ed.; Elsevier Scientific Inc.: New York, 1999; Vol. 32, pp 267–385.

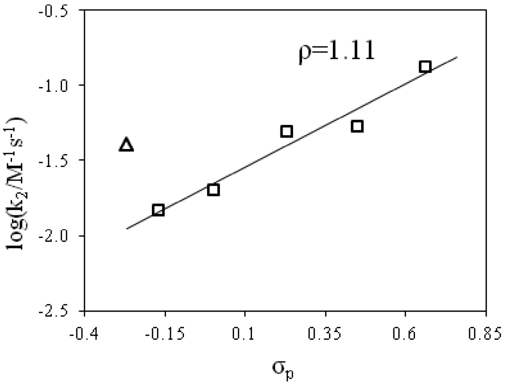


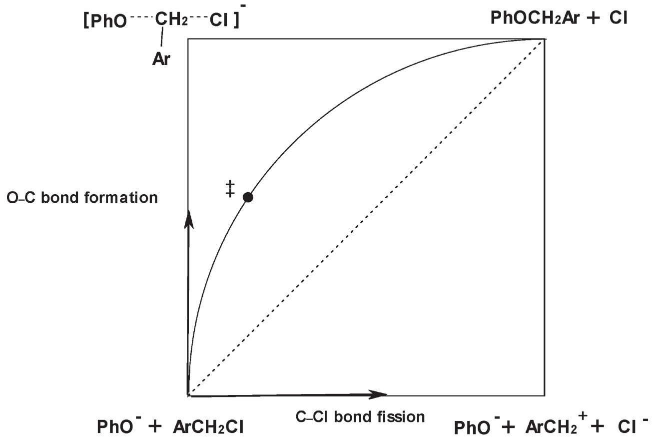
FIGURE 7. Hammett plot for the reaction between 4-substituted benzyl chloride with phenoxide anion in LNH_3 at 25 °C, opened triangle (△) shows the positive deviation of 4-methoxybenzyl chloride.

mechanism from S_N2 to S_N1 as the kinetics are still clearly first order in phenoxide ion. The most likely explanations are either: (i) a change in the structure of the transition state for a single mechanism but with a differing degree of bond formation and cleavage, so that the 4-methoxy derivative causes a shift to a transition state with more positive charge on the central carbon atom[46a] or (ii) a single transition state structure but with the 4-methoxy substituent stabilizing the transition state with a different balance of polar and resonance effects.[46b,c] The ρ value of 1.11 for the reaction of phenoxide ion with 4-substituted benzyl chlorides, excluding the 4-methoxy derivative (Figure 7), suggests that appreciable charge has been transferred from phenoxide oxygen to benzylic carbon in the transition state and which is more than that lost to the departing chloride ion. The ρ value of 1.11 contrasts markedly with that of zero for the solvolysis reaction. Overall the transition state structure for phenoxide-ion substitution is negatively charged compared with a neutral one for solvolysis so it is not surprising that the rate with phenoxide-ion is enhanced by electron-withdrawing groups.

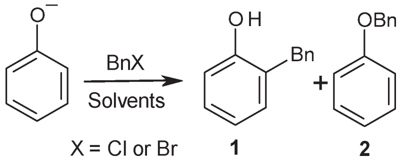
The changes in transition state structure can be envisaged on a Jencks-More O'Ferrall reaction coordinate-energy diagram (Scheme 4) with separate axes for O−C and C−Cl bond formation and cleavage, respectively. The Hammett and Brønsted plots indicate that most of the negative charge is distributed between the attacking phenoxide oxygen and the benzylic methylene and aromatic ring with little transferred to the leaving chloride anion, therefore, there is relatively little C−Cl bond fission in the transition state.

Phenoxide ion is a well-known ambident nucleophile[47] and it can undergo both C- and O-alkylation (Scheme 5) and which reaction dominates depends very much on the medium. In liquid ammonia, with 0.3 M sodium phenoxide and 0.1 M benzyl chloride there is less than 0.5% solvolysis product and no C-alkylated product (**1**) formed, giving a selectivity for O-alkylation (**2**) of almost 100% within half an hour. In diethyl ether as solvent, under heterogeneous conditions, the reaction between benzyl bromide and phenoxide ion, after 3 days at 35 °C, the major product (75%) is the C-alkylated one.[47] Presumably, the differing solvation of the phenoxide anion, including tight ion-pair formation, affects the relative negative charge density on oxygen and the ring carbons as well as the stability of the two transition states leading to C-alkylation in ether and protic solvents.

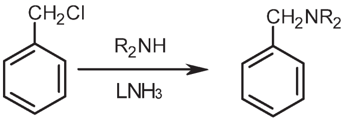
SCHEME 4



SCHEME 5



SCHEME 6



(iv). Nucleophilic Substitution with Nitrogen Nucleophiles. The background solvolysis reaction in liquid ammonia obviously involves nucleophilic attack by a nitrogen nucleophile, but benzyl chloride also reacts with secondary amines in liquid ammonia to give predominantly the substituted product (Scheme 6). The pseudo first order rate constants for the aminolysis of benzyl chloride and the reactions of benzyl chloride with nitrogen anionic nucleophiles were obtained by the general sampling method and measuring the formation of the product and the disappearance of the reactant by GC analysis.

The reaction between benzyl chloride and neutral amines may give neutral or charged products depending on the pK_a of the product relative to the ammonia solvent. Although the overall charge of the transition state structure is neutral, charge is created on the N-nucleophile during the formation of the activated complex, assuming no general base catalysis by the solvent. The differences in solvation of the reactant amines by aprotic and dipolar aprotic solvents is not as marked as for anions and the rate differences between protic and dipolar aprotic solvents is not so pronounced as that seen for anionic oxygen nucleophiles.

There is a first order dependence on the concentration of the amine of the pseudo first order rate constant for the aminolysis of benzyl chloride by morpholine (Figure 8,

---

(47) (a) Kornblum, N.; Lurie, A. P. *J. Am. Chem. Soc.* **1959**, *81*, 2705–2715. (b) Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* **1963**, *85*, 1148–1154.

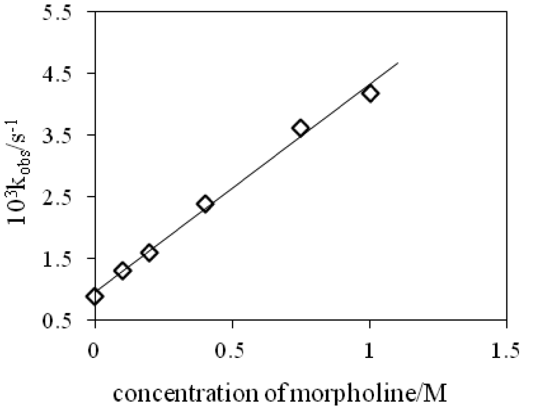


FIGURE 8. First order dependence of rate for the substitution of benzyl chloride by morpholine on the concentration of amine in LNH_3 at 25 °C.

TABLE 6. Second Order Rate Constants for Benzyl Chloride with Various N-Nucleophiles in LNH_3 at 25 °C

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

[a] Corresponding aqueous pK_a's of amines are from refs 21 and 48. [b] Hydrazine dihydrochloride (1 M) was used.

Supporting Information Table S25), which again confirms that these reactions follow a bimolecular S_N2 type mechanism. The rate constant for hydrazine was obtained by adding 1 M hydrazine dihydrochloride to liquid ammonia to generate the free base and so to correct for the effect of 2 M NH_4Cl produced from 1 M $N_2H_6Cl_2$, the rate of solvolysis of benzyl chloride with was measured in the presence of 2 M NH_4Cl ($k_{obs} = 3.42 \times 10^{-3}\ s^{-1}$) and the derived second order rate constant (Table 6) is that for ionic strength 2.0 M. There is no reaction of neutral imidazole or triazole with benzyl chloride in liquid ammonia, but there is with their anionic salts, indicating that these anions remain deprotonated in liquid ammonia.

The second order rate constants for the aminolysis of benzyl chloride with various amines (Table 6) generate a reasonable Brønsted plot using the aqueous pK_a of the amine to give a β_{nuc} of 0.21 (Figure 9). This plot includes both neutral and negatively charged amines and yet both types give a reasonable single plot. Given the work described earlier which showed that all amines exist in their free base unprotonated form in liquid ammonia it is not possible to evaluate a Brønsted plot using the pK_a of the aminium ions in this solvent. Nonetheless, the apparent value of 0.21 using the aqueous pK_a does indicate that there is some dependence on the basicity of the amine nucleophile, but much less than that for oxygen nucleophiles suggesting a transition state with little charge developed on the amine nitrogen in the transition state or charge removal in the case of negatively charged amine anions.

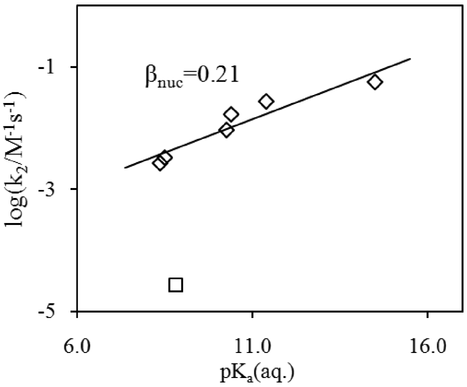


FIGURE 9. Brønsted plot for the substitution of benzyl chloride by various amines in LNH3 at 25 °C, ammonia (□) is negatively deviated from the line.

The second order rate constant for ammonia shows a large negative deviation from the Brønsted plot explaining why aminolysis by amines is easily observed in liquid ammonia. This could result from the attack of a secondary amine on benzyl chloride which converts a weakly solvated nucleophile to a more strongly solvated one due to hydrogen bond donation from the partially positively charged R_2NH^+ in the transition state compared with three from ammonia, resulting in either a considerable energetic cost in terms of solvent reorganization or a lack of hydrogen bond stabilization/solvation, making ammonia less reactive. Conversely, the rate constant for azide ion shows a large positive deviation, although it is only about 150-fold[41a] greater in liquid ammonia than that in methanol. This relatively modest rate difference is in sharp contrast to the 2500-fold rate enhancement for phenoxide anion and benzyl chloride in liquid ammonia compared with that in methanol.[40] Presumably, the difference in solvation energies of azide anion in liquid ammonia and methanol is relatively smaller than that of phenoxide ion.

1,2,4-Triazolate and benzotriazolate anions are widely used in the agriculture and pharmaceutical industries[49] and, as they are ambident nucleophiles,[50] the regioselectivity of their nucleophilic reactions is important. In liquid ammonia, in a few hours, the major product of equimolar reaction between benzyl chloride and sodium triazolate is 1-benzyl-1,2,4-triazole (**3**) rather than 4-benzyl-1,2,4-triazole (**4**) in a ratio of 12: 1 (Scheme 7). Previous studies of this reaction in other solvents, often under heterogeneous conditions, preferentially also gives 1-substituted triazole products, but with much lower selectivity and longer reaction times.[51]

Also 1-benzyl-1,2,3-benzotriazole is the main product of the reaction of 0.1 M benzotriazolate and benzyl chloride

---

(48) Tehan, B. G.; Lloyd, E. J.; Wong, M. G.; Pitt, W. R.; Gancia, E.; Manallack, D. T. *Quant. Struct. Act. Relat.* **2002**, *21*, 473–485.

(49) For examples, see: (a) Wamhoff, H. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 5. (b) Poyla, J. P. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press, Oxford, 1984; Vol. 5. (c) Kartritzky, A. R.; Chang, H. X.; Yang, B. *Synthesis* **1995**, *5*, 503–505.

(50) For examples of 1,2,4-triazolate as an ambident nucleophile, see: (a) Potts, K. T. *Chem. Rev.* **1961**, *61*, 87–127. (b) Bentley, T. W.; Jones, R. V. H.; Wareham, P. J. *Tetrahedron Lett.* **1989**, *30*, 4013–4016. (c) Sano, S.; Tanba, M.; Nagao, Y. *Heterocycles* **1984**, *38*, 481–486. For examples of benzotriazolate as an ambident nucleophile, see: (d) Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. *J. Chem. Res.* **2004**, 344–346.

(51) (a) Begtrup, M.; Larson, P. *Acta Chem. Scand.* **1990**, *44*, 1050–1057. (b) Smith, K.; Small, A.; Hutchings, M. *Chem. Lett.* **1990**, 347–350.

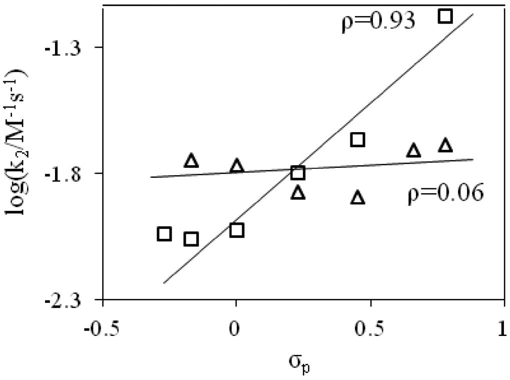
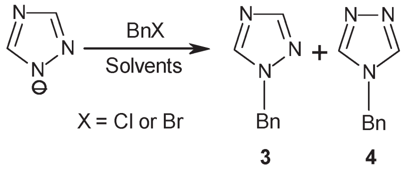
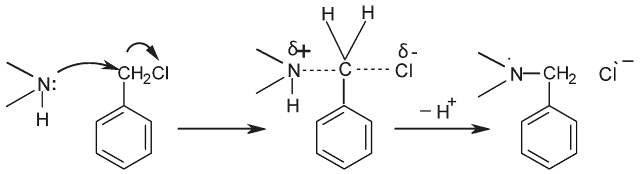


FIGURE 10. Hammett plot for the reaction between 4-substituted benzyl chloride with piperidine (△) and triazolate anion (□) in LNH_3 at 25 °C.

SCHEME 7



SCHEME 8



in liquid ammonia at 25 °C. The rate of reaction between hydrazine and benzyl chloride with 2 M NH_4Cl does not show a pronounced α-effect, in common with its general reactivity for nucleophilic attack at sp^3 carbon centers.[52]

In order to see if the difference in the susceptibility of the rate of nucleophilic substitution to the substituent in substituted benzyl chlorides between solvolysis (Hammett $\rho = 0$) and phenoxide-ion ($\rho = 1.11$) is a function of basicity, charge or nature of the attacking nucleophilic element (O vs N), the rate constants for the reaction of piperidine and triazolate with 4-substituted benzyl chloride were determined. A Hammett plot of the second order rate constants (see Supporting Information Tables S26–S27) again shows the typical deviation for 4-methoxybenzyl chloride (Figure 10). Interestingly the reaction with the neutral amine piperidine is insensitive to the para-substitutent in benzyl chloride, similar to that seen for solvolysis. By contrast, the ρ value for the triazolate anion with 4-substituted benzyl chloride is 0.93, similar to that seen with phenoxide anion. It appears that the increased sensitivity to aromatic ring substituents is due to the requirement to accommodate a negative charge in the transition state.

Conclusions

The ionization constants of phenols ions in liquid ammonia are the product of those for ion-pair formation and dissociation to the free ions which can be separated by evaluating the effect of added ammonium ions. There is a linear relationship between the pK_a of phenols in liquid ammonia and those in water of slope 1.68. Aminium ions exist in their unprotonated free base form in liquid ammonia.

Liquid ammonia acts like a typical dipolar aprotic solvent in its effect on aliphatic nucleophilic substitution reactions. The activation parameters, substituent and salt effects, and the stereochemistry all indicate that the mechanism of solvolysis and of aminolysis with neutral amines of benzyl chlorides in liquid ammonia is forced to be a concerted S_N2 mechanism proceeding through a transition state structure that has little charge development on the incoming nucleophile and the departing nucleofuge and little or no change in charge on the central benzylic carbon compared with that in the reactant state (Scheme 8).

On the other hand, the transition state of nucleophilic substitution between O-anions and benzyl chloride has an unsymmetrical transition structure with a relatively appreciable transfer of negative charge from the anion to the carbon center and very little charge on the nucleofuge. The concerted mechanism is probably largely due to the difficulty of expelling a leaving group anion in liquid ammonia and enhanced nucleophilicity of nucleophiles in this solvent. These observations show that the reactivity of the nucleophile and the nucleofugality of the leaving group can greatly affect the transition structure of the aliphatic nucleophilic substitution reaction in liquid ammonia. The high selectivity of O-alkylation of phenol and of 1-alkylation of 1,2,4-triazole in liquid ammonia may be of industrial interest.

Experimental Section

Materials. Liquid ammonia was purchased from a commercial source, 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 buret, no further purification procedure was made before using as reaction solvent. All chemicals and solvents were purchased from commercial suppliers and used directly without further purification except where otherwise noted. (1*S*,2*S*)-(+)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (*S*,*S*-TsDPEN, 99.5%) was from Johnson Matthey Catalysis & Chiral Technologies. Benzyl azide,[53] *N*-benzylpyrrolidine, *N*-benzylpiperidine and *N*-benzylmorpholine,[54] 1-benzyl-1,2,4-triazole, 4-benzyl-1,2,4-triazole,[55] and 1-benzylimidazole[56] were prepared and purified by general flash column chromatography methods. Sodium phenoxides, sodium triazolate and sodium benzotriazolate were prepared according to the references.[57](*S*)-α-methyl benzyl alcohol and (*S*)-α-methyl benzyl chloride were prepared according to the literature.[58]

---

[52] Buncel, E.; Um, I. K. *Tetrahedron* **2004**, *60*, 7801–7825. and references cited therein.

[53] Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413–414.

[54] García, R.; Gómez-Hortigüela, L.; Díaz, I.; Sastre, E.; Pérez-Pariente, J. *Chem. Mater.* **2008**, *20*, 1099–1107.

[55] Claramunt, R. M.; Elguero, J.; Garceran, R. *Heterocycles* **1985**, *23*, 2895–2906.

[56] Owen, C. P.; Dhanani, S.; Patel, C. H.; Shahid, I.; Ahmed, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4011–4015.

[57] For the preparation of phenoxides, see: Kunert, M.; Dinjus, E.; Nauck, M.; Sieler, J. *Chem. Ber./Recueil* **1997**, *130*, 1461–1465. For the preparation of triazolates, see: Kazhemekaite, M.; Yuodvirshis, A.; Vektarene, A. *Chem. Heterocycl. Compd.* **1998**, *34*, 252–253.

[58] Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1991**, *118*, 2521–2522.

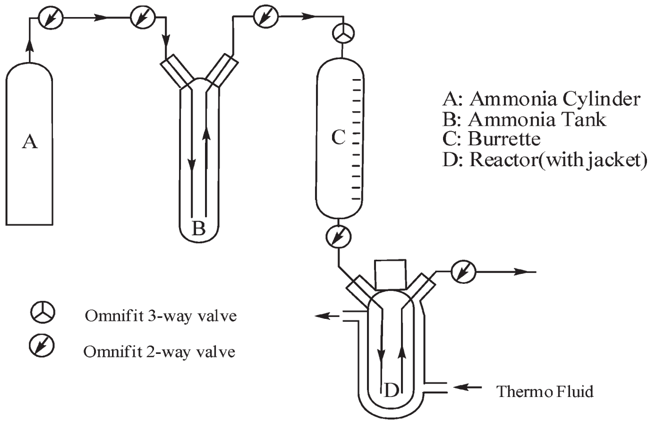


FIGURE 11. Diagram of the pressure equipment used for studies in liquid ammonia. B, C and D are made of glass, are pressure tested up to 35 bar. B, C and D are fixed into a 60 × 40 cm wooden board by clamps. B and C are placed inside a wooden protection box with a Perspex front window and a protection sheet is placed in front of D when A is charged with liquid ammonia. The maximum working temperature allowed for the system is 45 °C.

Kinetics. The equipment (Figure 11) and general procedures were similar as described previously.[18] 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 buret C (maximum volume 30 mL).The buret 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 buret during the liquid ammonia transfer from C to D. Generally, one of the reactants is precharged into D and the system is maintained at required temperature accurately by thermoregulation instrument. An amount of liquid ammonia (normally 10 mL) is released into D and is equilibrated with the surrounding temperature for an hour, another reactant is injected by a pressure syringe through an Omnifit septum into D.[59] 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, 1 M HCl or 1 M NaOH, was added into the vial, and extracted by dichloromethane or toluene. The kinetics of some reactions were measured by a competition method, so 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 analyzed by GC or HPLC equipment, and the data were processed using commercial data-fitting software. 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. 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 0.01−0.02 M.

UV Investigation of Ionization of Phenols. All the UV−vis spectra of phenols in various solvents were acquired at room temperature. The spectra were recorded with the dual beam method and the absorbance of phenols was relative to the solvent blank sample. Pressure UV cells were based on a design by Gill.[60] The body of the pressure UV cell is made of PTFE, and with an inlet and outlet controlled by Kel-F valves, the windows of the UV cell are made from CaF_2, the path length between two windows is 10 mm. The top of the UV cell has a standard Swagelok fitting which can be connected to the Omnifit valves, thus the cell can be connected with D (Figure 11) and allows the phenol liquid ammonia solution transferred from D to the cell. Normally, a standard phenol ether solution was prepared and injected into glass pressure vessel (D) through a microliter syringe (normally 10−50 μL), then 10 mL liquid ammonia was released from buret (C) to D. The concentration of phenol in liquid ammonia was between 10^{-5} M to 10^{-4} M, depending on the molar extinction coefficient of phenol under investigation. The molar extinction coefficient of each phenol was measured at least 3 different concentrations, the average value was obtained from the slope of absorbance against concentration.

NMR Investigation of Ionization of Ammonium Salts. All the ^{1}H NMR spectra of ammonium salts were acquired from 400 or 500 MHz NMR spectrometers, the chemical shifts of compounds in liquid ammonia at 25 °C were determined by referencing to the trace DMSO (δ_H = 2.50 and δ_C = 39.50) in DMSO-d_6 which was used as deuterium lock. The proton peak of solvent ammonia is large so that any proton signals between 0 and 1 ppm could not be measured and integrated. Pressure NMR tubes were purchased from a commercial source with an O.D. of 5 mm, a tube length of 7 in. and were thin-walled (0.38 mm) ones which were specially designed for 500 Hz NMR instruments. The top inlet valve of the pressure NMR tube has a standard Swagelok connection which allows the connection to the Omnifit valve, thus the ammonia solution can be transferred from pressure vessel (D) to the tube. Normally, the concentration of solute in liquid ammonia for NMR investigation was 0.1M, with 2% (v/v) of DMSO-d_6 as deuterium lock.

Acknowledgment. P.J. acknowledges a postgraduate scholarship from the University of Huddersfield. We also thank financial support from IPOS (Innovative Physical Organic Solutions) group of the university. Special thanks to Dr. N. McLay for his help with NMR studies.

Supporting Information Available: Analysis of chiral starting materials and products; the UV absorbance and extinction coefficient of phenols, NMR shifts of amines and the rate constants of the individual kinetic experiments in liquid ammonia. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(59) 0.1−0.2 mL standard diethyl ether solution of reactant and internal standard was injected by a pressure syringe into 10 mL liquid ammonia for all the kinetic measurement, so the reaction system under investigation contained 1−2% (v/v) diethyl ether.

(60) Gans, P.; Gill, J. B.; MacInnes, Y. M.; Reyner, C. *Spectrochim. Acta* **1986**, *42A*, 1349–1354.