The Site of Protonation of Aniline

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Abstract: The long-standing question concerning the protonation site of gaseous aniline has been addressed by allowing partially deuterium-labeled aniline ions to react with nitrogen bases in a dual-cell Fourier transform ion cyclotron resonance device. The results show unambiguously that nitrogen is the kinetically favored protonation site of gaseous aniline.

Introduction

Aniline is a well-known nitrogen base in aqueous solution. However, the site of proton attachment in *gaseous* aniline has been a topic of lively dispute for almost twenty years.[1−8] The experimental determination of the gas-phase basicity of aniline in 1976 first suggested that it may be energetically feasible to protonate aniline on a ring carbon.[1] Molecular orbital calculations later showed that although the nitrogen atom is the thermodynamically preferred protonation site, it is only favored by 1−3 kcal/mol over the energically most favorable site in the ring, the *para* position.[2,5] Experimental evidence in support of gaseous aniline acting as a nitrogen and not as a carbon base was obtained by correlating the proton affinities of differently substituted anilines with the ionization energies of the nitrogen 1s electron.[2]

The investigations described above were rapidly followed by other studies. Mass spectrometry experiments involving collision-activated dissociation of partially deuterated aniline ions suggested preferential ring protonation under chemical ionization conditions.[4,6,7] This finding was proposed[4] to reflect thermodynamic control over the protonation site. More recently, ion mobility spectrometry/mass spectrometry was used to show that protonation of gaseous aniline at atmospheric pressure yields two isomeric ions.[8] These isomers were tentatively assigned to have the nitrogen- and ring-protonated structures. The former structure was proposed to be associated with the lower mobility.[8] Based on these assumptions, the results were interpreted to indicate a preference for nitrogen protonation in aniline.[8]

We report here an examination of the reactions of partially deuterium-labeled aniline ions with bases. The findings presented demonstrate that when protonated under kinetic control, gaseous aniline is predominantly a nitrogen base.

Experimental Section

All experiments were carried out using an Extrel Model 2001 Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR).[9] This instrument contains a dual cell that consists of two identical cubic 2-in. cells joined by a common wall (the conductance limit). The cell is differentially pumped. It is aligned collinearly within the magnetic field produced by a 3.0 T superconducting magnet operated at about 2.8 T. The base pressure in the cell was $<10^{-9}$ Torr and it was maintained with two Balzers turbomolecular pumps (330 L/s), each backed by an Alcatel 2012 mechanical pump.

Samples were introduced into the instrument by using two Extrel single batch inlet systems equipped with a variable leak valve, or by using a Varian leak valve. The nominal partial pressure of aniline was 3×10^{-8} to 6×10^{-8} Torr, as measured with an ionization gauge. The chemical ionization reagent (CH_4, CD_4, or isobutane) was used at a higher nominal pressure (1×10^{-7} Torr). Electron impact on this mixture yielded mostly ions originating from the chemical ionization reagent. The ion signal was optimized for each experiment by varying the electron energy (typically 20 to 50 eV), emission current (either 4 or 8 μA), and ionization time (typically 30 to 50 ms). The initially generated ions either were directly used to ionize aniline (e.g., proton transfer from $(CH_3)_3C^+$ formed from isobutane) or were allowed to react with the chemical ionization reagent gas to yield the desired reagent ion (e.g., CH_5^+ formed upon reactions of $CH_4^{\bullet+}$ and CH_3^+ with CH_4) which then transferred a proton or deuteron to aniline. The time allowed for ionization of aniline was varied from 0.85 up to 1.3 s.

The aniline ions generated as described above were transferred from the cell in which they were formed into the other cell. Before ion transfer, ions were removed from the destination cell by applying a negative potential (−10 V) to the remote trapping plate of that cell (typically for 5 ms). Ion transfer was carried out by grounding the conductance limit plate (typically for 100 μs), which allowed the ions to pass through the 2-mm hole in this plate. At all other times, this plate and the other two trapping plates perpendicular to the magnetic field lines were kept at +2 V. The transferred ions were kinetically and internally cooled through several collisions (≥50) with argon introduced via a set of pulsed valves into the cell at a nominal peak pressure of 1×10^{-5} Torr. A short cooling time (500−600 ms) and a high argon pressure were used to ensure that the aniline ions collided with argon and not with the base present in the cell at a much lower pressure (see below). After collisional cooling, all undesired ions were removed from the cell by using radio frequency voltage pulses and sweeps or the stored-waveform inverse Fourier-transform excitation method[10] (Extrel SWIFT module). Care was taken to avoid kinetic excitation of the ions to be studied.

[®] Abstract published in *Advance ACS Abstracts*, July 1, 1995.

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[7] See also: Maquestiau, A.; Van Haverbeke, Y.; Mispreuve, H.; Flammang, R.; Harris, J. A.; Howe, I.; Beynon, J. H. *Org. Mass Spectrom.* **1980**, *15*, 144.

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[9] For example, see (a) Smith, R. L.; Franklin, R. L.; Stirk, K. M.; Kenttämaa, H. I. *J. Am. Chem. Soc.* **1993**, *115*, 10348. (b) Stirk, K. M.; Smith, R. L.; Orlowski, J. C.; Kenttämaa, H. I. *Rapid Commun. Mass Spectrom.* **1993**, *7*, 392.

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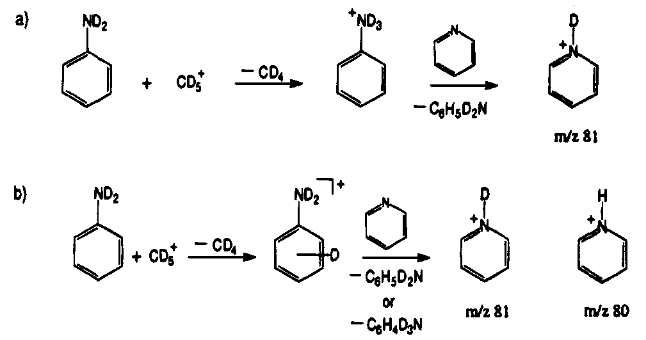
Scheme 1



The isolated ions were allowed to react with a base (pyridine at a nominal pressure of 4×10^{-8} to 6×10^{-8} Torr or triethylamine at about 9×10^{-8} Torr) for a variable time period. Reaction rate constants (k) were determined from the decay of the reactant ion abundance as a function of time and an estimated pressure, as described earlier.[9] Reaction efficiencies were obtained by dividing each rate constant k with the calculated collision rate constant k_{coll}.[11]

All the spectra discussed are an average of at least twenty transients obtained by exciting the ions either by a frequency sweep ("chirp") of 124 V_{p-p} amplitude, 2.7 MHz band width, and 3.0 kHz/μs sweep rate or by stored waveform inverse Fourier-transform excitation yielding a 0.5 cm final radius for all ions. The spectra were recorded as 32k data points at a digitizer rate of 5.3 MHz and were subjected to one zero fill before Fourier transformation.

All chemicals were obtained commercially and were checked for purity by gas chromatography and by mass spectrometry. Prior to experimentation, all deuterated reagents were allowed to equilibrate with the inside surfaces of the stainless steel inlet system of the mass spectrometer until the mass spectrum showed that the compound was no longer exchanging deuterium atoms with the walls of the inlet system. This procedure assured that the neutral reagent had the desired number of deuteriums when used in the experiments.

Results and Discussion

The nitrogen- and carbon-bonded hydrogens of aniline were distinguished by using two labeled compounds, aniline-*N*,*N*-d_2 and aniline-d_5. A proton or a deuteron was added to these molecules by using different ionic Brϕnsted acids. A relatively short reaction time and low partial pressure of neutral aniline were used to ensure that the aniline ions could not undergo equilibration by deprotonation/protonation involving neutral aniline. An average of one to two collisions occur under these conditions; i.e., the protonation/deuteration of aniline occurred under kinetic control.

The exact bonding site of the proton or deuteron added to the anilines was probed by allowing the ions to react with two strong bases, pyridine and triethylamine. Proton/deuteron abstraction by these bases from the nitrogen- and carbon-protonated anilines is highly exothermic and will occur readily (the proton affinities[12] of pyridine and triethylamine are 220.8 and 232.3 kcal/mol, respectively; that measured[12] for aniline is 209.5 kcal/mol). Indeed, the reaction efficiencies (k/k_{coll}) were found to be high, ranging from 28% to 70% (reactions with triethylamine are more efficient than those of pyridine; labeled and unlabeled aniline ions react at the same efficiency). Under these conditions, the carbon- and nitrogen-protonated anilines can be expected to react at the same rate (near the collision rate). Therefore, the product distributions obtained from these reactions will reflect the distribution of the isomeric reactant ions.

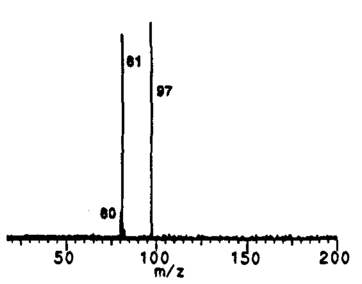
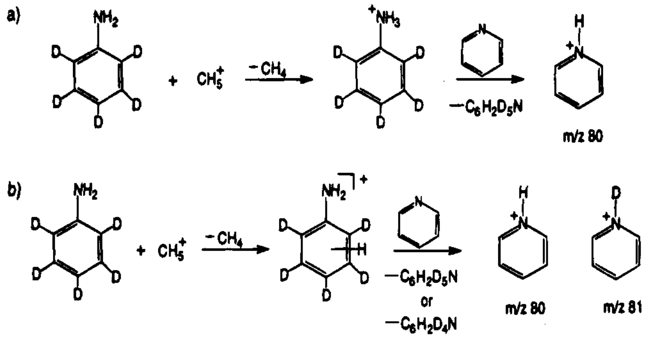


Figure 1. The ion (*m/z* 97) obtained by adding a deuteron to aniline-*N*,*N*-d_2 predominantly transfers a deuteron to pyridine (product ion of *m/z* 81). For this experiment, the reaction time was 1.5 s and the nominal pyridine pressure was 4×10^{-8} Torr.

Scheme 2



Protonated aniline-*N*,*N*-d_2 was found to transfer predominantly deuteron ($\approx$1.5:1) to pyridine. The ring-protonated ions derived from aniline-*N*,*N*-d_2 can only transfer a proton to a base while deuteron transfer will compete with proton transfer for the nitrogen-protonated ion. Hence, the finding of predominant deuteron transfer strongly suggests that aniline-*N*,*N*-d_2 is mostly protonated at the nitrogen atom. This preliminary finding was further tested by the following experiments.

Transfer of a deuteron from CD_5^+ to the nitrogen atom of aniline-*N*,*N*-d_2 would yield an ion (*m/z* 97) with only deuteriums at the acidic site. This ion can only transfer a deuteron to a base (Scheme 1a). However, if the added deuteron were bonded to the phenyl ring (Scheme 1b), both proton and deuteron transfer should occur. Proton transfer is expected to dominate by about a factor of 5 since the ring protons of ring-protonated aromatic molecules have been reported to undergo randomization.[13] This randomization was verified in the present study by allowing protonated benzene-d_6 to react with pyridine: a deuteron was transferred to the base nearly six times as often as a proton. Also, deuteron transfer to toluene was found to yield an ion that transfers a proton to pyridine five times as often as a deuteron (at 50% efficiency). Under the same conditions, the ion generated by deuteron transfer to aniline-*N*,*N*-d_2 donates predominantly deuterons to pyridine (*m/z* 81: *m/z* 80 = 10:1; Figure 1). This result indicates that the deuteron is attached to the nitrogen atom in approximately 86% of the reactant ions.[14]

A similar experiment was carried out by using the reversed labeling arrangement. Aniline-d_5 was protonated with CH_5^+ and in a separate experiment by $(CH_3)_3C^+$. The ring-protonated ion, if formed, is expected to react with a base by deuteron as well as proton transfer (Scheme 2b), and deuteron transfer should dominate by about a factor of 5. However, if protonation

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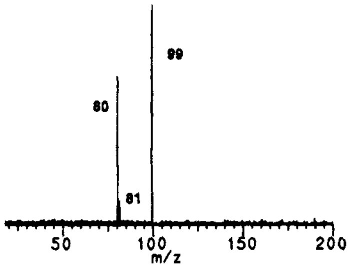

Figure 2. Reaction of pyridine (nominal pressure 6.0 × 10^{-8} Torr) with protonated aniline-d_5 (*m/z* 99) occurs by predominant proton transfer (product ion of *m/z* 80). The reaction time was 1 s.

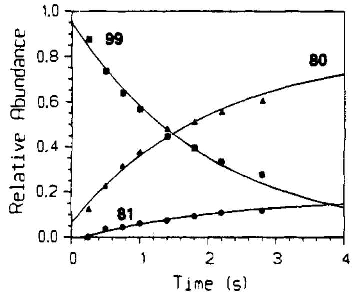

Figure 3. Temporal variation of ion abundances upon reaction of pyridine (nominal pressure 6.0 × 10^{-8} Torr) with protonated aniline-d_5 (*m/z* 99) to yield the ions of *m/z* 80 and 81. The lines drawn through the data represent the best fit to the pseudo-first-order rate equation involving two competitive product channels.

of aniline-d_5 occurred on the nitrogen, exclusive proton transfer should be observed (Scheme 2a). Proton transfer was found to be the predominant pathway upon reaction of the ion with both triethylamine and pyridine (*m/z* 80; Figure 2). In both cases, the results indicate that 88% of the reactant ions have the nitrogen-protonated structure.[14] This finding is independent of the time (0.1−5 s) allowed for the reaction with the different bases (Figure 3) and the type of reagent ion used for protonation of aniline-d_5 (CH_5^+ or $(CH_3)_3C^+$). Hence, nitrogen is concluded to be the kinetically favored protonation site of aniline.

Conclusions

Examination of the reactions of partially deuterium-labeled aniline ions with strong bases unambiguously demonstrates that nitrogen is the kinetically favored protonation site of gaseous aniline. Almost 90% of the aniline molecules were found to be protonated on the nitrogen atom. This quantitative result is in excellent agreement with that proposed in an earlier study.[8,15]

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[14] For [aniline-*N,N*-d_2 + D^+]: The abundance of the nitrogen-protonated ions was estimated from the abundance of the product ion of *m/z* 81 after correction for the ^{13}C isotope contribution from the ion of *m/z* 80. A correction was also made for the statistical probability of transferring a proton or deuteron by the ring-protonated ion. For example, 1/6 of the ring-protonated molecules transfer a deuteron and 5/6 transfer a proton to a base. Thus, an estimate for the abundance of the nitrogen-protonated ions was obtained by subtracting 1/5 of the abundance of the ion of *m/z* 80 (arising from proton transfer) from the abundance of the ion of *m/z* 81 and by adding the same amount to the abundance of the ion of *m/z* 80. Kinetic isotope effects were ignored since the calibration experiments using protonated benzene-d_6 and toluene suggest that they are small (see text).

[15] C. Wesdemiotis and M. J. Nold recently reported in the Annual Conference on Mass Spectrometry and Allied Topics (1995) the formation of N- and C-protonated aniline in the gas phase. Their findings suggest that N-protonation is favored thermodynamically.