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Site of protonation of N-alkylanilines

Alex. G. Harrison*, Ya-Ping Tu

Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada

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Abstract

The MH^+ ions of N-methylaniline, N,N-dimethylaniline, N-ethylaniline, and N-N-diethylaniline, when prepared by CH_4 chemical ionization, show significant elimination of H_2 in both metastable ion and low energy collision-induced fragmentation. In contrast, the MH^+ ions of the same species produced by fast atom bombardment (FAB) ionization show no elimination of H_2 in either metastable ion or collision-induced fragmentation. Other metastable ion fragmentation reactions involve loss of CH_3 for the methylanilines and loss of C_2H_4 and C_2H_5 for the ethylanilines. The MH^+ ions prepared using CH_3OH or $(CH_3)_2CO$ as Brønsted acid reagents also show H_2 elimination whereas protonation using i-$C_4H_9NH_2$ as reagent produces MH^+ ions that show essentially no H_2 elimination. It is concluded that FAB ionization leads to the N-protonated species whereas protonation in the gas phase using CH_4, CH_3OH, or $(CH_3)_2CO$ as reagents leads to substantial formation of the ring-protonated tautomer. Protonation of the ring is endothermic for i-$C_4H_9NH_3^+$ as reagent ion. Because N-protonation is thermodynamically favoured, the results provide further evidence for kinetic control in gas-phase Brønsted acid chemical ionization. (Int J Mass Spectrom 195/196 (2000) 33–43) © 2000 Elsevier Science B.V.

Keywords: Protonation site; N-alkylanilines; Chemical ionization of alkylanilines; Low energy CID

1. Introduction

There is a continuing interest in the site of protonation of benzene derivatives, many of which not only have the aromatic ring but also the substituent as basic sites capable of being protonated [1]. From the observed correlation of the proton affinities of monosubstituted benzenes with σ^+ (para) [2] for the substituent, Lau and Kebarle [3] concluded that, at equilibrium, aniline, anisole, phenol, toluene, ethylbenzene, chlorobenzene, and fluorobenzene were ring protonated. Benzaldehyde, benzonitrile, and nitrobenze showed higher proton affinities than predicted from the correlation leading to the conclusion that they were protonated at the substituent. The conclusions of Lau and Kebarle with respect to anisole and benzaldehyde are supported by the correlation of the proton affinities of oxygen-containing compounds with the O(1s) core ionization energies [4]. However, the conclusion with respect to ring protonation of aniline is suspect because more detailed studies [5] have shown that the ring and nitrogen proton affinities of aniline are very similar with that for the nitrogen being 1–3 kcal mol^{-1} greater. A number of substituted anilines are preferentially ring protonated in the gas phase at equilibrium; these include *m*-anisidine, *m*-toluidine, *m*-phenylenediamine, and *m*-thio-

* Corresponding author. E-mail: aharriso@alchemy.chem.utoronto.ca

Dedicated to the memory of Bob Squires, a brilliant scientist and an outstanding individual who is sorely missed.

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Table 1
Metastable ion fragmentation of protonated N-alkylanilines

		Neutral lost (%)			
Aniline	Preparation	$-H_2$	$-CH_3$	$-C_2H_4$	$-C_2H_5$
N-Me	CH_4 CI	49.4	50.6		
	FAB		100		
N-Me_2	CH_4 CI	37.5	62.5		
	FAB		100		
N-Et	CH_4 CI	60.7		37.5	1.8
	CH_3OH CI	59.8		36.6	3.6
	$(CH_3)_2CO$ CI	34.1		60.9	5.0
	FAB			90.0	10.0
N-Et_2	CH_4 CI	69.8		20.7	9.5
	CH_3OH CI	59.2		25.3	15.6
	$(CH_3)_2CO$ CI	38.8		42.6	18.5
	FAB			63.6	36.4

methoxyaniline [6,7]. On the other hand N-alkyl substituted anilines are reported to be protonated at nitrogen under conditions of thermodynamic equilibrium [8].

In Brønsted acid chemical ionization studies protonation may occur under kinetic control rather than thermodynamic control with the results that the site of protonation may not be the same as that determined from equilibrium studies [9,10]. Thus, although the thermodynamically favoured site of protonation of fluorobenzene is the aromatic ring [3], there is substantial evidence [11–15] that protonation occurs at fluorine to a considerable extent under CH_4 CI conditions. On the other hand, numerous studies [16–18] have concluded that, under CH_4 CI conditions, nitrobenzene is protonated at the nitro group, the thermodynamically favoured site [3]. Recent studies [19,20] have concluded that phenyl *n*-propyl and phenyl *i*-propyl ethers protonate at both the ring and the oxygen under chemical ionization conditions although the ring is the thermodynamically favoured site.

There have been numerous investigations [16,21–26] of the site of protonation of aniline under Brønsted acid CI conditions. In early studies Martinson and Buttrill [16] observed clustering of protonated aniline with H_2O and concluded that predominantly N-protonation had occurred. From CID studies of labeled anilines, Cooks and co-workers [22] concluded that protonation occurred largely on the ring, whereas, from a study of proton-transfer reactions of protonated partially deuterium-labeled anilines with nitrogen bases, Kenttämaa and co-workers [25] concluded that aniline was protonated at nitrogen. Nold and Wesdemiotis [26], from neutralization–reionization studies, concluded that the ring-protonated species was the predominant product formed with a variety of gaseous Brønsted acid reagents; by contrast, fast atom bombardment (FAB) ionization produced predominantly the anilinium ion (N-protonated tautomer). Karpas et al. [23] observed two species in ion mobility experiments and concluded that both the ring-protonated and N-protonated species were formed. It appears likely that both tautomers are formed under CI conditions and that the results observed depend on the reagent gas, the lifetime of the ions sampled, and the method of sampling. In the present work we report a study of the site of protonation of N-alkylanilines. Although protonation at the nitrogen is thermodynamically favoured [8], the results obtained indicate that significant protonation occurs on the aromatic ring under Brønsted acid CI conditions.

2. Experimental

Metastable ion studies and low-energy CID studies were carried out using a VG Analytical (Manchester, UK) ZAB-2FQ hybrid BEqQ mass spectrometer that has been described in detail previously [27]. Briefly, the instrument is a reversed-geometry (BE) double-focusing mass spectrometer equipped with either a combined EI/CI source or a FAB source. The high resolution BE stage is followed by a deceleration lens system, a rf-only quadrupole collision cell, *q*, and a quadrupole mass analyzer *Q*. In the metastable ion studies the appropriate ion beam was mass selected by the BE double-focusing mass spectrometer at 6 keV ion energy, decelerated to ~20 eV kinetic energy and introduced into the rf-only quadrupole cell *q* in the absence of collision gas. The products of unimolecular fragmentation in the cell were analyzed by scanning the final mass-analyzing quadrupole *Q*. Low-energy CID experiments were carried out in the same

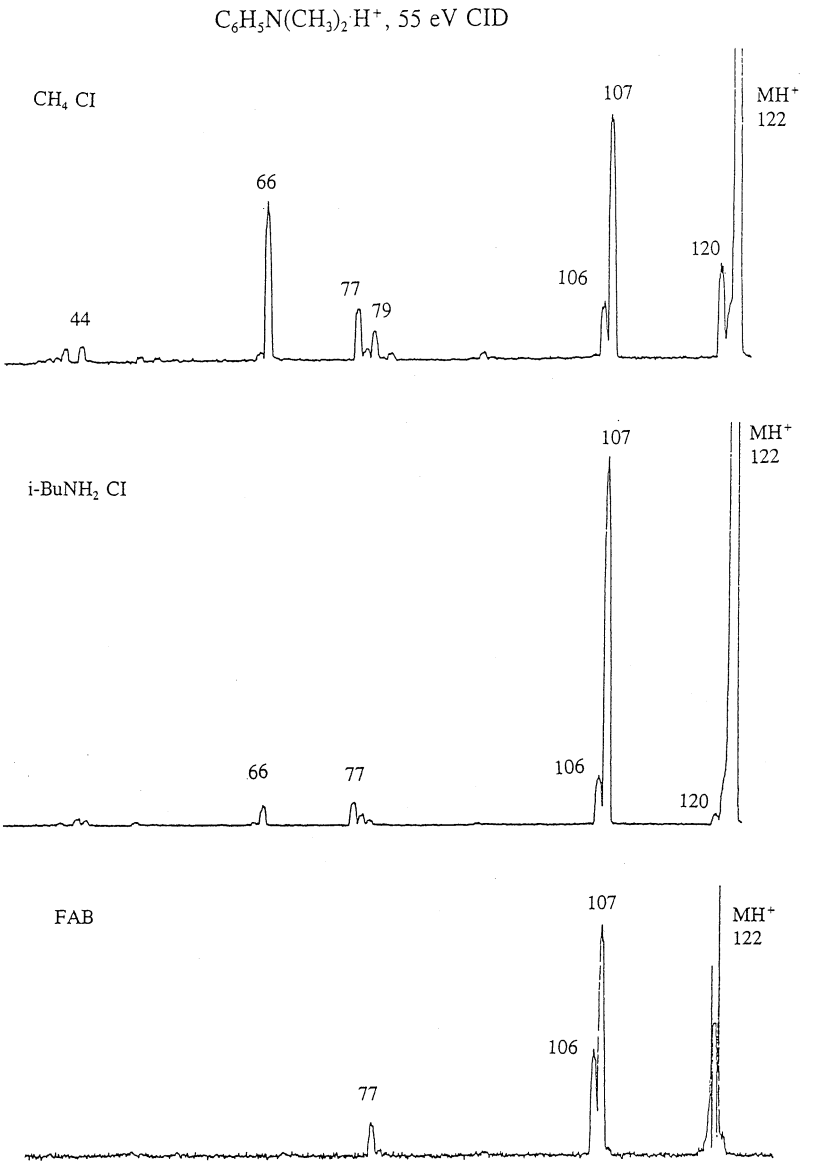
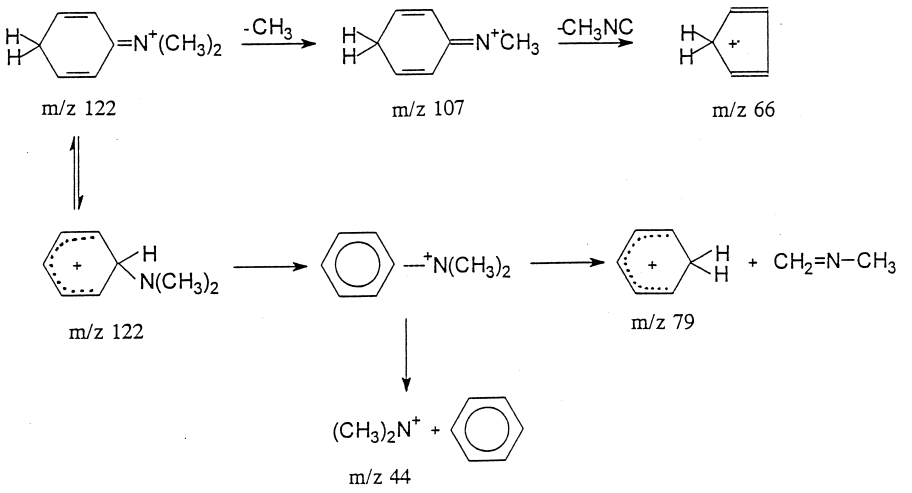


Fig. 1. 55 eV CID mass spectra of protonated N,N-dimethylaniline prepared by different methods.

fashion but with the addition of N_2 collision gas at a pressure of 1–2 $\times$ 10^{-7} Torr (1 Torr = 133.3 Pa) as indicated by the ionization gauge attached to the pumping line for the quadrupole section. In the CID experiments either the collision energy was kept constant while ions from different sources were compared or the collision energy was varied, typically, from 5–45 eV (laboratory scale). The results of the latter energy-resolved experiments [28–30] are presented in the following in the form of breakdown graphs showing the fractional fragment ion abundances as a function of the collision energy.

In the chemical ionization experiments the ZAB instrument was operated in the CI mode with a source



Scheme 1.

temperature of 200 °C. Methane [PA(CH_4) = 129.9, PA(C_2H_4) = 162.1], methanol [PA(CH_3OH) = 180.2], acetone {PA[$(CH_3)_2CO$] = 194.1} and *i*-butyl amine [PA(*i*-$C_4H_9NH_2$) = 221.0] (all PAs in kcal mol^{-1} from [31]) were used as Brønsted acid reagents to explore the effect of protonation exothermicity on protonation site. The methane was introduced through the CI reagent gas inlet line whereas the other reagents were introduced through the heated inlet along with the aniline. CD_4 was used as reagent gas to produce MD^+ ions. MH^+ ions of the anilines also were produced by FAB ionization using a 1:1 thioglycerol/2,2-dithiodiethanol matrix saturated with oxalic acid and an argon atom beam of 7–8 keV energy.

N-Methylaniline, N-N-dimethylaniline, N-ethylaniline, and N-N-diethylaniline were obtained from Aldrich Chemical Co. (Milwaukee, WI) and showed no impurities in their mass spectra.

3. Results and discussion

Table 1 presents the results obtained for the unimolecular fragmentation of the MH^+ ions of N-methylaniline, N,N-dimethylaniline, N-ethylaniline, and N,N-diethylaniline. For the two methylanilines the MH^+ ions were also prepared by CH_4 CI and by FAB, whereas for the two ethylanilines the MH^+ ions were also prepared with CH_3OH and $(CH_3)_2CO$ as reagent gases. The most striking result is the substantial ion signal for elimination of H_2 from the MH^+ ions prepared by chemical ionization and the complete absence of this ion signal for the MH^+ ions prepared by FAB ionization. We interpret this difference as indicating that predominantly, if not exclusively, the N-protonated alkylaniline is formed by FAB ionization but that a significant fraction of the MH^+ ions produced by gas-phase chemical ionization are the ring-protonated tautomer. Although the mechanism of ion formation in FAB has not been completely resolved [32–37], there is evidence for preformation of ions in solution [32,37] and for formation of gaseous ions by desolvation of charged clusters [35]. Anilines are N-protonated in solution because of the more effective solvation of the N-protonated species and either of these mechanisms of ion formation by FAB would lead to the N-protonated species. An earlier study [24] of the hydrogen/deuterium (H/D) exchange of protonated anilines with ND_3 has presented evidence that the N-protonated species are

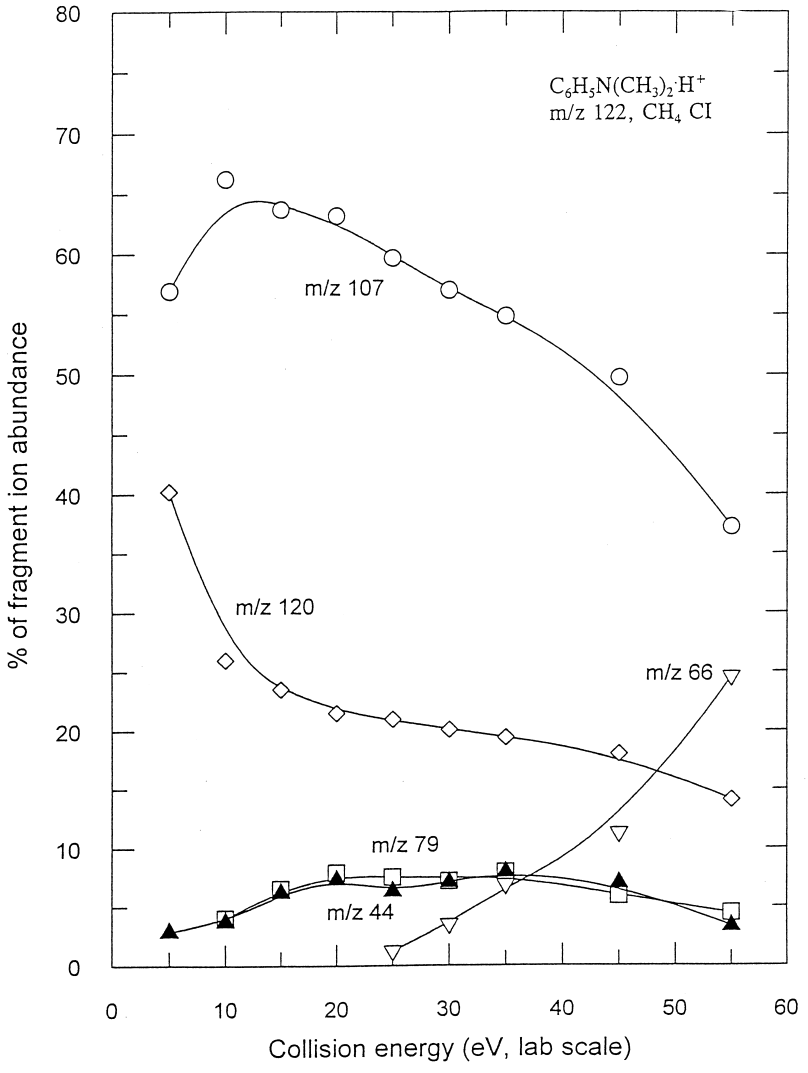


Fig. 2. Breakdown graph for protonated N,N-dimethylaniline prepared by CH_4 CI.

preferentially formed by FAB ionization whereas Nold and Wesdemiotis [26] have reported that FAB ionization of aniline produces more of the N-protonated tautomer than does gas-phase chemical ionization. The MD^+ ions of the alkylanilines prepared by CD_4 CI showed loss of both H_2 and HD in metastable ion fragmentation and in collision-induced fragmentation. The ratio $-H_2/-HD$ was 6.0 ± 0.3 independent of collision energy. Scrambling of the added D with the five phenyl hydrogens prior to fragmentation should lead to $-H_2/-HD = 2$; clearly there is a large isotope effect favouring H_2 loss over HD loss. The lower metastable ion signal for H_2 loss for acetone chemical ionization (Table 1) indicates that there is less ring protonation with acetone as the CI reagent than with CH_4 or methanol as the CI reagent.

The proton affinities $PA(C_6H_5NHCH_3) = 219.1$ kcal mol^{-1}, $PA[C_6H_5N(CH_3)_2] = 224.9$ kcal mol^{-1}, $PA(C_6H_5NHC_2H_5) = 221.0$ kcal mol^{-1} and

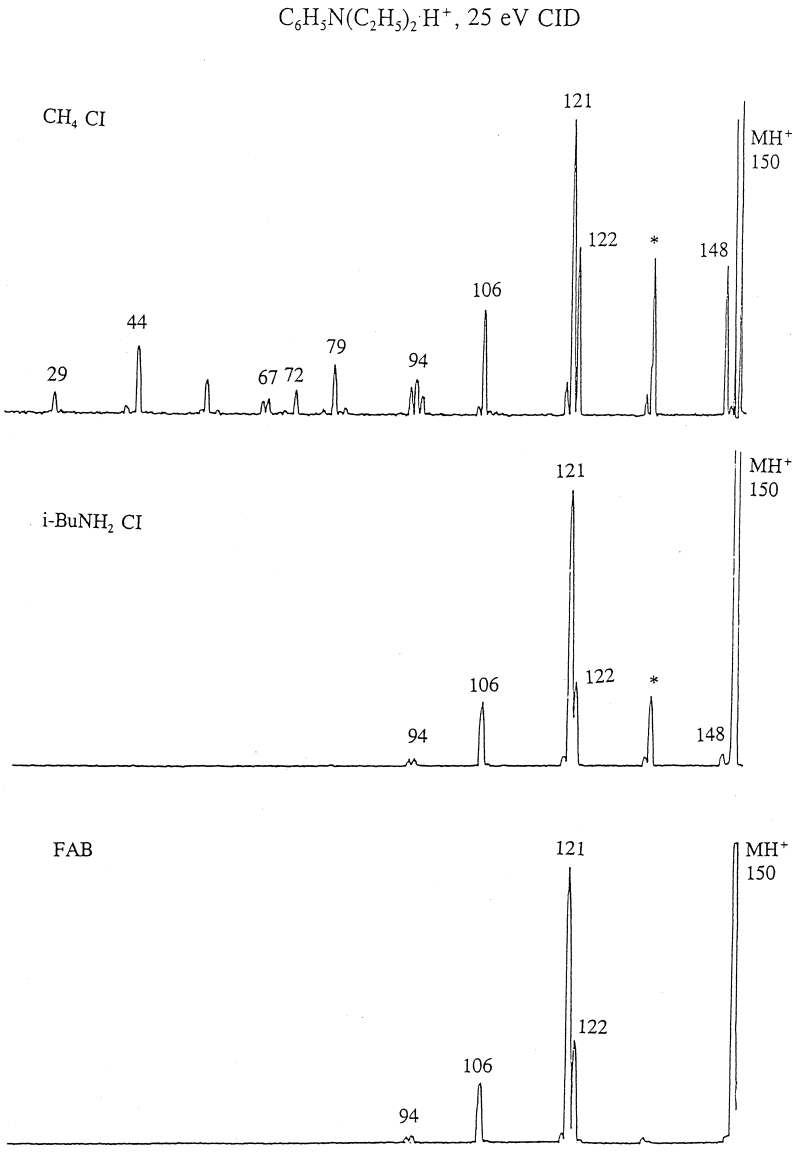
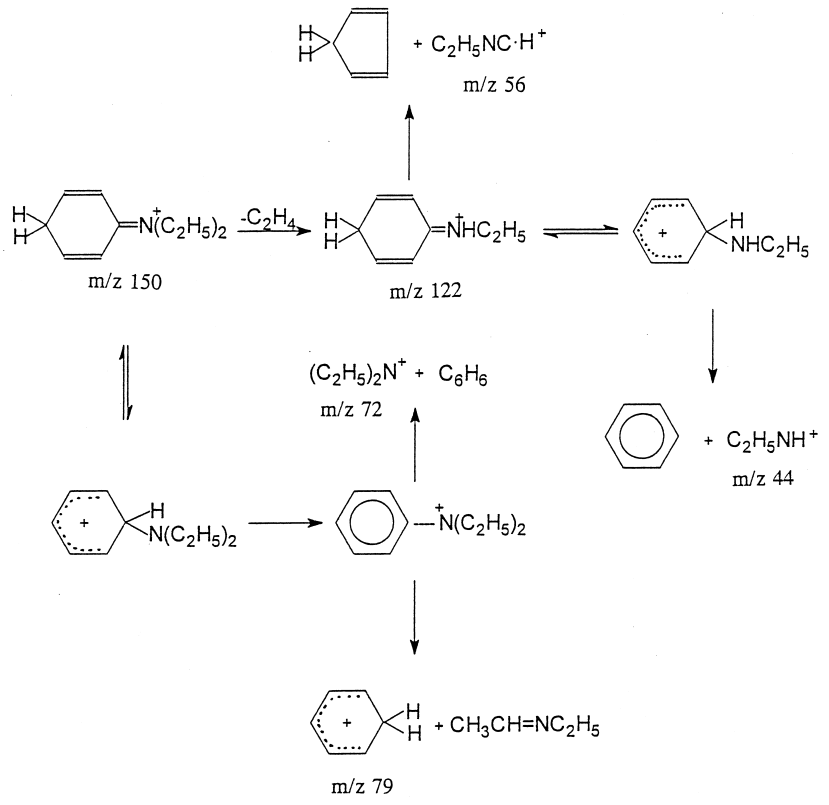


Fig. 3. 25 eV CID mass spectra of protonated N,N-diethylaniline prepared by different methods. Asterisk indicates peak arising from fragmentation of ^{13}C isotope of $M^{+\cdot}$.

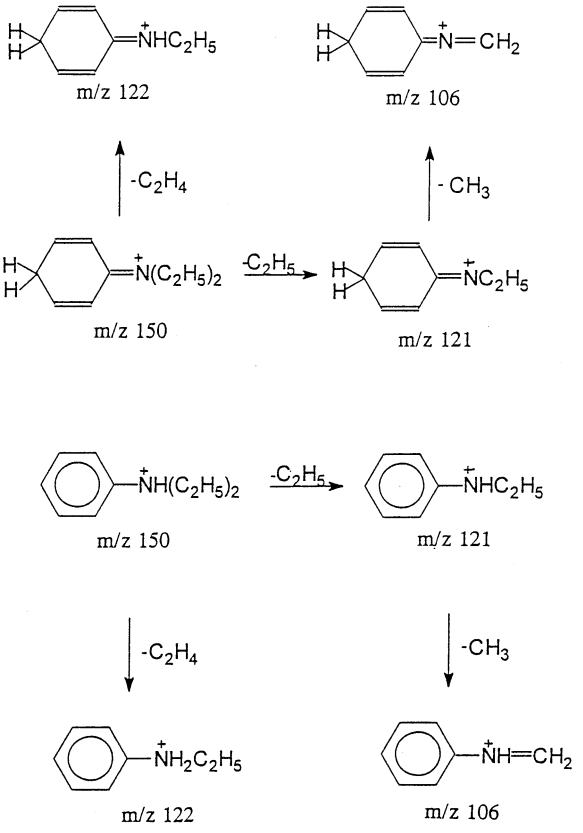
$PA[C_6H_5N(C_2H_5)_2] = 229.4$ kcal mol^{-1} are recorded by Hunter and Lias [31]; the studies of Lau et al. [8] concluded that these refer to protonation on nitrogen in each case. From the correlation of the proton affinities of monosubstituted benzenes that are ring protonated with σ^+ (para) for the substituent [3], we estimate the ring proton affinities of the N-alkylated benzenes to be in the range 214–220 kcal mol^{-1} using σ^+ (para) values recommended by Hansch et al. [38]. It is clear that $CH_5^+/C_2H_5^+$, $CH_3OH_2^+$, or



Scheme 2.

$(CH_3)_2COH^+$ are capable of protonation of either the ring or the nitrogen in exothermic reactions. However, i-$C_4H_9NH_3^+$ (PA(i-$C_4H_9NH_2$) = 221 kcal mol^{-1} [30]) might be expected to be more selective in its site of protonation. Fig. 1 compares the 55 eV CID mass spectra of the MH^+ ion of N,N-dimethylaniline prepared by CH_4 CI, by i-$C_4H_9NH_2$ CI and by FAB ionization. Clearly, the CID spectra of the MH^+ ions produced by CH_4 CI and by FAB ionization are distinctly different, indicating that different tautomers or different mixtures of tautomers are formed in the two cases. The CID spectrum of the MH^+ ions prepared by i-$C_4H_9NH_2$ CI is very similar to that of the MH^+ ions produced by FAB ionization. Because protonation of the ring should be endothermic for i-$C_4H_9NH_3^+$ as reagent, we are led to the conclusion that N-protonation occurs predominately for both i-$C_4H_9NH_2$ CI and FAB ionization. However, there are low-intensity signals at both *m/z* 120 and *m/z* 66 in the CID of the MH^+ ion produced by i-$C_4H_9NH_2$ CI indicating a small amount of ring protonation presumably from reaction of reagent ions with excess internal energy. The fragment ions observed at *m/z* 79, *m/z* 66, and *m/z* 44 in the CID spectrum of the MH^+ ions prepared by CH_4 CI are consistent with fragmentation of a ring-protonated species as outlined in Scheme 1. The breakdown graph (Fig. 2) for the MH^+ ion produced by CH_4 CI shows that formation of *m/z* 66 is a relatively high-energy process and is observed only at collision energies above ~25 eV.

Fig. 3 compares the 25 eV CID mass spectra obtained for the MH^+ ion of N,N-diethylaniline



Scheme 3.

prepared by CH_4 CI, by *i*-$C_4H_9NH_2$ CI and by FAB ionization. Again the CID spectra of the MH^+ ions produced by CH_4 CI and by FAB ionization are distinctly different, indicating different structures or mixtures of structures for the MH^+ ions produced by the two methods. The low intensity of the *m/z* 148 ion signal in the spectrum of the MH^+ ion produced by *i*-$C_4H_9NH_2$ CI indicates very little ring protonation in this case with the result that the CID spectrum is very similar to that of the MH^+ ion produced by FAB ionization. Apart from the *m/z* 148 (MH^+-H_2) ion signal, the CID spectrum of the MH^+ ion produced by CH_4 CI is unique in that a number of low-intensity low-mass ion signals are observed. A number of these can be rationalized in terms of fragmentation of a ring-protonated species as outlined in Scheme 2. An open question is whether the fragment ions of *m/z* 122, 121, and 106 have the same structures when originating from the MH^+ ions produced by CH_4 CI and by FAB ionization. One can propose fragmentation sequences leading to these products from either the ring-protonated or N-protonated forms as outlined in Scheme 3. Thus, it is possible that the major fragment ions have different structures in the two spectra; experiments to characterize the structures have proven inconclusive to date. The mechanism of fragmentation of the phenylalkyl ammonium ions will be discussed in detail in a future article.

Fig. 4 presents the breakdown graph for the MH^+ ion of N-ethylaniline prepared by FAB ionization whereas Fig. 5 presents the breakdown graph for the MH^+ ion prepared by CH_4 CI. The breakdown graph

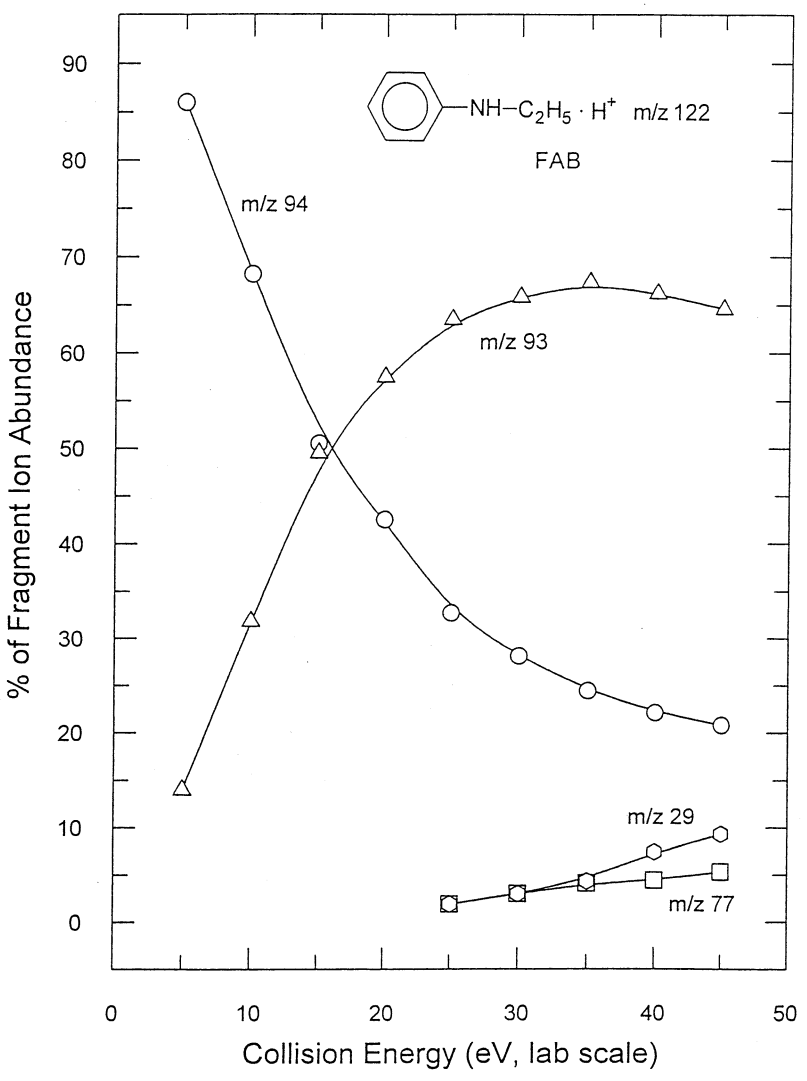


Fig. 4. Breakdown graph for protonated N-ethylaniline prepared by FAB ionization.

of Fig. 4 is very simple, showing dominant elimination of ethylene (*m/z* 94) at low collision energies with elimination of C_2H_5 (*m/z* 93) increasing in importance as the collision energy increases. There is also very minor formation of $C_2H_5^+$ and $C_6H_5^+$ at higher collision energies. By contrast, the breakdown graph (Fig. 5) for the MH^+ ion prepared by CH_4 CI is much more complex. Not only is elimination of H_2 observed, decreasing in importance with increasing collision energy, but there is also a much more pronounced formation of $C_2H_5^+$ (*m/z* 29) at higher collision energies. It appears that the latter must originate from fragmentation of the ring-protonated species; N–C bond fission in the N-protonated species should lead to ionized aniline rather than the ethyl ion because the ionization energy of aniline (7.72 eV) [39] is lower

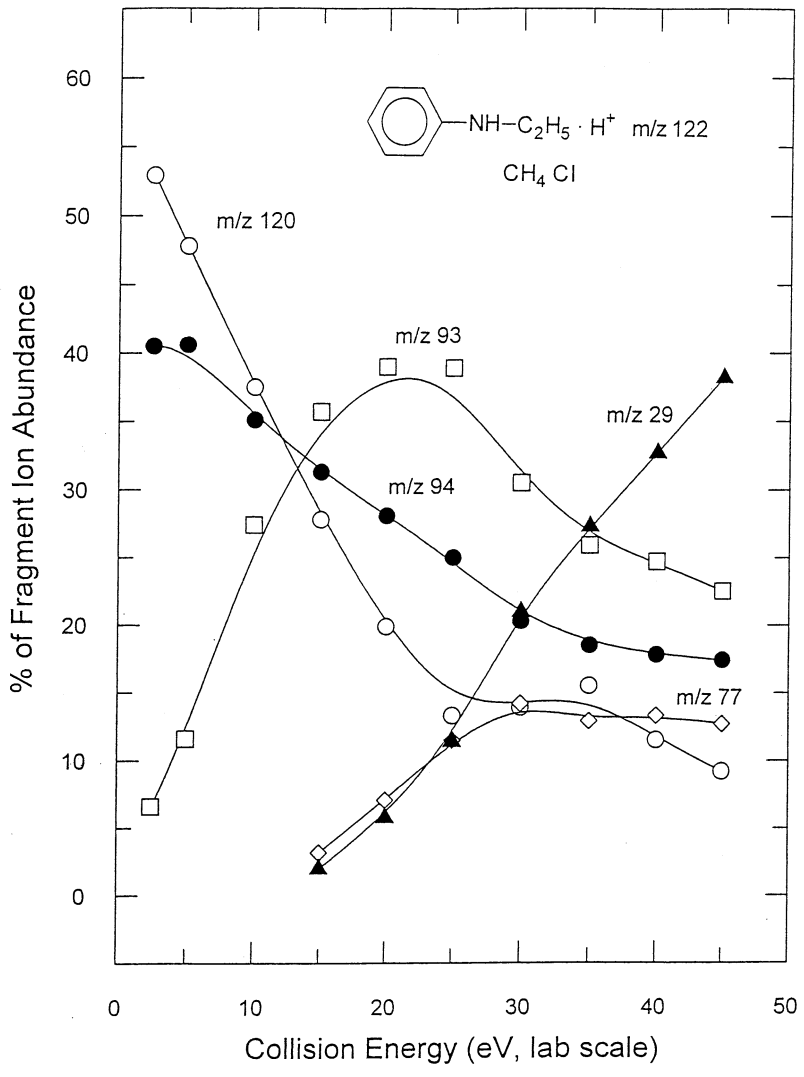


Fig. 5. Breakdown graph for protonated N-ethylaniline prepared by CH_4 CI.

than the ionization energy of the ethyl radical (8.13 eV) [39]. Again it is not clear whether the *m/z* 94 and *m/z* 93 products have the same or different structures in the two spectra.

4. Conclusions

The present work has been shown that protonation of N-alkylanilines in the gas phase with the Brønsted acid reagents CH_4, CH_3OH, and $(CH_3)_2CO$ leads to significant, if not exclusive, formation of the ring-protonated tautomer. By contrast, protonation of N-alkylanilines by FAB ionization leads to N-protonation, the thermodynamically favoured site of protonation. It is clear that protonation of the N-alkylanilines in gas-phase chemical ionization is under kinetic control. This preferential ring protonation presumably reflects interaction of the Brønsted acid reagent ion with the negative charge site of the ring in the polar alkylanilines. Although we have written of

ring protonation as occurring at the *para* position, it is clear from the results with CD_4 as reagent that the added proton samples all ring positions prior to fragmentation of MH^+.

Acknowledgement

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