

Ionization of Carbon Acids in Liquid Ammonia

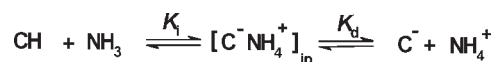
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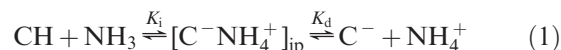
ABSTRACT



The acidities of various carbon acids in liquid ammonia (LNH₃) at room temperature were determined by NMR and rates of D-exchange. There is a reasonable linear correlation of the p*K*_as in LNH₃ with those in water and DMSO of slope 0.7 and 0.8, respectively. Carbon acids with an aqueous p*K*_a of less than 12 are fully ionized in liquid ammonia. Nucleophilic substitution of benzyl chloride by carbanions in liquid ammonia generates a Brønsted β_{nuc} = 0.38.

The acidity of carbon acids and their rates of deprotonation and the rates of protonation of their conjugate base carbanions have contributed to our understanding of electronic effects¹ and the “imbalance” between various motions required in the transition states of their reactions.² The solvent plays an important role in these phenomena both in terms of the stability of the carbanion and solvent reorganization that is often required for charged delocalized species.³ We are interested in using liquid ammonia as a promising solvent for organic reactions to replace dipolar aprotic solvents in a number of industrial processes.⁴ 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 vapor pressure of 10 bar at 25 °C.⁵ The nitrogen lone pair makes ammonia a good H-bond acceptor and liquid

ammonia strongly solvates cations;⁶ however, unlike water, it is not a good hydrogen bond donor and does not significantly solvate anions.⁷ Its autoprotolysis constant corresponds to a p*K*_a of 27.6 (25 °C).⁸ Although liquid ammonia has a low dielectric constant (16.9 at 25 °C),⁹ many salts are highly soluble.¹⁰ In view of the relatively low dielectric constant of liquid ammonia, the ionization of carbon acids in liquid ammonia may give rise to ion-pairs in equilibrium with the dissociated species (eq 1), where the product *K*_i*K*_d corresponds to the normal ionization constant *K*_a.



Carbonyl activated carbon acids that have an aqueous p*K*_a of less than 11 (< 15 in DMSO) are fully ionized in liquid ammonia at 25 °C as shown by ¹H and ¹³C NMR spectra. So relatively strong carbon acids such as dimedone (5,5-dimethylcyclohexane-1,3-dione), which has an aqueous p*K*_a of 5.25,¹¹ is deprotonated to its monoanion in liquid ammonia but, as expected, is un-ionized in CDCl₃

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and DMSO- d_6 (DMSO- d_6 (0.1 M) shows no H-D exchange with liquid ammonia at room temperature after several weeks, monitored by ^1H NMR). ^1H NMR and DEPT 135 spectra of dimedone in liquid ammonia show only one proton attached to carbon 2 between the two carbonyl groups, and the carbon shift of the carbonyl carbons in liquid ammonia is about 10 ppm lower than that at 200 ppm in CDCl_3 .¹¹ Diethyl malonate, which has an aqueous $\text{p}K_a$ of 12.9¹² and one of 15.9 in DMSO,¹³ is not ionized in liquid ammonia but shows a broad single peak of the central methylene protons, probably due to a fast exchange of these protons with the solvent. Acetylacetone and 2-acetylcyclohexanone with aqueous $\text{p}K_a$ s of 9.0 and 10.1, respectively,¹² (13.3¹³ and 15.5¹⁴ respectively in DMSO) react in liquid ammonia to give their corresponding enamines, confirmed by GC-MS analysis.

Monocyano-activated carbon acids, such as benzyl cyanide with a $\text{p}K_a$ of 21.9 in DMSO,¹⁵ are not ionized in liquid ammonia. Unlike other solvents, liquid ammonia causes the relaxation time of the methylene protons of benzyl cyanide to be fast compared with the aromatic protons and, consequently, it takes 10 s relaxation time to obtain the expected integration ratio between aromatic protons and methylene protons in liquid ammonia.

Dicyano derivatives are, however, fully ionized in liquid ammonia; the ^1H NMR spectrum of benzylmalonodinitrile does not show a proton attached to the methine carbon and the ^{13}C chemical shift is upfield (11.5 ppm) for the central carbon compared with that in CDCl_3 , as expected from an increased negative charge density in the carbanion. Ionization in liquid ammonia is further supported by DEPT 135 spectra, which show no coupling between the methine carbon and its attached proton present in neutral benzylmalonodinitrile. The surprisingly large downfield ^{13}C shift of the cyano groups (145.1 ppm) is similar to the 144.3 ppm reported for the cyano group of the lithium salt of benzyl cyanide anion in THF.¹⁶

Malonodinitrile, MDN, with an aqueous $\text{p}K_a$ of 11.2¹² (11.1 in DMSO¹³) shows very unusual behavior in liquid ammonia. In stark contrast to that observed in other solvents, its ^1H NMR spectrum at 25 °C shows no protons attached to the central methylene carbon present in neutral MDN. It would be surprising if both protons of MDN have been removed to form a carbon dianion, but the lack of a proton signal is not due to H-D exchange with the deuterated dimethyl sulfoxide used to “lock” the spectrometer as the same result is observed with toluene- d_8 or benzene- d_6 as a lock. A similar spectrum is also seen when one equivalent of acetonitrile is added using its three methyl hydrogens as an internal standard, apparently

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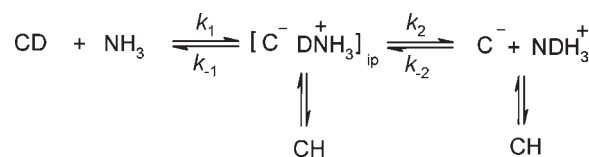
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Scheme 1



indicating that there is less than 1% MDN with hydrogen still attached. There are no ^1H NMR signals associated with the methylene carbon of MDN at -40 °C so if this is due to a rapid exchange mechanism leading to a very broad signal that is not observable, this lower temperature is insufficient to slow the rate of exchange. Ionization of MDN would transfer the protons to ammonia to form ammonium ions but the addition of ammonium chloride does not affect the ^1H NMR spectrum. Of course, within the ion-pair (eq 1) added ammonium ions would not alter the equilibrium with the undissociated species.

The ^{13}C NMR spectrum of MDN in liquid ammonia at 25 °C shows a high field carbon signal at -3.12 ppm, consistent with the formation of a negatively charged carbon, and contrasts with the methylene carbon signal of 8.4 ppm for MDN in DMSO. These observations are not due to a chemical reaction of MDN which is stable in liquid ammonia—after two days at room temperature, evaporation of the ammonia, acid neutralization and extraction yields unreacted MDN. The carbon chemical shifts of MDN with 2 equiv of NaH in liquid ammonia are similar to those without the added base. Although it is not clear whether MDN actually forms a carbon dianion in liquid ammonia or simply forms a monoanion with unusual NMR properties, the signal at -3.12 ppm is significantly further upfield compared with that of 11.5 ppm of benzylmalonodinitrile monoanion in liquid ammonia.

The carbon shift of MDN in liquid ammonia is upfield, but this could be due to a poorly solvated monoanion leading to a relatively larger negative charge density on the central carbon in liquid ammonia compared with other solvents. Earlier work on NMR data for the ionization of MDN is inconclusive, one¹⁷ reports the monoanion shift in DMSO as -0.25 ppm, but another¹⁸ quotes the monoanion shift in HMPT as -2.1 and -2.2 ppm, but then gives as shift of $+32$ ppm for the dianion. Very highfield carbon shifts are seen for carbon dianions or quasi-dianions in other solvents, for example, carbon suboxide has a very negative carbon shift of -14.6 ppm in CDCl_3 at -40 °C,¹⁹ while iminopropadienones have shifts of -3.8 to -6.8 ppm in CDCl_3 at room temperature.²⁰ It has been proposed that the resonance stabilization of α -cyano carbanions is not

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Table 1. Ionization of Carbon Acids in Liquid Ammonia at 25 °C Compared with pK_a Values in Water and DMSO

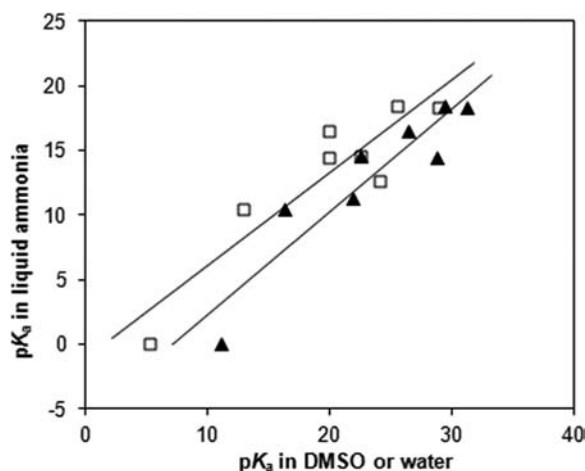
carbon acid	pK_a (aq)	pK_a (DMSO)	ionization in LNH_3	k_{obs} for D-exchange in LNH_3 25 °C/s ⁻¹	apparent pK_a (LNH_3)	second order rate constant for reaction with benzyl chloride in LNH_3 25 °C/M ⁻¹ s ⁻¹
dimedone	5.3 ^a	11.2 ^b	ionized		<0	
HCN	9.2 ^c	12.9 ^b	ionized			2.18×10^{-3}
acetylacetone	9.0 ^a	13.3 ^c	ionized			
2-acetylcyclohexanone	10.1 ^d	15.5 ^f	ionized			6.44×10^{-3}
malonodinitrile	11.2 ^d	11.1 ^e	ionized			8.88×10^{-3}
diethyl malonate	12.9 ^d	16.4 ^b	not ionized	<1	<10.5	2.27×10^{-3}
benzyl cyanide	N.A.	21.9 ^g	not ionized	0.23	11.3	1.40
fluorene	N.A.	22.6 ^h	not ionized	1.13×10^{-4}	14.6	
acetophenone	19.1	19.8	not ionized			0.256
phenyl acetylene	20.0 ⁱ	28.8 ^j	not ionized	1.75×10^{-4}	14.4	
acetone	20.0 ^k	26.5 ^h	not ionized	1.45×10^{-6}	16.5	
chloroform	24.1 ⁱ	N.A.	not ionized	1.16×10^{-2}	12.6	
ethyl acetate	25.6 ^l	29.5 ^h	not ionized	2.80×10^{-8}	18.2	
acetonitrile	28.9 ^m	31.3 ^g	not ionized	2.65×10^{-8}	18.3	

^a Reference 23. ^b Reference 24. ^c Reference 25. ^d Reference 12. ^e Reference 13. ^f Reference 14. ^g Reference 15. ^h Reference 26. ⁱ Reference 27. ^j Reference 28. ^k Reference 29. ^l Reference 30. ^m Reference 21.

significant and the negative charge is localized at the α -carbon, which may explain why there is such a highfield signal for MDN anion in liquid ammonia.²¹

The acidity of carbon acids that do not ionize in liquid ammonia can be estimated from the rates of proton exchange in the deuteriated derivatives. However, a problem arises depending on whether exchange occurs from the ion-pair or from the fully dissociated species (Scheme 1).

If isotopic exchange occurs with the dissociated carbocation, then the rate of protonation can be assumed to be diffusion-controlled which, based on a viscosity of 1.35×10^{-4} N s m⁻² for liquid ammonia,²² can be estimated to be 4.9×10^{10} M⁻¹ s⁻¹. However, if exchange occurs within the ion-pair then the rate of reprotonation could be much faster—possibly 10^{12} s⁻¹. The rates of isotopic exchange of deuteriated carbon acids in liquid ammonia were determined by ¹H NMR and GC-MS and first order rate constants are given in the Table 1. The rates of H-exchange of ethyl *d*₃-acetate and *d*₃-acetonitrile are very slow and were followed by initial rates over four weeks, during which period only one D was exchanged giving CHD₂

**Figure 1.** pK_a of carbon acids in liquid ammonia against their pK_a in water (□) and DMSO (▲).

with the expected quintet in the ¹H NMR spectrum at 2.0 ppm and 2.08 ppm, respectively. The corresponding “ pK_a ” values were calculated using the estimated diffusion-controlled rate constant and are uncorrected for any primary kinetic isotope effect on the rate of exchange, which, if k_1 is the rate-limiting step, would increase the relative values. Upper and lower limits are given for those carbon acids which undergo exchange either too quickly or slowly to be measured accurately. Given the variety of carbon acids examined, there is a reasonable correlation between the apparent ionization constants in liquid ammonia and those in DMSO and water (Figure 1) which have slopes of about 0.7 and 0.8, respectively. This contrasts with the 1.68 observed for the ionization of phenols in liquid ammonia against their aqueous pK_a .^{4b}

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Liquid ammonia is a useful solvent for carbanion reactions and pK_a values for carbon acids are useful for interpreting linear free-energy relationships. Nucleophilic substitution by those carbon acids that are deprotonated in liquid ammonia can occur without the aid of strong bases. For example, the reaction between 0.2 M 2-acetylhexanone with 0.01 M benzyl chloride in liquid ammonia at 25 °C forms the monobenzylated product within 5 min, whereas benzyl cyanide reacts with benzyl chloride only when converted to its anion by sodamide in liquid ammonia to give a monobenzylated product. The second order rate constants for cyanide ion reacting with benzyl chloride ($2.18 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$) in liquid ammonia is similar to that in DMF ($3.20 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$) at 25 °C.³¹ The second

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order rate constants for some carbanions reacting with benzyl chloride in liquid ammonia (Table 1) generate a Brønsted $\beta_{\text{nuc}} = 0.38$ with a positive deviation of malonodinitrile carbanion. This small value is similar to that seen for amine nucleophiles,^{4b} and suggests that the nucleophilic substitution of benzyl chloride by carbanions occurs with a transition state in which only a small amount of charge is removed from the carbanion in liquid ammonia.

Supporting Information Available. General experimental procedure, preparation of deuterium starting materials and NMR spectra of individual carbon acid in liquid ammonia. This material is available free of charge via the Internet at <http://pubs.acs.org>.