University of Huddersfield Repository

Griffin, Joseph, Atherton, John and Page, Michael I.

The ammonolysis of esters in liquid ammonia

Original Citation

Griffin, Joseph, Atherton, John and Page, Michael I. (2013) The ammonolysis of esters in liquid ammonia. Journal of Physical Organic Chemistry, 26 (12). pp. 1032-1037. ISSN 1099-1395

This version is available at http://eprints.hud.ac.uk/id/eprint/25459/

The Ammonolysis of Esters in Liquid Ammonia

Joseph Griffin, John Atherton and Michael I Page*

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

e-mail: m.i.page@hud.ac.uk

Phone: +44(0)1484 472534

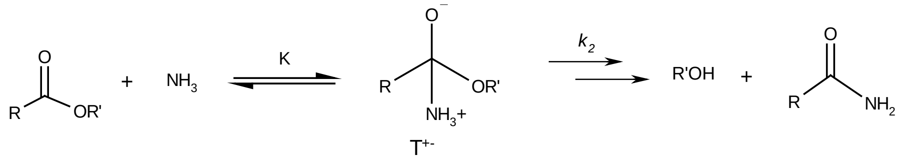
KEYWORDS: ammonolysis, ester solvolysis, liquid ammonia, Bronsted plots, mechanism

The rates of ammonolysis of alkyl benzoate and phenylacetate esters in liquid ammonia increase with the acidity of the leaving group alcohol and show relatively large Bronsted β_{lg} values of -1.18 and -1.34, respectively, when plotted against the aqueous pK_a of the alcohol. The Bronsted β_{lg} obtained using the pK_a of the leaving group alcohol in liquid ammonia is significantly reduced to ~ -0.7, which indicates that the rate limiting step involves a reaction of the tetrahedral intermediate with little C-OR bond fission in the transition state. The solvolysis reaction is subject to significant catalysis by ammonium ion, which, surprisingly, generates a similar Bronsted β_{lg} indicating little interaction between the ammonium ion and the leaving group. It is concluded that the rate-limiting step for the ammonium-ion catalysed solvolysis of alkyl esters in liquid ammonia is the diffusion controlled protonation of the zwitterionic tetrahedral intermediate T^{+-} to give T^{+}, which is rapidly deprotonated to give T^{0} which is compatible with the rate limiting step for the uncatalysed reaction being the formation of the neutral T^{0} by a 'proton switch'.

Introduction

The nature of the solvent can influence both the kinetics and mechanisms of organic reactions.[1] Dipolar aprotic solvents (e.g. DMSO, DMF, DMAc and NMP) are used in around 10% of chemical manufacturing processes but they are expensive, have toxicity concerns and are difficult to recycle due to their water miscibility and are frequently disposed by incineration. Liquid ammonia is a promising candidate to replace dipolar aprotic solvents in a number of applications. Ammonia has only one lone pair for three potential N-H hydrogen bonds leading to relatively weak association in the liquid state and a boiling point of -33°C and a vapour pressure of 10 bar at 25°C.[2] 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.[3] Despite the low dielectric constant of liquid ammonia (16.0 at 25°C)[4] many salts and organic compounds have good solubility.[5, 6] The nitrogen lone pair makes ammonia a good H-bond acceptor and liquid ammonia strongly solvates cations[7] but, unlike water, it is not a good hydrogen bond donor[8] and does not significantly solvate anions.[9] Liquid ammonia thus renders anionic nucleophiles more "naked" than in water which are therefore expected to be more reactive and, conversely, make anionic leaving groups poorer relative to that in water. The normalised donor number (DN^N) of liquid ammonia is 1.52, greater than that of HMPTA (1.0),[10] while its autoprotolysis constant gives a pK_a of 27.6 (25°C), compared with 14.0 for water (25 °C).[11,12]

The aminolysis of esters is of wide biochemical interest e.g. the biosynthesis of proteins involves the N-terminal amino group of the growing peptide attacking the transfer RNA 3′-hydroxy ester of the carboxyl group of the next amino acid to be added[13]. The mechanism of aminolysis of esters generally involves the reversible formation of a tetrahedral intermediate T^{+-} as expulsion of the attacking amine is often faster than that of the leaving group alkoxide or aryloxide ion (Scheme 1)[14]. The reaction is commonly susceptible to general base catalysis which removes a proton from the amine after covalent bond formation because the acidity of the NH is dramatically changed in T^{+-} sometimes leading to diffusion controlled but rate-limiting encounter of the tetrahedral intermediate and the base[15]. Liquid ammonia could fundamentally alter the energetics of this process because of its effect on both pK_a's and on nucleophilicity/nucleofugality[16]. For example, aminium ions are fully deprotonated in liquid ammonia and so exist as their free bases; the equilibrium **(eqn.1)** lies well over to the right, suggesting that ammonia solvent stabilises the ammonium ion (NH_4^+) more than the aminium ions (RNH_3^+)[17].



Scheme 1

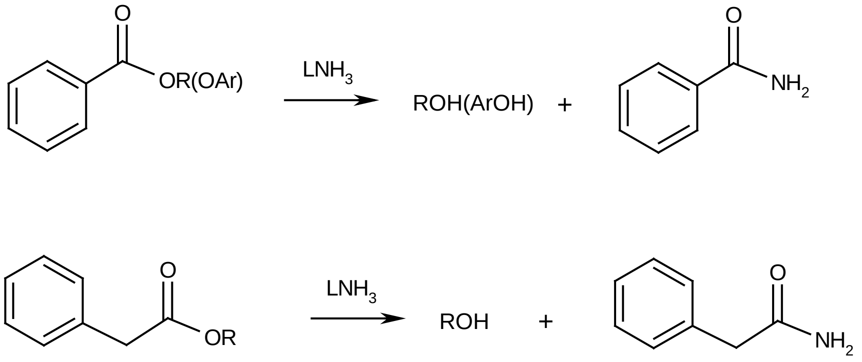
$$RNH_3^+ + NH_3 \xrightleftharpoons{K} RNH_2 + NH_4^+ \qquad (1)$$

Herein, we report on the kinetics and mechanism of the solvolysis/ ammonolysis in liquid ammonia of esters and catalysis of this reaction by ammonium ions.

Results and Discussion

(i) Solvolysis

The solvolysis of a series of alkyl benzoates and alkyl phenylacetates and aryl benzoates in liquid ammonia gives the corresponding amide and alcohol/phenol (**Scheme 2**). The rates of these reactions were determined at 25^{o}C by monitoring the exponential decrease of the ester and increase in amide concentrations with time. The corresponding pseudo first order rate constants vary significantly with the substituent (**Table 1**) with the esters of more acidic alcohols being more reactive. Alkyl esters are more reactive than the corresponding aryl ester with the same pK_a of the leaving group alcohol/phenol and the phenylacetate esters are about 5-fold more reactive than the corresponding benzoate ester. There is a good Brønsted correlation of the rate constants for the solvolysis of the alkyl esters with the *aqueous* pK_a of the alcohol (**Fig.1**). The relatively large β_{lg} values of -1.34 and -1.18 for the solvolysis of the alkyl phenylacetate and benzoate esters in liquid ammonia, respectively, appear to indicate a significant development of negative charge on the leaving group alcohol oxygen relative to that in the starting ester. At first sight, it is tempting to think this is indicative of rate-limiting breakdown of the tetrahedral intermediate expelling the alkoxide anion. The effective charge on oxygen in the ester is = 0.7+ and the β_{lg} indicates the change in effective charge on oxygen



Scheme 2

in the transition state.[18] However, ideally, to interpret structure-activity relationships of reactions in liquid ammonia knowledge of how the ionisation constant of the leaving group alcohol varies with substituents in this solvent is required.

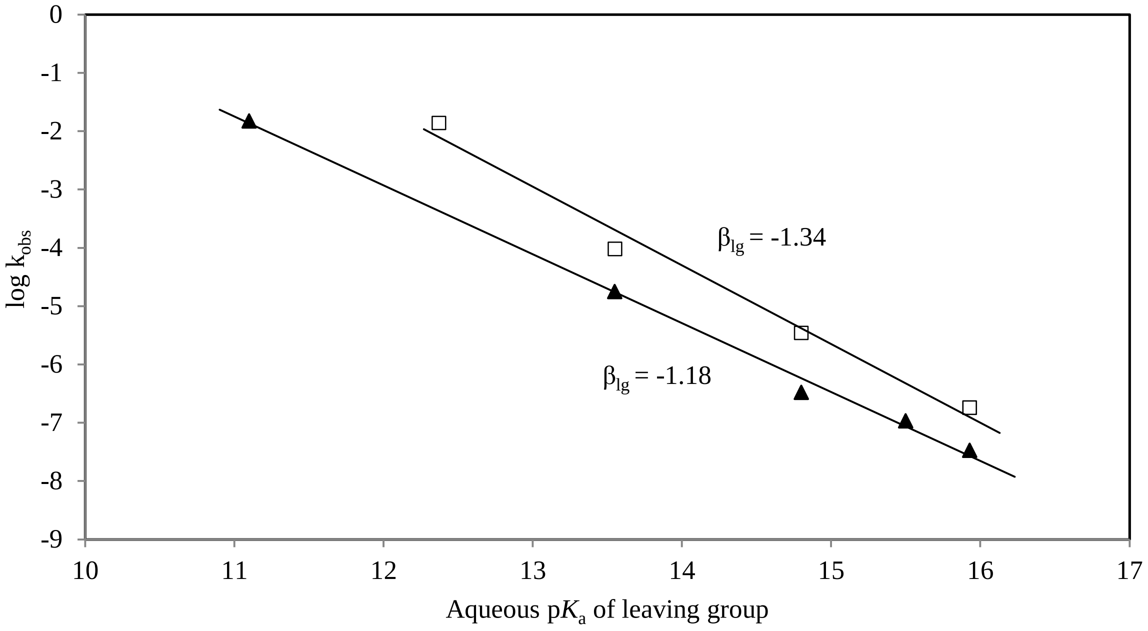


Figure 1. Brønsted plot for the pseudo first order rate constants for the solvolysis of alkyl esters of phenylacetic (□) and benzoic (▲) acid in liquid ammonia at 25°C against the aqueous pK_a of the leaving group alcohol.

Table 1. Observed pseudo first order rate constants for the solvolysis of various esters in liquid ammonia at 25°C

Ester type	alcohol	pK_a (aq) of alcohol[a]	k_{obs} (s^{-1})
Benzoates	ethyl	15.93	$3.36 \pm 0.17 \times 10^{-8}$
	methyl	15.50	$1.07 \pm 0.05 \times 10^{-7}$
	2-methoxyethyl	14.80	$3.31 \pm 0.16 \times 10^{-7}$
	propargyl	13.55	$1.78 \pm 0.09 \times 10^{-5}$
	vinyl	11.10[b]	$1.47 \pm 0.07 \times 10^{-2}$
	4-methoxyphenyl	10.21	$1.24 \pm 0.06 \times 10^{-3}$
	phenyl	10.00	$7.45 \pm 0.27 \times 10^{-3}$
Phenylacetates	ethyl	15.93	$1.81 \pm 0.09 \times 10^{-7}$
	2-methoxyethyl	14.80	$3.47 \pm 0.15 \times 10^{-6}$
	propargyl	13.55	$9.58 \pm 0.38 \times 10^{-5}$
	2,2,2-trifluoroethyl	12.37	$1.38 \pm 0.06 \times 10^{-2}$

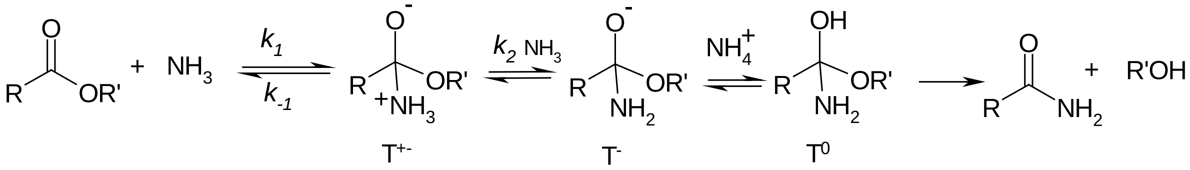
a. H. A. Sober and W. P. Jencks 1968 *in Handbook of Biochemistry,* ed. H. A. Sober, pp. J150–J189, Chemical Rubber Co., Cleveland, OH. b. J.P. Guthrie, Can. J. Chem., 1979, 57, 1177-1185

Liquid ammonia is a basic solvent with a very low self-ionisation constant (pK_a = 27.6 at 25^{o}C)[11,12] and the ionisation of acids in this solvent generates equivalent amounts of the conjugate base and ammonium ion (**eqn. 2**). Many ionic species will be strongly associated because of the low dielectric constant of liquid ammonia and conductivity

$$\mathrm{HA} + \mathrm{NH_3} \overset{K_i}{\rightleftharpoons} [\mathrm{A}^- \ \mathrm{NH_4^+}]_{ip} \overset{K_d}{\rightleftharpoons} \mathrm{A}^- + \mathrm{NH_4^+} \qquad (2)$$

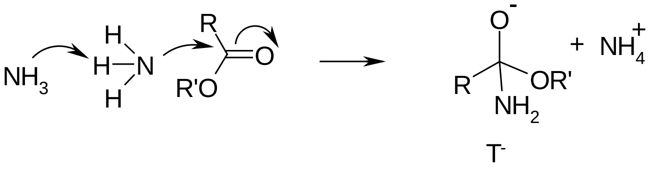
data shows that ion-pairing occurs even at low concentrations and larger aggregates may form at higher concentrations.[19] Several methods have been used to determine ionisation and dissociation constants including spectroscopic, conductivity and NMR.[20] Phenols with aqueous $pK_a < 7.0$, but not those with $pK_a > 8.5$, are fully ionised in liquid ammonia at room temperature[21] and there is a linear relationship between the apparent pK_a values in liquid ammonia and the corresponding aqueous ones with a slope of 1.68. 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 non-aqueous solvent so their stability is more dependent on negative charge delocalization through the substituent. The ionisation of alcohols in liquid ammonia has not been determined, but, for example there is no conductance of 39mM trifluoroethanol in liquid ammonia, despite an aqueous $pK_a = 12.4$. It is a reasonable assumption that a plot of the pK_a values of alcohols in liquid ammonia and the corresponding aqueous ones would show a slope of at least 1.7, given the value of 1.68 observed for phenols and that the negative charge on alkoxide ions is likely to be more localised than that in phenols. The Bronsted β_{lg} obtained from a plot of the log rate constants against the pK_a of the leaving group alcohol in liquid ammonia would thus be significantly reduced to ~ -0.7, which indicates that the rate limiting step involves a reaction of the tetrahedral intermediate with little C-OR bond fission in the transition state, as discussed later.

Anions are poorly solvated in liquid ammonia compared with that in water and other polar solvents and so are more reactive. For example, 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.[21,22] These rate increases on going from protic to dipolar aprotic solvents are attributable to the specific solvation 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.[23] This is also shown by the large positive Gibbs transfer energies of anions from protic solvents to non-polar and dipolar aprotic solvents.[24] Similarly, it is expected that anions will generally be poor leaving groups in liquid ammonia compared with polar solvents. Hence, it is anticipated that the ammonolysis of esters in liquid ammonia will proceed by the nucleophilic attack of ammonia on the ester carbonyl group to form the zwitterionic tetrahedral intermediate T^{+-} reversibly, because expulsion of ammonia k_{-1} will be faster than that of alkoxide-ion (**Scheme 3**). Furthermore, aminium ions are fully deprotonated in liquid ammonia and so exist as their free bases **(eqn.1)** and so deprotonation of the zwitterionic tetrahedral intermediate by solvent ammonia is thermodynamically favourable and very rapid (k_2) to give the anionic T^-. However, the breakdown of T^- cannot be the rate-limiting step as this is incompatible with the rate law for the uncatalysed solvolysis. Given the relative instability of anions in liquid ammonia, the most stable form of the tetrahedral intermediate is the neutral T^0, which, in the absence of an external catalyst could be formed by a ‘proton switch’ through the ammonium ion formed within the ion-pair by proton transfer to a solvent molecule[13,25]. Alternatively, T^- may be formed directly by a termolecular reaction involving two molecules of solvent with one acting as a general base (**Scheme 4**), similar to that proposed for some ‘spontaneous’ pH independent hydrolysis reactions. However, ammonia is much less acidic than water and so



Scheme 3

proton removal from the attacking ammonia is energetically unfavourable until after significant N-C bond formation generating substantial positive charge on N, so this concerted mechanism is probably less likely than the stepwise formation of T^-. Similarly, a concerted cyclic mechanism involving the direct formation of T^0 seems unlikely. The reasons for postulating rate-limiting stepwise formation of T^0 will be discussed further in the next section.



Scheme 4

(ii) *General-acid catalysed solvolysis by ammonium ions*

The observed pseudo first order rate constants for the solvolysis of propargyl benzoate in liquid ammonia significantly increase with increasing ammonium chloride concentration at constant ionic strength, I = 0.1M (**Figure 2**). Ionic strength itself has little effect upon the rate of solvolysis, $k_0 = 1.78 \times 10^{-5}\ s^{-1}$ compared with $1.97 \times 10^{-5} s^{-1}$ with 0.1M $KClO_4$, but 0.1M ammonium chloride increases k_{obs} nearly 10-fold. The corresponding second order rate constant $k_{NH4+} = 1.90 \times 10^{-3}\ M^{-1}s^{-1}$ for the ammonium ion catalysed solvolysis which is thus overall a third order rate equation (**eqn.3**). Ammonium ion in liquid ammonia is, of course, equivalent to H_3O^+ in water but will be referred to as a general acid catalyst.

$$\text{Rate} = k[\text{ester}][NH_3][NH_4^+] \qquad (3)$$

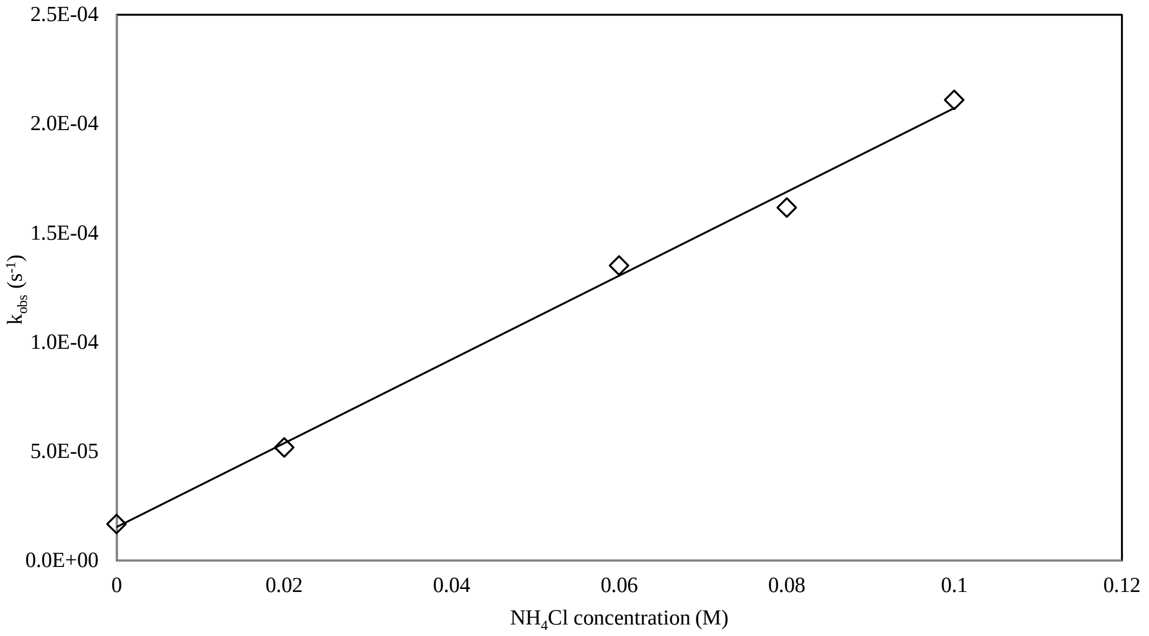
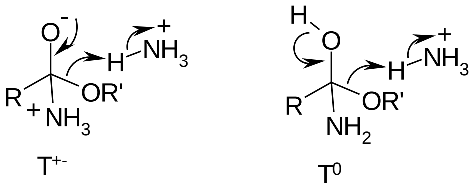
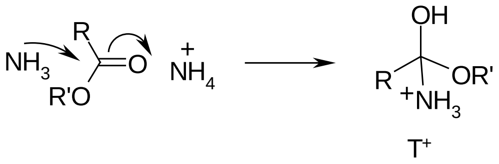


Figure 2. The dependence of the observed pseudo first order rate constants for the ammonolysis of propargyl benzoate on the ammonium chloride concentration in liquid ammonia at 25°C (I = 0.1M $KClO_4$).

Catalysis by the ammonium cation could be due to general acid catalysed breakdown of the zwitterionic T^{+-} or neutral T^0 tetrahedral intermediate by acting as a proton donor to the leaving group alkoxide (**Scheme 5**). An alternative explanation could be the acid catalysed formation of the tetrahedral intermediate T^+ (**Scheme 6**) with rate limiting concerted nucleophilic attack and proton transfer, although rate-limiting formation of T^+ does not appear to overcome the difficulty of expelling alkoxide-ion compared with ammonia. Any ammonium ion-pair stabilisation of T^- would be expected to collapse to the neutral tetrahedral intermediate T^o in liquid ammonia due to its low dielectric constant.



Scheme 5



Scheme 6

The second order rate constant for the ammonium ion catalysed solvolysis of methoxyethyl benzoate, $k_{NH4+} = 2.80 \times 10^{-6}\ M^{-1}s^{-1}$, which, using just two data points, generates a Brønsted $\beta_{lg} = -1.46$. If the comparable two data points for the uncatalysed solvolysis reactions are used to generate a Brønsted plot this gives a similar value $\beta_{lg} = -1.38$. This surprising observation indicates that the effective charge on the alcohol oxygen in the transition state is similar in the two reactions, which implies that the ammonium ion does not interact directly with the alcoholic oxygen. It is concluded that the rate-limiting step for the ammonium-ion catalysed solvolysis of alkyl esters in liquid ammonia is the diffusion controlled protonation of the zwitterionic tetrahedral intermediate T^{+-} to give T^{+}, which is rapidly deprotonated to give T^{0}. This is compatible with the suggestion above that the rate limiting step for the uncatalysed reaction is the formation of the neutral T^{0} by a ‘proton switch’.

The effect of substituents in the carboxylic acid residue of alkyl esters was investigated using the solvolysis of alkyl p-nitrobenzoates in liquid ammonia, which are about 100-fold more reactive than the corresponding benzoates (Table 2).

Table 2. Observed pseudo first order rate constants for the ammonolysis of alkyl benzoates and alkyl p-nitrobenzoates in liquid ammonia at 25°C.

Alkyl ester	benzoate ester k_{obs} (s^{-1})	p-nitrobenzoate ester k_{obs} (s^{-1})
propargyl	1.78×10^{-5}	-
2-methoxyethyl	3.31×10^{-7}	2.97×10^{-5}
methyl	1.07×10^{-7}	6.97×10^{-5}
ethyl	3.36×10^{-8}	5.42×10^{-6}

Experimental

Materials: Reagents were of analytical grade and obtained from scientific suppliers Sigma-Aldrich, TCI UK and Fischer Scientific. Esters were synthesised from benzoyl chloride and phenol or from phenylacetyl chloride and the alcohol with a purity of >98% (GC) and characterised by ^{1}H NMR and ms.

*Equipment for reactions in liquid ammonia:*The ammonia condensing vessel and burette (Figure) were pressure tested up to 35 bar and made by HGL Ltd. (Southampton, UK). The ammonia tank was not calibrated and has a total volume of approximately 40ml, whereas the burette was calibrated and has a volume capacity of about 30ml. The calibration of the burette permitted a minimum volume of 0.5ml and therefore allowed accuracy when dispensing liquid ammonia for reactions, as usually 5-10ml was required. Both the vessel and burette were fitted with standard Omnifit necks which allow practical, gas-tight connections between all the glassware via connectors, valves, tubing and septa. Three types of reaction vessels were used each having a total volume capacity of ~15ml, although for safety reasons the maximum amount of liquid ammonia used was 10ml. As with the condensing vessel and burette, the reaction vessels were obtained from HGL and pressure tested up to 35 bar. The maximum working temperature of reactions in the vessels was 45°C. The vessels are each equipped with a standard GL14 neck, which can be fitted with a GL14 screw-on lid. The lid contains a silicone rubber seal coated in polytetrafluoroethylene (PTFE). The vessels also have two standard Omnifit necks for various uses such as filling the vessels with liquid ammonia, injecting solutions through an Omnifit septa, for sampling through tubing, or venting the ammonia to reduce any dangerous pressure build up.

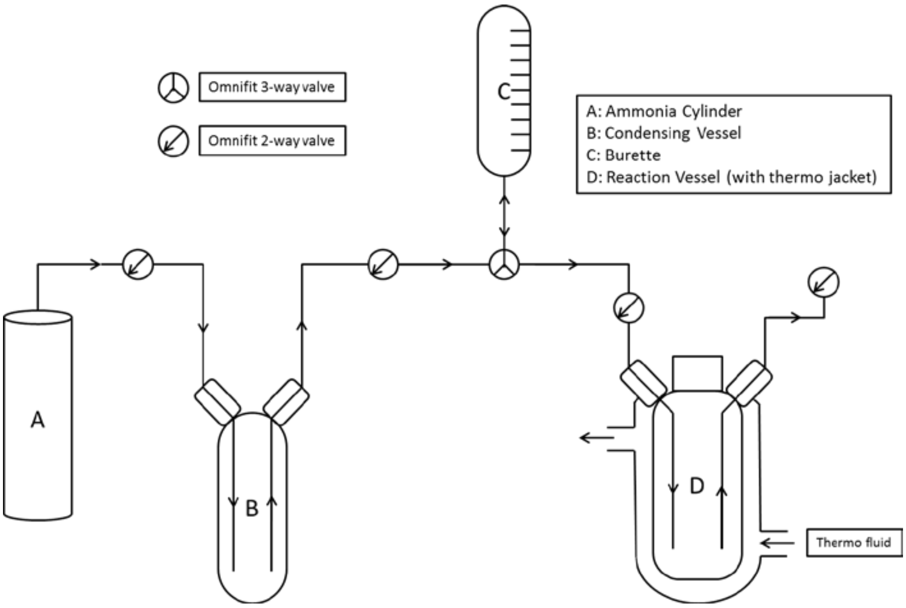


Figure Pressure glassware set-up for the handling of liquid ammonia

The Figure shows the general set up for the safe handling of liquid ammonia in preparation for reactions. Ammonia gas is released from the ammonia gas cylinder (A) and condensed into the condensing vessel (B) submerged in an ice bath. The glassware, vessels and cylinder are all linked via Omnifit® connectors and 1/16 inch PTFE tubing. The 2-way and 3-way valves are also products of Omnifit®. Approximately 15ml of ammonia is condensed into the ice-chilled vessel before the ammonia cylinder valve is shut, the ice bath removed and the condensing vessel allowed to warm to room temperature. The liquid ammonia is then transferred up to the burette by opening the 3-way valve. The burette ensures that the required amount of liquid ammonia, generally 10ml, can be transferred accurately and safely to the reaction vessel (D).

Thermo regulator: The vessel with the jacket allows connection with a Huber-Unistat Tango Nuevo thermo regulator which allows temperature control of the reaction vessel ranging from -40°C to 200°C with good accuracy (±0.01°C). Silicone based thermo oil is used in the vessel jacket.

Pressure Syringe: Some reactions were initiated by the addition of one of the reactants to the sealed pressure vessel already filled with liquid ammonia and other reactants/internal standards etc. This was done by injecting the reactant into the vessel using a high pressure syringe (from SGE analytical science) pressure rated to 33bar (500psi) and equipped with a side-hole needle (71mm) and an outside diameter (O.D.) of 1.07mm. The syringe has a standard Swagelok fitting and a gas tight PTFE on/off valve.

Analytical equipment: GC retention times of the ester and amide product were determined using an Agilent 7980 with flame ionization detection (FID). GC-MS analysis used an Agilent 7890A QQQ, with an Agilent J+W 19091J-433 HP-5column with dimensions 30m x 0.25mm x 0.25µm. The inlet temperature was set at 250°C, with an injection volume of 1µl and split ratio of 50:1. The carrier gas was helium at a constant pressure of 16.1 psi and flow rate of 1.5mL/min. The oven temperature was initially 45°C, holding for 2 minutes, before increasing the temperature at a ramping rate of 20°C/min. The final oven temperature was 320°C which was held for 2 minutes.

General solvolysis reaction conditions: The reaction vessel was thoroughly cleaned before each experiment and purged with ammonia. An internal standard, biphenyl (15mM), was added to the reaction vessel. The vessel was sealed, and liquid ammonia (10ml) was carefully added from the burette. The temperature control on the thermo regulator was set to 25°C and the solution was left to equilibrate for 1 hour, with constant, vigorous stirring. Diethyl ether solutions of the ester (0.5M or 1M) and 0.1-0.3mL of these solutions were injected into the vessel via the pressure syringe to give an ester concentration of 5mM- 30mM. To obtain the observed solvolysis rate constants (k_{obs}) at timed intervals, a sample (0.5ml) was collected into a 5ml sample vial by opening and closing the 2-way Omnifit valve and the ammonia was then allowed to boil off. The samples were quenched by dilution in 2ml dichloromethane (DCM) and analysed by GC. It was necessary to monitor the extent of quenching by dilution. A quenched sample was repeatedly analysed by GC over a period of hours or days. If the chromatogram areas remained at a constant then the reaction was conclusively terminated by dilution quenching.

Data analysis and curve fitting: For any sample taken at a particular interval, a chromatogram was obtained and if GC-MS was used, a mass spectrum was also available to identify any unknown peaks if required. The gas chromatogram was the main tool used for monitoring the reactions in liquid ammonia. The majority of these reactions in liquid ammonia were carried out under pseudo-first order conditions, where by the attacking nucleophile, ammonia, is always in vast excess. First order rate plots were made by following the concentration of the starting material and product as the reaction proceeds to completion. In terms of gas-chromatography, the integrated area of a peak is proportional to its concentration, and therefore a plot of peak area against time would produce a curve fit in which the reaction rate, or more specifically observed rate constant, k_{obs}, can be extrapolated. However because the sampling method is not consistent, each sample collected may slightly vary in volume unknowingly. This would mean that the peak area of each chromatogram would not be a true representation of the relative amount of compound. To account for this inconsistency, an internal standard is used to express the precise relative amount of compound present, regardless of sampling volume.

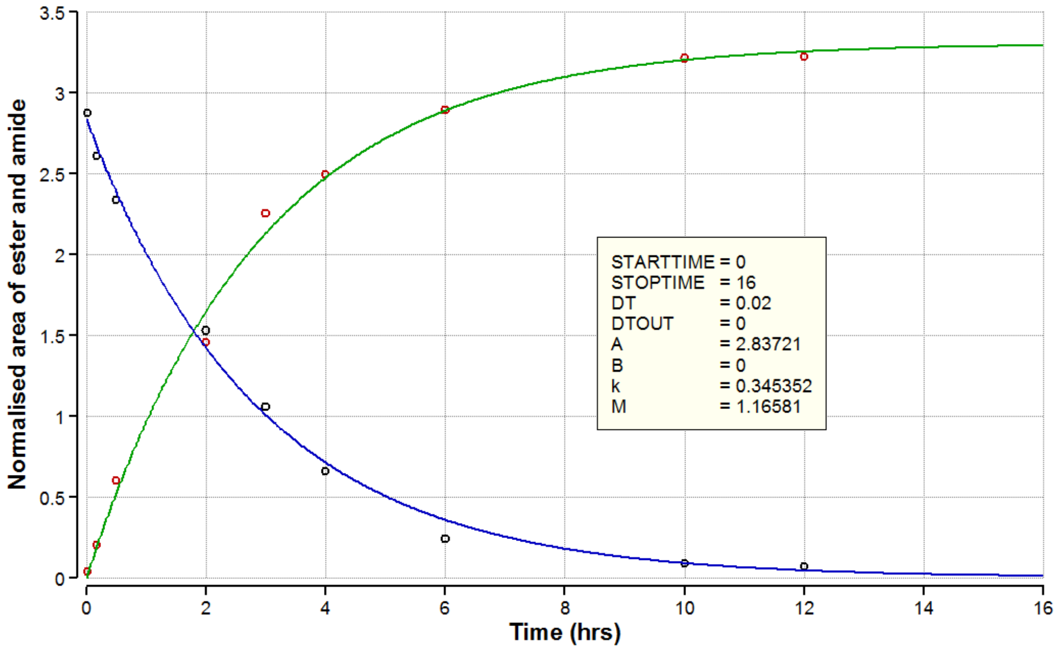


Figure. Berkeley Madonna© model fitting for the ammonolysis of propargyl phenylacetate in liquid ammonia at 25°C.

References:

---

[1] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed., Wiley-VCH, Verlag GmbH&Co. KGaA, Weinheim, **2003.**

[2] D. Nicholls, *Inorganic chemistry in liquid ammonia*, ed. R. J. H. Clark, Topic in Inorganic and General Chemistry, Monograph 17, Elsevier Scientific Publishing Company, Amsterdam, **1979**.

[3] P. Ji, J. H. Atherton and M. I. Page, *J. Chem. Soc. Faraday Discuss.* **2010**, *145*, 15–25

[4] G. Billaud and A. Demortler, *J. Phys. Chem.*, **1975**, *79*, 3053-3055.

[5] D. H. Howard, Jr., F. Friedrich and A. W. Browne, *J. Amer. Chem. Soc.*, **1934**, *56*, 2332- 2340.

[6] H. Smith, *Organic Reactions in Liquid Ammonia*, ed. G. Jander, H. Spandau, C. C. Addison, Chemistry in Nonaqueous Ionizing Solvents, Vol. 1, Part 2, John Wiley&Sons Inc., New York-London, **1963**.

[7] M. Herlemand and A. I. Popov, *J. Amer. Chem. Soc.*, **1972**, *94*, 1431-1434.

[8] D. D. Nelson, Jr., G. T. Fraser and W. Klemperer. *Science*, **1987**, *238*, 1670-1674; D. C. Luehurs, R. E. Brown and K. A. Godbole, *J. Solution Chem.*, **1989**, *18*, 463-469.

[9] Y. Marcus, *Pure Appl. Chem.*, **1983**, *55*, 977-1021.

[10] J. Rydberg, M. Cox and C. Musikas, *Solvent Extraction Principles and Practice*, 2nd ed., CRC Press, **2004**, Chapter 3, 101.

[11] J. J. Lagowski, *Synthesis and Reactivity in Inorganic, Metal-organic and Nano-metal Chemistry*, **2007**, *37*, 115-153.

[12] L. V.Coulter, J. R. Sinclair, A. G. Cole and G. C. Rope, *J. Am. Chem. Soc.* **1959**, *81*, 2986-2989

[13] J. McMurry, in 'Organic Chemistry A Biological Approach', Thomson, CA, USA, **2007**, p.987

[14] A. C. Satterthwaite , W.P. Jencks, *J. Amer. Chem. Soc.*, **1974**, *96*, 7018- 7031

[15] W.P. Jencks, *Acc. Chem. Res.*, **1976**, *9*, 425-432; W.P. Jencks, *Chem. Revs.*, **1972**, *72*, 705-718

[16] P. Ji, J. H. Atherton and M. I. Page, *J. Chem. Soc. Faraday Discuss.* **2010**, *145*, 15–25

[17] P. Ji, N. T. Powles, J. H. Atherton and M. I. Page, *Org. Lett.*, **2011**, *13*, 6118–6121; P. Ji, J. H. Atherton and M. I. Page, **Org. Biomol. Chem., 10,** 5732-5739 (2012)

---

[18] M. I. Page and A. Williams in ‘Organic and Bio-Organic Mechanisms’, Longmans **1997,** p.67**;** A. Williams, Adv. Phys. Org. Chem. **1992,** *27*, 1-55

[19] J. J. Lagowski, *Pure Appl. Chem.* 1971, **25**, 429-456; R. E. Cuthrell, E. C. Fohn and J. J. Lagowski, *Inorg. Chem.* **1966,** *5*, 111-114; J. A. Zoltewicz and J. K. O’Halloran, *J. Org. Chem.*, **1974**, *39*, 89-92 .

[20] C. A. Kraus and W. C. Bray, *J. Am. Chem. Soc.* **1913**, *35*, 1315-1434; J. Badoz-lambling, M. Herlem and A. Thiebault, *Anal. Lett.* **1969**, *2*, 35-39; T. Birchall and W. L. Jolly, *J. Am. Chem. Soc.* **1966**, *83*, 5439-5443.

[21] P. Ji, J. H. Atherton, , M. I. Page, *J. Org. Chem.*, **2011**, *76*, 1425–1435;

[22] Y. Fang, Z. Lai, K. C. Westaway, *Can. J. Chem.* **1998**, *76*, 758-764.

[23] A.J. Parker, *Chem. Rev.* **1969**, *69*, 1-32; J. Miller, A. J. Parker, *J. Am. Chem. Soc.* **1961**, *83*, 117-123; B. G. Cox, *Modern Liquid Phase Kinetics*, in Oxford Chemistry Primers, ed. R. G. Compton, Oxford University Press, New York, 1994.

[24] Y. Marcus, M. J. Kamlet, R. W. Taft, R. W. *J. Phys. Chem.* **1988**, *92*, 3613-3622; A. J. Parker, *Quart. Rev. Chem. Soc.* **1962**, *16*, 163-187.

[25] J.P. Fox, M. I. Page, A. C. Satterthwaite and W. P. Jencks, *J. Am. Chem. Soc.* **1972**, *94*, 4729- 4731