Supplementary Material Available: Additional details of the methodology used throughout this work; tables including the more relevant structural and energetic data of **1a-c**, **2a-i** (in both (*E*) and (*Z*) configurations), **3a-o**, **8b-i**, **9b-i**, and **11b-i** (from both (*E*) and (*Z*) imines) and stationary points **8**, **9**, and **11** corresponding to different approaches between ketenes **1b,c** and imines **2g-i** in both (*E*) and (*Z*) configurations; complete ab initio data of the stationary points **9a** and **11a** computed at RHF/6-31G* and TCSCF/6-31G* levels of theory (17 pages). Ordering information is given on any current masthead page.

Electrophilic Aromatic Cl^+ Addition and $CO^{\cdot+}$ Substitution in the Gas Phase

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Abstract: Chlorine cation addition to benzene, aniline, anisole, styrene, chlorobenzene, and nitrobenzene was studied using NH_3Cl^+, $ClC{\equiv}O^+$, protonated CH_3Cl, and Cl^+ as reagent ions. The reactions of protonated monochloramine were followed using a direct insertion membrane probe for sample introduction and a pentaquadrupole mass spectrometer for product characterization. The other reagent ions $ClC{\equiv}O^+$, Cl^+, and protonated CH_3Cl were generated by electron ionization of acetyl chloride and carbon tetrachloride and by methane chemical ionization of CH_3Cl, respectively. The main reactions of NH_3Cl^+ with aromatic compounds are electrophilic Cl^+ and H^+ addition and charge exchange to form the aromatic radical cation. Reactions of $ClC{\equiv}O^+$ with aromatic compounds include (i) Cl^+ addition, (ii) $CO^{\cdot+}$ substitution for a hydrogen atom, and (iii) formation of the molecular radical cation of the substrate. The naked Cl^+ ion does not chlorinate aromatic compounds but does undergo charge exchange. Protonated CH_3Cl also fails to add Cl^+ to the aromatic compounds, proton transfer being the main reaction observed. Ion/molecule reaction products were characterized by comparing sequential product ion mass spectra (MS/MS/MS) to the MS/MS product ion mass spectra of reference ions, generated by chemical ionization of appropriate chlorine-substituted compounds. The sequential product spectra collected with the pentaquadrupole instrument show that both the Cl^+ addition products and the $CO^{\cdot+}$ substitution products are σ-bonded to the aromatic compound. Comparisons with the MS/MS spectra of model ions suggest that both Cl^+ and $CO^{\cdot+}$ add principally to the para position in aniline. Reaction occurs at the same position for anisole, although contributions from reactions at other sites are not excluded. Substitution of hydrogen by $CO^{\cdot+}$ in aniline and anisole also proceeds principally at the para position, although it also occurs at the nitrogen of aniline. Evidence is given for Cl^+ binding to the β-carbon in styrene and to the ring in chlorobenzene. Nitrobenzene, the least reactive compound, gave only traces of a Cl^+ addition product and did not undergo substitution of $CO^{\cdot+}$ for hydrogen. However, it did display one unique reaction, the substitution of NO_2' by Cl^+. The evidence provided by the MS^3 experiments for the site of Cl^+ addition was tested against—and found to be consistent with—the sites predicted to have the highest Cl^+ affinity by semiempirical AM1 molecular orbital calculations.

Introduction

The importance of electrophilic aromatic substitution in solution has made it a well-studied ion/molecule reaction. Mass spectrometric methods[1-6] have been used in many studies of protonation[1] as well as alkylation[1b,e,i,2] and acetylation[3] of aromatic compounds. Higher-pressure experiments have employed radiolytic methods to study alkylation reactions of various aromatic compounds.[7-12]

Among the electrophilic substitution reactions, halogenation of aromatic compounds in the gas phase has received limited attention because of the lack of appropriate halogenation reagents. Chlorine cation addition to aromatic compounds in the gas phase apparently occurs in an ion trap mass spectrometer,[6a] but it proceeds by charge exchange with the neutral aromatic compound followed by reaction of the aromatic molecular ion with molecular chlorine. The gas-phase bromination and iodination of aromatic compounds of the type C_6H_5X (X = F, Cl, Br, CH_3) have been investigated using Br^+ and I^+ produced by a radiolytic method.[11] Bromination and iodination occur but with low positional selectivity compared to the corresponding solution-phase reactions. Other authors have also reported, although incidentally, on the formation of halogenated aromatic compounds in the gas phase.[13] For example, in a study on the reactions of the pyridine molecular

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(1) (a) Lau, Y. K.; Kebarle, P. *J. Am. Chem. Soc.* **1976**, *98*, 7452. (b) Kruger, T. L.; Flammang, R.; Litton, J. F.; Cooks, R. G. *Tetrahedron Lett.* **1976**, *50*, 4555. (c) Pollack, S. K.; Devlin, J. L., III; Summerhays, K. D.; Taft, R. W.; Hehre, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 4583. (d) Maquestiau, A.; Van Haverbeke, Y.; Mispreuve, H.; Flammang, R.; Harris, J. A.; Howe, I.; Beynon, J. H. *Org. Mass Spectrom.* **1980**, *15*, 144. (e) Wood, K. V.; Burinsky, D. J.; Cameron, D.; Cooks, R. G. *J. Org. Chem.* **1983**, *48*, 5236. (f) Lau, Y. K.; Nishizawa, K.; Tse, A.; Brown, R. S.; Kebarle, P. *J. Am. Chem. Soc.* **1981**, *103*, 6291. (g) Liauw, W. G.; Harrison, A. G. *Org. Mass Spectrom.* **1981**, *16*, 388. (h) Houriet, R.; Schwarz, H.; Zummack, W.; Andrade, J. G.; Schleyer, P. v. R. *Nouv. J. Chim.* **1981**, *5*, 505. (i) Pachuta, S. J.; Isern-Flecha, I.; Cooks, R. G. *Org. Mass Spectrom.* **1986**, *21*, 1. (j) Mason, R.; Milton, D.; Harris, F. *J. Chem. Soc., Chem. Commun.* **1987**, 1453. (k) Fernandez, M. T.; Jennings, K. R.; Mason, R. S. *J. Chem. Soc., Faraday Trans. II* **1987**, *83*, 159. (l) McMahon, A. W.; Chadikun, F.; Harrison, A. G.; March, R. E. *Int. J. Mass Spectrom. Ion Proc.* **1989**, *87*, 275.

(2) (a) Sen Sharma, D. K.; Kebarle, P. *J. Am. Chem. Soc.* **1982**, *104*, 19. (b) Isern-Flecha, I.; Cooks, R. G.; Wood, K. V. *Int. J. Mass Spectrom. Ion Proc.* **1984**, *62*, 73. (c) Harrison, A. G. *Can. J. Chem.* **1986**, *64*, 1051. (d) Burinsky, D. J.; Campana, J. E. *Org. Mass Spectrom.* **1988**, *23*, 613. (e) Holman, R. W.; Gross, M. L. *J. Am. Chem. Soc.* **1989**, *111*, 3560. (f) Nourse, B. D.; Brodbelt, J. S.; Cooks, R. G. *Org. Mass Spectrom.* **1991**, *26*, 575.

(3) (a) Dunbar, R. C.; Shen, J.; Olah, G. A. *J. Am. Chem. Soc.* **1972**, *94*, 6862. (b) Chatfield, D. A.; Bursey, M. M. *J. Am. Chem. Soc.* **1976**, *98*, 6492.

(4) Ausloos, P. *Kinetics of Ion-Molecule Reactions*; Plenum Press: New York, 1979.

(5) (a) Benezra, S. A.; Hoffman, M. K.; Bursey, M. M. *J. Am. Chem. Soc.* **1970**, *92*, 7501. (b) Ausloos, P.; Lias, S. G. *Int. J. Chem. Kinet.* **1978**, *10*, 657.

0002-7863/93/1515-1004$04.00/0

ion with compounds of the type $CH_2{=}CHCH_2X$ (X = Cl, Br, I), halogenated pyridine ions were observed, but neither the mechanism nor the position of addition was elucidated.[13a] Similarly, in earlier work from this laboratory, reactions of the pyrene-derived ions $M^{\bullet+}$, $(M - H)^+$, and $(M - H_2)^{\bullet+}$ with alkyl iodides were investigated using an ion trap mass spectrometer,[13b] and an abundant ion/molecule reaction due to iodine atom addition to the $(M - H)^+$ ion was observed.

The present study of gas-phase halogenation arose from an interest in the halogenation of amines by monochloramine, NH_2Cl, in aqueous solution. Product distributions were measured using on-line membrane introduction mass spectrometry, which allows their selective transfer from solution into vacuum.[14a,b] The active chlorination agent is protonated monochloramine,[15] and therefore NH_3Cl^+ was chosen as a chlorination reagent in the present gas-phase study. Gaseous protonated monochloramine can be produced readily by chemical ionization of neutral monochloramine, the rather unstable neutral compound being conveniently transferred from aqueous solution into the ion source of a mass spectrometer via a silicone membrane.[14a] Membrane introduction mass spectrometry[14c] has the notable advantage of allowing the study of species which are stable in the aqueous phase but intractable by other methods.

Given the observation of chlorine cation addition to aromatic compounds by protonated chloramine, it became of interest to know whether other chlorine-containing ions react similarly. Other reagents investigated were Cl^+, $ClC{\equiv}O^+$, and protonated methyl chloride. The Cl^+ ion was used because it was of interest to know whether Cl^+ can add directly to aromatic compounds at the pressures employed or if a good leaving group, like NH_3 in the case of NH_3Cl^+ reagent ion, is necessary to stabilize the nascent product. The other ions were selected on the basis of their expected ability to eliminate the neutral molecules CO and CH_4 from the initial ion/molecule adduct.

A further aim of this study was to examine the dependence of Cl^+ addition and substitution of $CO^{\bullet+}$ for H^+ on the nature of the substrate, and this was done by examining aromatic compounds bearing both activating and deactivating substituents. Aromatic substituents selected included activating ortho/para-directing (NH_2, OCH_3, and $CH{=}CH_2$), deactivating ortho/para-directing (Cl), and deactivating meta-directing (NO_2) substituents in electrophilic aromatic substitution.[16] The ability to perform MS^3 experiments in the pentaquadrupole facilitates investigation of the site selectivity of these reactions. The pentaquadrupole instrument has, in addition to the ion source, two separate reaction regions in which either ion/molecule reactions or collision-activated dissociation (CAD) can be performed.[17a] The ability to mass-analyze ions before and after the sample enters each of these regions provides additional selectivity when ion/molecule reactions of specific reagent ions and/or the structures of ion/molecule reaction product ions are of interest. This type of analysis is facilitated by the set of powerful MS^3 scans available when using the pentaquadrupole instrument.[17b] The value of the pentaquadrupole instrument in studies of ion/molecule reactions has previously been demonstrated.[17c,d] The MS^3 sequential product ion spectra (viz. spectra showing fragmentation of an ion/molecule product itself formed from a mass-selected ion reacting in an earlier stage of the experiment) were recorded in order to determine the preferred site of Cl^+ addition by comparison to the MS/MS product spectra of reference compounds.

AM1[16] calculations have been successfully used in many problems of chemical interest.[19] The reliability of this method in the calculation of ionic affinities is established,[20] and the extension of the method to include halogenated compounds has proved to be successful.[20c] In view of this, AM1 calculations of Cl^+ affinities were judged to be a useful approach to complement the experimental results of this study.

Experimental Section

The experiments were performed using either a custom-built pentaquadrupole mass spectrometer,[17a] consisting of three mass-analyzing (Q1, Q3, Q5) and two collision quadrupoles (Q2, Q4), or a Finnigan Model 4500 triple quadrupole mass spectrometer with some additional data taken using a Finnigan Model 700 triple quadrupole. Ion/molecule reactions were performed in Q2 of the pentaquadrupole instrument after selection of the reagent ion with Q1. In these experiments, Q5 was used to record the ion/molecule product spectra while Q3 was operated in the nonanalyzing RF-only mode. The ion/molecule reaction products were characterized using sequential product scans, an MS^3 experiment (see ref 17b). In this scan mode, Q1 is used to select the reagent ion, and after reaction in Q2, Q3 is used to select the desired ionic reaction product, which is subsequently fragmented in Q4. In the final step, Q5 is scanned to record the sequential product spectrum. The nominal sample pressure in Q2 was typically 5×10^{-6} Torr, and when a neutral collision gas (argon) was employed in Q4 the total pressure was typically 5×10^{-5} Torr, corresponding to multiple-collision conditions in both cases. These pressures were measured by an ionization gauge mounted on the vacuum chamber, and the actual pressures within the sealed collision quadrupoles are expected to be significantly higher. The collision energy, calculated as the voltage difference between the grounded ion source and the collision quadrupole, was typically near 0 eV for ion/molecule reactions and 10 eV for collision-activated dissociation (CAD). Reagent ions were formed either by electron ionization (EI, 70 eV) or by chemical ionization (CI) using methane as reagent gas. Other reagent gases were used as indicated.

Product ion spectra of reference compounds were normally recorded using the Finnigan 4500 triple quadrupole instrument in the tandem mass spectrometry (MS/MS) mode. These samples were ionized by chemical

(6) (a) Haney, C. A.; Purrington, S. T.; Voyksner, R. D. Paper presented at the 12th International Mass Spectrometry Conference; Amsterdam, The Netherlands, 1991. (b) Reents, W. D., Jr.; Freiser, B. S. *J. Am. Chem. Soc.* **1980**, *102*, 271. (c) Dunbar, R. C.; Shen, J.; Melby, E.; Olah, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7200. (d) Speranza, M. *Adv. Heterocycl. Chem.* **1986**, *40*, 25.

(7) (a) Cacace, F. *Acc. Chem. Res.* **1988**, *21*, 215. (b) Speranza, M. *Gazz. Chim. Ital.* **1983**, *113*, 37. (c) Cacace, F. In *Kinetics of Ion–Molecule Reactions*; Ausloos, P., Ed.; Plenum Press: New York, 1979; p 199.

(8) (a) Attinà, M.; Cacace, F. *J. Am. Chem. Soc.* **1983**, *105*, 1122. (b) Attinà, M.; Cacace, F.; de Petris, G. *J. Am. Chem. Soc.* **1985**, *107*, 1556. (c) Aliprandi, B.; Cacace, F.; Fornarini, S. *Tetrahedron* **1987**, *43*, 2831.

(9) (a) Speranza, M. *Pure Appl. Chem.* **1991**, *63*, 243. (b) Bucci, R.; Grandinetti, F.; Filippi, A.; Laguzzi, R.; Occhiucci, G.; Speranza, M. *J. Am. Chem. Soc.* **1991**, *113*, 4550. (c) Filippi, A.; Occhiucci, G.; Sparapani, C.; Speranza, M. *Can. J. Chem.* **1991**, *69*, 740.

(10) (a) Attinà, M.; Cacace, F.; Yañez, M. *J. Am. Chem. Soc.* **1987**, *109*, 5092. (b) Attinà, M.; Cacace, F. *Gazz. Chim. Ital.* **1988**, *118*, 241. (c) Cacace, F.; Crestoni, M. E.; Fornarini, S.; Gabrielli, R. *Int. J. Mass Spectrom. Ion Proc.* **1988**, *84*, 17.

(11) (a) Cacace, F.; Stöcklin, G. *J. Am. Chem. Soc.* **1972**, *94*, 2518. (b) Knusi, E. J.; Halpern, A.; Stöcklin, G. *J. Am. Chem. Soc.* **1974**, *96*, 3733.

(12) (a) Giacomello, P.; Speranza, M. *J. Am. Chem. Soc.* **1977**, *99*, 7918. (b) Occhiucci, G.; Cacace, F.; Speranza, M. *J. Am. Chem. Soc.* **1986**, *108*, 872. (c) Speranza, M.; Laguzzi, G. *J. Am. Chem. Soc.* **1988**, *110*, 30.

(13) (a) Freeman, J. A.; Johnson, J. V.; Yost, R. A. Paper presented at the 38th ASMS Conference on Mass Spectrometry and Allied Topics; Tucson, Arizona; 1990, p 1495. (b) Nourse, B. D.; Cox, K. A.; Cooks, R. G. *Org. Mass Spectrom.* **1992**, *27*, 453.

(14) (a) Kotiaho, T.; Lister, A. K.; Hayward, M. J.; Cooks, R. G. *Talanta* **1991**, *38*, 195. (b) Kotiaho, T.; Hayward, M. J.; Cooks, R. G. *Anal. Chem.* **1991**, *63*, 1794. (c) Kotiaho, T.; Lauritsen, F. R.; Choudhury, T. K.; Cooks, R. G.; Tsao, G. T. *Anal. Chem.* **1991**, *63*, 875A.

(15) (a) Snyder, M. P.; Margerum, D. W. *Inorg. Chem.* **1982**, *21*, 2545. (b) Isaac, R. A.; Morris, J. C. *Environ. Sci. Technol.* **1985**, *19*, 810.

(16) (a) Norman, R. O. C. *Principles of Organic Synthesis*; Wiley: New York, 1978. (b) Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley & Sons: New York, 1990.

(17) (a) Schwartz, J. C.; Schey, K. L.; Cooks, R. G. *Int. J. Mass Spectrom. Ion Proc.* **1990**, *101*, 1. (b) Schwartz, J. C.; Wade, A. P.; Enke, C. G.; Cooks, R. G. *Anal. Chem.* **1990**, *62*, 1809. (c) Eberlin, M. N.; Majumdar, T. K.; Cooks, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 2884. (d) Shay, B. J.; Eberlin, M. N.; Cooks, R. G.; Wesdemiotis, C. *J. Am. Soc. Mass Spectrom.* In press.

(18) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(19) For recent examples see: (a) O'Shea, K. E.; Fox, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 611. (b) Dewar, M. J. S.; Hwang, J. C.; Kuhn, D. R. *J. Am. Chem. Soc.* **1991**, *113*, 735. (c) Kim, K. H.; Martin, Y. C. *J. Med. Chem.* **1991**, *34*, 2056. (d) Lahti, P. M.; Ichimura, A. S. *J. Org. Chem.* **1991**, *56*, 3030. (e) Larumbe, D.; Moreno, M.; Gallardo, I.; Bertrán, J.; Andrieux, C. P. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1437. (f) Katritzky, A. R.; Karelson, M. *J. Am. Chem. Soc.* **1991**, *113*, 1561. (g) Kim, K. H.; Martin, Y. C. *J. Org. Chem.* **1991**, *56*, 2723.

(20) (a) Dewar, M. J. S.; Dieter, K. M. *J. Am. Chem. Soc.* **1986**, *108*, 8075. (b) Myton, D. M.; O'Brien, R. J. *Anal. Chem.* **1991**, *63*, 1201. (c) Dewar, M. J. S.; Zoebisch, E. G. *J. Mol. Struct. (THEOCHEM)* **1988**, *180*, 1.

Table I. Summary of Electrophilic Aromatic Chlorine Cation Addition and Other Reactions[a]

	reagent			
	NH_3Cl^+		$ClC{\equiv}O^+$	
analyte	$(M + Cl)^+$	$(M + H)^+$	$(M + Cl)^+$	$(M - H + CO)^+$
benzene	*b*	*b*	*b*	*b*
aniline	*b*	*b*	*b*	*b*
anisole	*b*	*b*	*b*	*b*
styrene	*b*	*b*	*b*	*c*
chlorobenzene	*b*	*b*	*b*	*b*
nitrobenzene	*c*	*b*	*b,d*	*c*

[a] The bare Cl^+ ion does not add to any of these compounds. [b] Reaction occurs. [c] No addition product formed. [d] Only traces of Cl^+ addition product observed.

ionization using either methane, isobutane, or ammonia as the reagent gas. The reagent gas pressure in the ion source for Cl measurements was 0.5 Torr. A collision gas pressure of 1 mTorr of argon and 20-eV collision energy was normally selected when recording MS/MS product ion spectra. Note that the reagent and collision gas pressures for the pentaquadrupole instrument and the triple quadrupole instrument cannot be directly compared due to the different locations of the pressure gauges. For comparison to the 4500 triple quadrupole results, some of these experiments were repeated on the pentaquadrupole and on the Model 700 instrument.

Protonated monochloramine (NH_3Cl^+) was prepared by methane chemical ionization of monochloramine. The aqueous monochloramine solution was prepared according to reported methods[14a,15a] and introduced into the ion source of the pentaquadrupole instrument using a direct insertion membrane probe as already described.[14a] The ions $ClC{\equiv}O^+$ and Cl^+ were prepared in the ion source of the pentaquadrupole mass spectrometer by EI on acetyl chloride and carbon tetrachloride, respectively. Protonated methyl chloride was prepared by methane chemical ionization. All the compounds were commercially available and were used without further purification other than a single liquid nitrogen freeze–evacuate–thaw cycle to remove noncondensable gases. Many of the experiments were repeated using reagent ions containing ^{37}Cl to verify reaction products. Unless specified, the masses cited are those containing the ^{35}Cl isotope.

The reference compounds used to study the position of Cl^+ addition were 2-, 3-, and 4-chloroaniline, 2-, 3-, and 4-chloroanisole, and 1,2-, 1,3-, and 1,4-dichlorobenzene. These compounds were ionized using the chemical ionization gases methane, isobutane, and ammonia to probe whether the site of protonation is dependent on the choice of reagent ion and hence the reaction exothermicity. Two reference ions were generated to examine the sites of $CO^{\bullet+}$ substitution. The first, formed by methyl loss from 4-aminoacetophenone upon 70-eV EI, yields the model ion for *para*-(CO^+)-substituted aniline. The second model ion, N-protonated phenyl isocyanate, was generated both by methyl loss from acetanilide upon EI and by protonating phenyl isocyanate using methane CI.

The AM1[18] calculations were carried out on a Sun SPARCstation 1+ at Universidade Estadual de Campinas using the MOPAC6 program.[21] Full geometry optimizations starting from several different conformations were performed, and $\Delta H_f°$ values were calculated for all neutral compounds and for the most stable isomers of the chlorinated ions. The Cl^+ affinities were then derived from the negative of the enthalpy change of the chlorination reaction: $M + Cl^+ \rightarrow MCl^+$, where M is the aromatic molecule. The experimental value of the heat of formation of Cl^+ (329.4 kcal/mol)[22] was used since poor estimates for Cl^+ (356.2 kcal/mol, Table III) (and also H^+[20a]) are given by the AM1 method, as expected for such small ions.

Results and Discussion

Table I summarizes the results of Cl^+ addition and $CO^{\bullet+}$ substitution for selected aromatic compounds with NH_3Cl^+ and $ClC{\equiv}O^+$ reagent ions. Protonated monochloramine reacts with aromatic compounds by Cl^+ transfer and by proton transfer, as exemplified for benzene in eqs 1a and 1b, and also by charge exchange. Equations 2 and 3 show the corresponding reactions with $ClC{\equiv}O^+$ and Cl^+. The ion $ClC{\equiv}O^+$ chlorinates, substitutes $CO^{\bullet+}$ for hydrogen (most likely via an addition/elimination mechanism), or simply undergoes charge exchange with the aromatic compound. Even without knowing details of the mechanisms, one can conclude that Cl^+ addition does not occur by dissociation of the reagent ion into Cl^+ and the neutral (NH_3 or CO) followed by addition of the free Cl^+ to the aromatic. For all of the aromatic compounds studied, the free Cl^+ ion, mass selected with Q1, does not form an addition product in the collision cell but reacts solely by charge exchange, forming the molecular radical cation.

The reactions in eqs 1 and 2 are each accompanied by elimination of a fragment from the reagent ion as a neutral molecule. This elimination process stabilizes the reaction products by removing excess energy from the initial ion/molecule adduct. The importance of the presence a good leaving group has also been observed in gas-phase nitration reactions.[3a,5,10a] The NO_2^+ ion does not add to aromatic compounds under mass spectrometric conditions,[5] but reagent ions like $C_2H_5ONO_2NO_2^+$,[5b] $CH_2ONO_2^+$,[3a] and $CH_3O(H)NO_2^+$,[10a] do add NO_2^+ to aromatics due to the good leaving groups $C_2H_5ONO_2$, CH_2O, and CH_3OH, respectively. Similar stabilization is achieved in gas-phase radiolytic experiments[6d,7a] where high pressures result in thermalizing collisions. The lack of reactivity of the Cl^+ ion at low pressures with aromatic[6a] and other organic[23] compounds has previously

Table II. Thermodynamics of Eqs 1–3 and Related Thermochemical Data

eq	ΔH_{rxn}, kJ/mol[a-c]	ΔH_{rxn} (AM1)[d]
1a	−35	−92
1b	111.4	54
2a	−42[a]	−143
2b	−141[a]	−242
3a	−633	
3b	−357	

reagent	ΔH_f, kJ/mol	ref
C_6H_6	83	24
NH_3	−46	24
$(C_6H_5Cl + H)^+$	821[b]	24
NH_2Cl	66.9	25
$(NH_2Cl + H)^+$	727[c]	
$(C_6H_6 + H)^+$	854.5	24
CO	−111	24
HCl	−92	24
$C_6H_5C{\equiv}O^+$	703	26
$FC{\equiv}O^+$	669[a]	27
Cl	122	28
$C_6H_6^{\bullet+}$	975	28
Cl^+	1371	28

[a] The Δ_{Hf} value of $ClC{\equiv}O^+$ ion was not found in the literature, and therefore the ΔH_f value of $FC{\equiv}O^+$ was used to calculate reaction enthalpies of eqs 2a and 2b. [b] For chlorinated benzene the ΔH_f value of protonated chlorobenzene was used. [c] The ΔH_f value of protonated monochloramine was calculated from the known ΔH_f value of monochloramine and the estimated proton affinity of monochloramine (PA + 871.5 kJ/mol). The proton affinity of monochloramine is estimated to be 18 kJ/mol higher than that of ammonia (PA = 853.5 kJ/mol[24]) on the basis of the fact that the proton affinity of hydrogen cyanide (HCN, PA = 717 kJ/mol[24]) increases by 18 kJ/mol when a hydrogen atom is substituted by a chlorine atom (ClCN, PA = 735 kJ/mol[24]). [d] Values calculated using AM1 $\Delta H_f°$ (NH_3Cl^+) = 784 kJ/mol and $\Delta H_f°(ClC{\equiv}O^+)$ = 770 kJ/mol. The AM1 $\Delta H_f°$(F-CO$^+$) of 677 kJ/mol agrees well with the experimental value above.

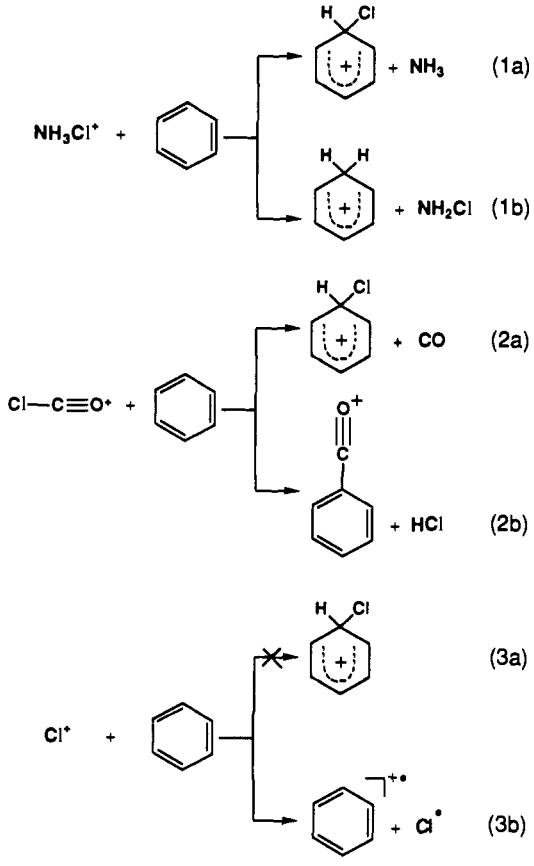
Table III. Chlorine Cation Affinities Calculated by the AM1 Method According to Site of Addition[a] in kcal/mol

	substituent	C2 ortho	C3 meta	C4 para
aniline	(N) 137.0	166.6	141.2	168.6
anisole	(O) 91.8	140.4	136.7	143.0
styrene	Cβ 163.0	148.1	142.9	150.1
	Cβ^b 169.6			
	Cα 141.4			
chlorobenzene	(Cl) 106.2	138.2	134.6	139.8
nitrobenzene	(O)[c] 96.8	118.7	122.5	118.1

[a] For an example of the structures used in the calculations, see Figure 8. [b] Assuming tropylium rearrangement. [c] Addition to the oxygen of the NO_2 substituent.

(21) MOPAC: A General Molecular Orbital Package. Stewart, J. J. P. *Quantum Chemistry Program Exchange* (QCPE no. 455), version 6.

(22) Wagman, D. D.; Evans, W. H.; Parker, V. B.; Schumm, R. H.; Halow, I.; Bailey, S. M.; Churney, K. L.; Nuttall, R. L. *J. Phys. Chem. Ref. Data* **1982**, *11*, Suppl. 2.



been reported. Note that the reaction in eq 2b involves electrophilic attack on benzene with elimination of a neutral molecule of HCl and therefore gives the substituted aromatic product, not the Wheland intermediate proposed in the other cases.

According to the thermochemical data collected in Table II, most of the reactions in eqs 1–3 are exothermic, which is the normal requirement for ion/molecule reactions to proceed rapidly.[2a,4,29] Estimates of the heats of reaction were made only for the case of the benzene reagent since the required thermochemical data were available, but it is expected that the thermochemistry is similar for the substituted compounds. The reaction in eq 2b proceeds even though it is endothermic by approximately 54 kJ/mol. Note also the high exothermicity of the unobserved process, eq 3a. An earlier report has shown that increasing the exothermicity of competitive ion/molecule reactions increases the probability of charge exchange.[5b]

For both the NH_3Cl^+ and $ClC{\equiv}O^+$ reagent ions, products from a number of secondary reactions are also observed. The molecular radical cations of the aromatic compounds occur as abundant secondary products, especially for the $ClC{\equiv}O^+$ reagent ion. They are believed to be formed mainly by fragmentation of the Cl^+ addition products or by charge exchange with reagent fragment ions such as Cl^+ or $CO^{\bullet+}$. Other secondary products are formed when the protonated aromatic molecules or the molecular radical cations of the aromatic compounds react with the corresponding neutral molecules. Structures of these secondary ion/molecule reaction products, although characterized (vide infra), are not of direct interest in this study. The experimental data are discussed

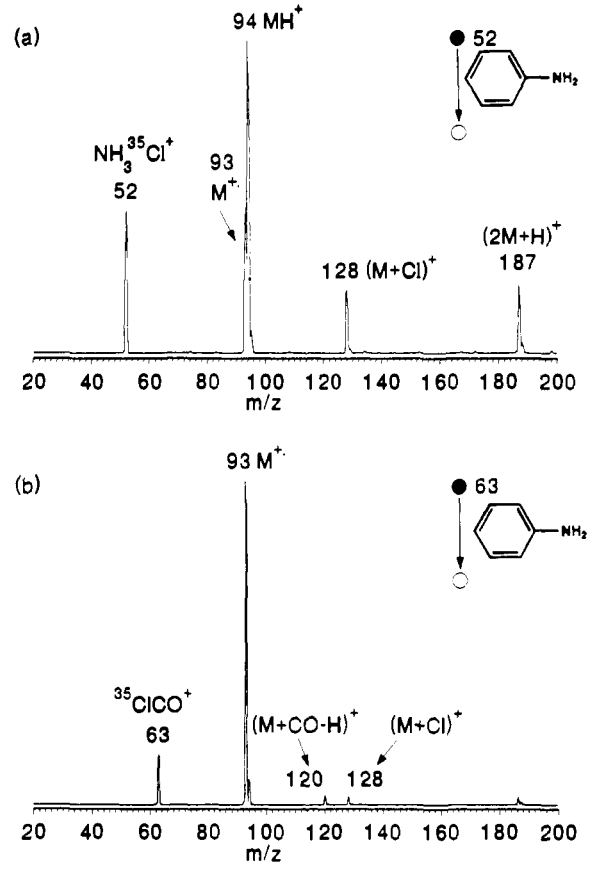


Figure 1. Ion/molecule reaction product ion spectra obtained for reactions of (a) $NH_3{}^{35}Cl^+$, m/z 52, and (b) $^{35}ClC{\equiv}O^+$, m/z 63, with aniline.

below for each of the substrates in turn.

Benzene. Reaction of benzene with $NH_3{}^{35}Cl^+$ produces an $(M + Cl)^+$ addition product at m/z 113, a proton transfer product at m/z 79, and secondary products at m/z 94, 105, 131, and 155 due to reactions of protonated benzene with neutral benzene. The third reaction channel was confirmed by protonating benzene in Q2 with Q1 mass-selected $C_2H_5^+$ ions and observing the same secondary product ions that occur with NH_3Cl^+ reagent ions. This same method was used for other reagent ions and neutrals to establish which ion/molecule reaction products are formed in secondary reactions. These processes are not of further interest.

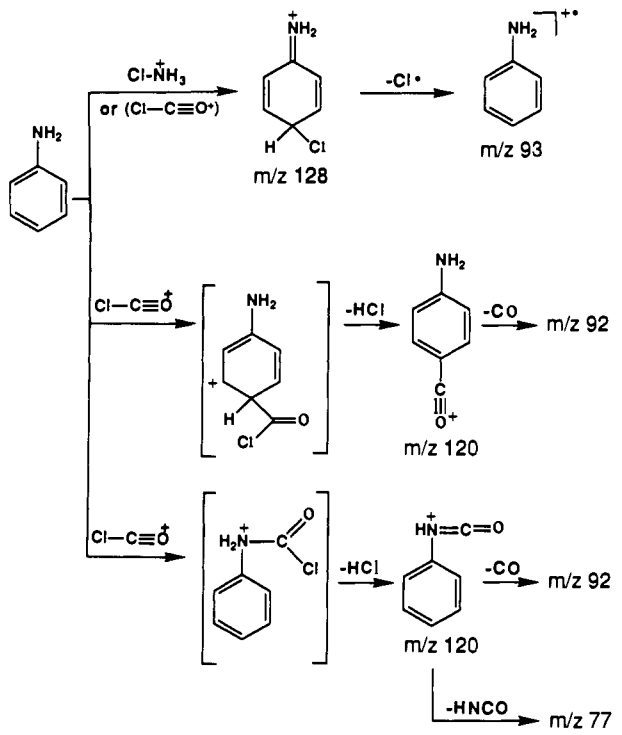
The structure of the $(M + Cl)^+$ product was studied by recording its sequential product ion spectrum. This showed only one fragment ion, the phenyl ion, formed by HCl elimination from the precursor ion. This fragmentation route is the same as the main fragmentation route of protonated chlorobenzene[30] and is consistent with a common structure for the MH^+ ion of chlorobenzene and the $(M + Cl)^+$ ion/molecule reaction product.

The $ClC{\equiv}O^+$ ion reacts with benzene mainly by substitution to produce the benzoyl ion $C_7H_5O^+$ (m/z 105) as well as yielding a small (15 times less abundant) amount of the $(benzene + Cl)^+$ addition product. Sequential product ion spectra of the $(M + CO - H)^+$ substitution product and the $(benzene + Cl)^+$ product both produce the phenyl ion at m/z 77 (by elimination of HCl and CO, respectively). The similarity of the sequential product spectra of the $(M + Cl)^+$ ions produced by $ClC{\equiv}O^+$ and NH_3Cl^+ is consistent with a common structure, that of protonated chlorobenzene.

The Cl^+ addition reaction was also attempted using protonated methyl chloride, but this reagent ion did not react with benzene by halogen transfer. Instead, methyl transfer occurred with simultaneous HCl elimination. Lack of Cl^+ addition can be rationalized by the inability to generate Cl^+ by methane loss due

(23) Rakshit, A. B. *Chem. Phys. Lett.* **1980**, *75*, 283.
(24) Lias, S. G.; Liebman, J. F.; Levin, R. D. *J. Phys. Chem. Ref. Data* **1984**, *13*, 695.
(25) Liveit, M. K.; Nagy-Felsobuki, E.; Peel, J. B.; Willeit, G. D. *Inorg. Chem.* **1978**, *17*, 1608.
(26) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl. I.
(27) Dyke, J. M.; Jonathan, N.; Morris, J. A.; Winter, M. J. *J. Chem. Soc., Faraday Trans. II* **1981**, *77*, 667.
(28) Rosenstock, H. M.; Draxl, K.; Steiner, B. W.; Herron, J. T. *J. Phys. Chem. Ref. Data* **1977**, *6*, Suppl. I.
(29) Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219.
(30) Bier, M. E.; Kotiaho, T.; Cooks, R. G. *Anal. Chim. Acta* **1990**, *231*, 175.

Scheme 1



to protonation on the Cl atom, as has previously been reported.[1k,31]

Aniline. The products arising from reaction between NH_3Cl^+ (m/z 52 in the ^{35}Cl isotopic form) or $ClC{\equiv}O^+$ (m/z 63 in the ^{35}Cl isotopic form) and aniline are presented in Figure 1. These spectra show many features typical of the reactions between the NH_3Cl^+ or $ClC{\equiv}O^+$ ion and aromatic compounds. The NH_3Cl^+ ions react principally by proton and Cl^+ transfer, generating the product ions MH^+, m/z 94, and $(M + Cl)^+$, m/z 128, respectively (Figure 1a). Note that the spectrum also shows an abundant reaction product at m/z 187 which is assigned as the proton-bound dimer of aniline. Figure 1b shows the products typical of reaction of $ClC{\equiv}O^+$ with aromatic compounds. These include Cl^+ addition and $CO^{\bullet+}$ substitution, producing ions at m/z 128, $(M + Cl)^+$, and m/z 120, $(M + CO - H)^+$, respectively. Note also that the molecular ion of aniline ($M^{\bullet+}$, at m/z 93), formed by fragmentation of the Cl^+ addition product (see below) or by charge exchange with reagent ion fragments such as Cl^+ and $CO^{\bullet+}$, is an abundant product for both NH_3Cl^+ and $ClC{\equiv}O^+$ reagent ions. Formation of the molecular radical cation was also observed for most of the other aromatic compounds studied, but this process is not discussed in the following sections because it is not of direct interest. Evidence for Cl^+ addition at the para position of aniline and $CO^{\bullet+}$ substitution at both the nitrogen and the para positions (see Scheme I) comes from MS^2 and MS^3 data, which will now be discussed.

The sequential product spectrum shown in Figure 2a is for the reaction of $NH_3{}^{35}Cl^+$ with aniline in Q2 to yield the product $(M + Cl)^+$ at m/z 128 with subsequent dissociation in Q4. This spectrum is identical to that obtained for the $(M + Cl)^+$ adduct formed using $ClC{\equiv}O^+$ as the reagent ion, consistent with the suggestion that both reagents transfer Cl^+ to the same positions in aniline. These spectra display only one product ion,[32] m/z 93, which is presumably the molecular ion of aniline. This ion is produced by chlorine radical loss from the even-electron precursor, which contravenes the odd–even electron rule. Numerous exceptions to this rule have been published, and reachieving aromaticity in this case is a sufficient driving force, as the thermochemistry shows (see below). Figure 2b, which displays the

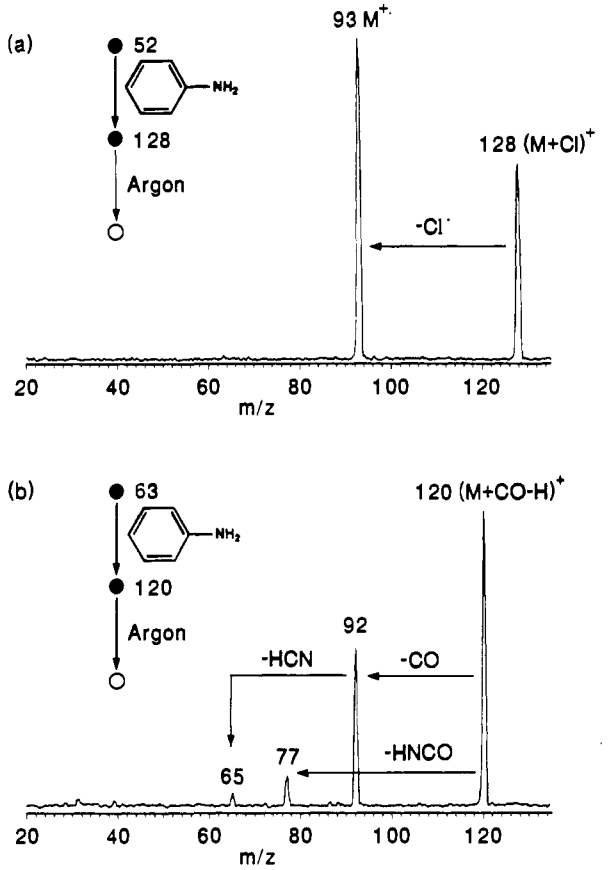


Figure 2. MS/MS/MS sequential product ion spectra for the reaction of (a) $NH_3{}^{35}Cl^+$ ion with aniline in Q2 with Q3 mass selection of products $(M + Cl)^+$, m/z 128, and (b) $^{35}ClC{\equiv}O^+$ ion with aniline in Q2 with Q3 mass selection of products $(M + CO - H)^+$, m/z 120, and subsequent dissociation using 10-eV collisions in Q4 in both cases.

product ion spectrum of the $CO^{\bullet+}$ substitution product, m/z 120, shows two main fragments, that at m/z 92 due to CO loss and that at m/z 77 due to loss of 43 (Scheme I). The latter process, most probably the direct loss of the stable HNCO molecule ($\Delta H_f°$ −25 kcal/mol)[26] or alternatively an unprecedented sequential loss of CO and NH, produces the phenyl ion $C_6H_5^+$, m/z 77, and provides evidence for reaction of $CO^{\bullet+}$ at the heteroatom. Further evidence for the sites of both Cl^+ and $CO^{\bullet+}$ addition will now be discussed.

To determine the site of chlorine cation addition, the fragmentation behavior of three reference compounds, protonated 2-, 3-, and 4-chloroaniline, was explored using MS/MS product spectra. Note that the model ions test the skeletal structure of the product ions; the sites of protonation are not modeled.[33] These samples were therefore protonated using methane, isobutane, and, for the 2-isomer, ammonia, as CI reagent gases (4-chloroaniline was not ionized effectively under ammonia CI conditions). The MS/MS product spectra (Figure 3) display the fragments of the mass-selected MH^+ species. Data for 3-chloroaniline are sufficiently similar to those for 4-chloroaniline that they are not reproduced in Figure 3.

The main fragmentation channels of protonated 2- and 4-chloroanilines are included in Scheme II. Protonated 2- and 4-chloroaniline are distinguishable (Figure 3) due to the well-known ortho effect. The neighboring ortho substituents on protonated 2-chloroaniline interact so that HCl loss occurs in competition with Cl radical loss, producing m/z 92 and 93, respectively, while almost no HCl loss occurs for protonated 4-chloroaniline

(31) Heck, A. J. R.; de Koning, L. J.; Nibbering, N. M. M. *Int. J. Mass Spectrom. Ion Proc.* **1991**, *109*, 209.

(32) At higher collision energies a small amount of additional fragmentation to yield m/z 65 and 66 is observed.

(33) Differences in time scales and internal energy in the reactions leading to formation and dissociation of the model ions compared to the corresponding reaction products make it impossible to achieve quantitative agreement between the reference and the unknown spectra, both of which are sensitive to collision energies and to instrumental conditions.

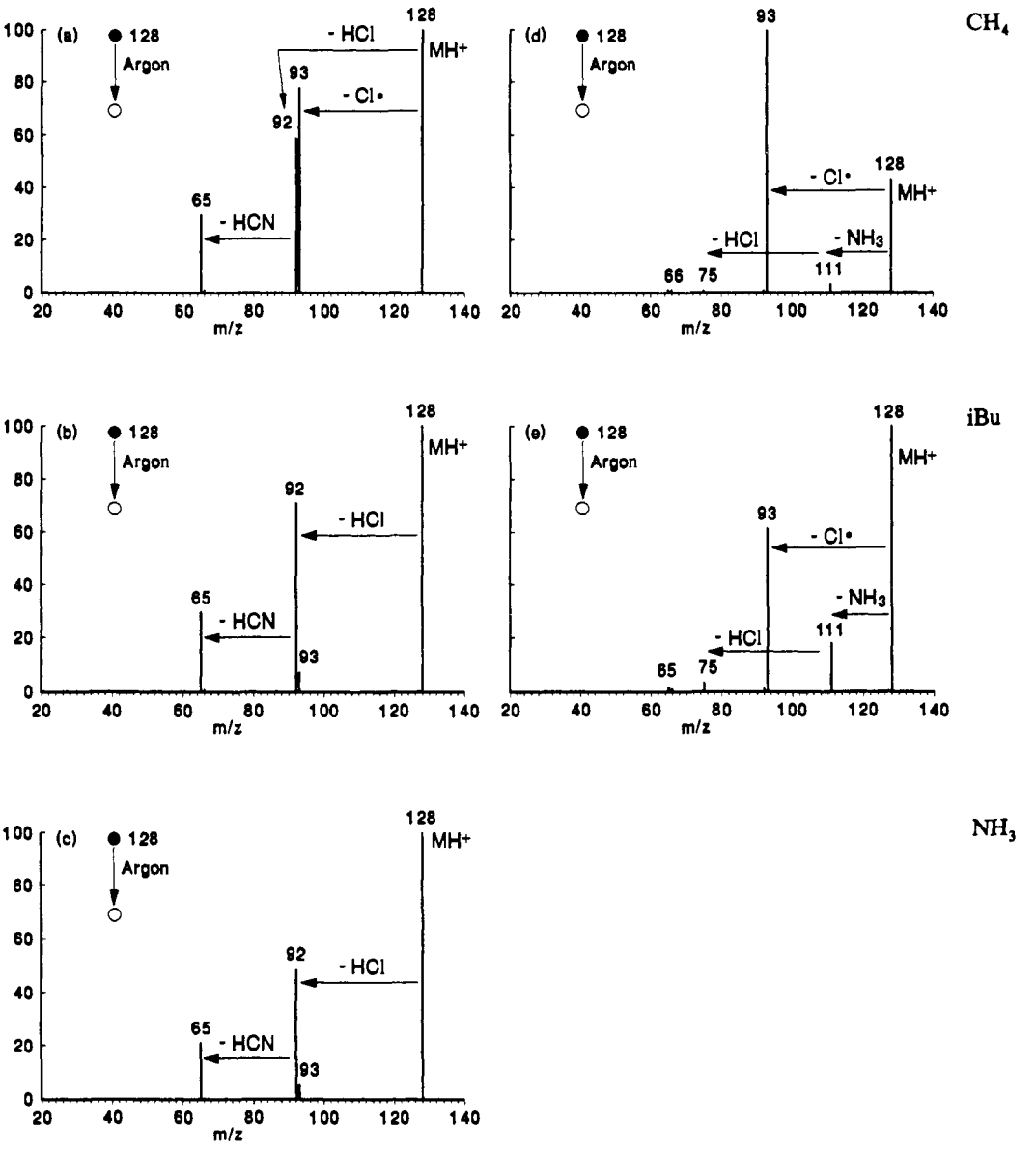
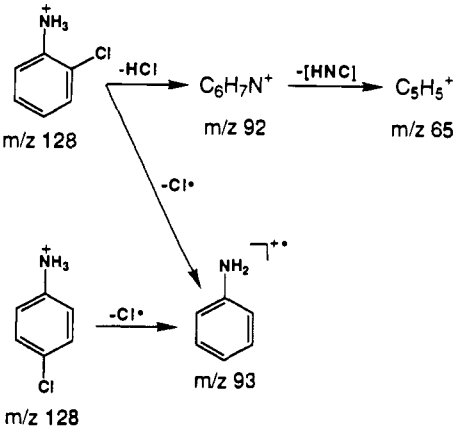


Figure 3. MS/MS product spectra of MH^+ ions of 2-chloroaniline (left spectra) and 4-chloroaniline (right spectra) ionized by chemical ionization using (a and d) methane, (b and e) isobutane, or (c) ammonia as Cl reagent gases. Collision energy 20 eV, argon collision gas pressure 1 mTorr.

(or 3-chloroaniline). The para isomer (Figures 3d and e) also fragments by loss of ammonia (NH_3), giving the fragment ion at m/z 111, which subsequently fragments further to give the ion m/z 75 by HCl elimination. Evidence for this fragmentation route is strengthened by the fact that as the relative abundance of the ion m/z 111 increases, the relative abundance of the ion m/z 75 also increases. Further fragmentation products of m/z 92 and 93 derived from protonated 2-chloroaniline were recognized using the sequential product ion scan 128 → 92 (or 93) → products with the pentaquadrupole instrument. These measurements showed that the main fragmentation routes of both of these ions is the loss of HCN to yield ions at m/z 65 and 66, respectively.

The main fragmentation routes of protonated chloroanilines change with the nature of the protonating CI reagent, as seen in Figure 3. A reasonable explanation for this change in fragmentation (HCl vs Cl• loss) is that the site of protonation of chloroanilines changes with different CI gases. The protonation site of aniline[1c-e] and substituted anilines[1f] has been studied previously, and under the conditions used in most of these studies nitrogen protonation[1c,d,f] is favored for aniline and substituted anilines, although other studies have used conditions under which ring

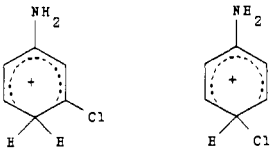
Scheme II



protonation[1e] is favored. Results of the present study suggest that isobutane or ammonia CI leads to protonation mainly at the most

basic site of the aniline molecule, namely the nitrogen atom, while methane CI, which utilizes the high-energy and less discriminating ion CH_5^+, yields mainly the ring-protonated form. This interpretation is based on the decreased ammonia loss from the MH^+ ion of 3- and 4-chloroaniline and on the increased extent of Cl• elimination from the MH^+ ion of 2-chloroaniline when methane is used as reagent gas.

The sequential product ion spectrum of the $(M + Cl)^+$ addition product matches most closely the MS/MS product spectrum of MH^+ ions of 4-chloroaniline (compare Figures 2a and 3d), with both showing principally Cl• loss. However, the $(M + Cl)^+$ product does not lose ammonia to form m/z 111, a process assigned in the model ion (Figure 3d) as the result of a small amount of N-protonation under methane CI conditions. On the basis of these results, chlorine cation addition to aniline occurs predominantly at the para position. Although allowed by the comparison of the MS[3] and MS/MS data, meta-bonding is considered unlikely for the following reasons. (i) The calculated Cl^+ affinities (Table III) for the meta position are considerably lower than those for the para. (ii) If the bond-forming processes are kinetically controlled, then the electronic effects of the NH_2 group will direct the reaction to the para and ortho positions. (iii) Although a stable 3-chloro-4,4-dihydroaniline cation (I, below) could conceivably



I II

be formed by meta-chlorination of aniline followed by a (slow) 3,4-H shift, this type of shift cannot explain why the initial Cl^+ addition (in solution or in the gas phase) will occur fast at the meta position. The same *m*-Cl ion could also be formed by initial (fast) *p*-Cl^+ addition followed by 4,3-Cl and 3,4-H shifts, but either of these formation routes involving migrations would require energy and would be favored only if the product gained a considerable amount of stability. The $\Delta H_f°$ of ion I (174.67 kcal/mol) is more stable than that of the 4-chloro-4-hydroaniline cation II ($\Delta H_f°$ 181.28 kcal/mol) as calculated by AM1, but the difference is hardly large enough to be a driving factor.

Although addition to nitrogen cannot be entirely dismissed, the N-addition product would be expected to show at least some NH_2Cl loss to form the relatively stable phenyl cation (m/z 77) which is not observed to any extent (Figure 2a). The fact that HNCO loss is observed for the product of $CO^{•+}$ substitution at nitrogen in the case of aniline confirms this expectation.

Evidence in favor of para rather than N-chlorination comes from estimates of the energetics of Cl• loss versus NH_2Cl loss from the N-chlorinated ion, which show the latter to be favored.

$$PhNH_2Cl^+ \rightarrow Ph^+ + NH_2Cl \qquad \Delta H_{rxn}° = -117 \text{ kcal/mol}$$

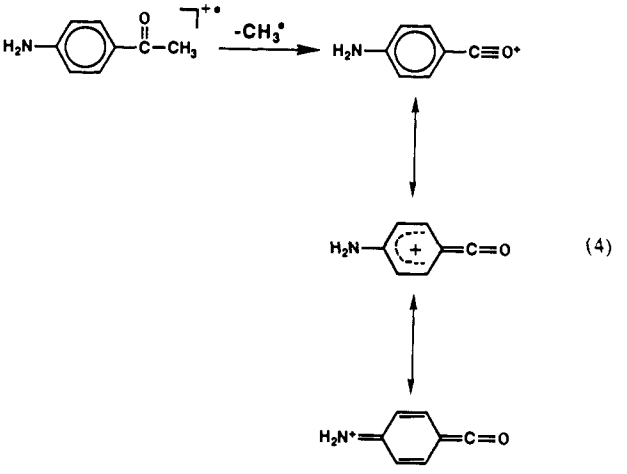
$$PhNH_2Cl^+ \rightarrow PhNH_2^{•+} + Cl^• \qquad \Delta H_{rxn}° = +15.3 \text{ kcal/mol}$$

$$\text{4-Cl-4-H-aniline}^+ \rightarrow PhNH_2^{•+} + Cl^• \qquad \Delta H_{rxn}° = +47.0 \text{ kcal/mol}$$

The $\Delta H_f°$ values are from Tables II and III and ref 26. The $\Delta H_f°$ of $PhNH_2Cl^+$ was calculated from the AM1 Cl^+ affinity (at N) of $PhNH_2$ and $\Delta H_f°(PhNH_2)$.

Observation of Cl• loss, together with the absence of NH_2Cl loss to form m/z 77 (Figure 2a), therefore argues against N-chlorination. On the other hand, the 4-Cl-4-H-aniline$^+$ product would be expected to lose mainly Cl•, forming aniline$^{•+}$, since aromaticity would be reachieved. Finally, the AM1 calculations provide further strong evidence for C_4-substitution. While the AM1 calculations show that the proton affinity[20a,b] for aniline is highest at the nitrogen (211.4 kcal/mol) and at the para carbon (209 kcal/mol), consistent with experimental results which show mainly nitrogen protonation but also under some conditions ring protonation, the data for Cl^+ affinities are very different. In this case the AM1 estimates show that the nitrogen has the lowest Cl^+ affinity and the C_4 position has the highest (Table III). These data must be considered with due regard for the fact that Cl^+ addition may occur under kinetic and not thermodynamic control.

Additional evidence for the site of $CO^{•+}$ substitution was obtained by fragmenting two reference ions. The first ion, formed by methyl loss from 4-aminoacetophenone upon electron impact, serves as a model for an ion with the CO group located para to the amino group. The second ion, formed by methyl loss from acetanilide upon EI, models the phenyl ion, with an HNCO group bonded to the ring through the nitrogen (eqs 4 and 5). The latter



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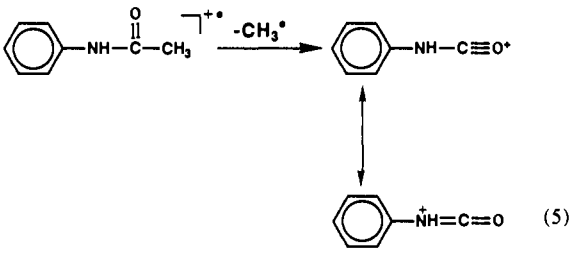


(5)

model ion was also generated by protonating phenyl isocyanate using methane CI, which is expected to lead to protonation at nitrogen. The MS/MS product spectra of the *p*-CO^+-substituted model ion, recorded at 5–25-eV collision energy, show loss of CO to form m/z 92, which in turn loses HCN to give an m/z 65 which grows in intensity to twice that of m/z 92 at the highest collision energy. No ion of m/z 77 due to loss of a fragment of mass 43 (HNCO) is seen. In contrast, both forms of the nitrogen–CO model ion fragment predominantly to m/z 77 by loss of 43 above 5-eV collision energy. The abundance of m/z 92 falls rapidly at high collision energies, and m/z 65 is formed with less than 5% of the total ion current at all collision energies. This model ion fragments to give m/z 77/92 intensity ratios greater than 2 at and above 10-eV collision energies and values of 0.6 and 2 at 5-eV when formed from the acetanilide and isocyanate, respectively. The extent of $CO^{•+}$ substitution at the nitrogen atom in aniline is low, as indicated by the low abundance of m/z 77 in Figure 2b (m/z 77/92 ratio of 0.2). The formation of even small amounts of m/z 77 arising from HNCO loss proves the occurrence of $CO^{•+}$ substitution at the nitrogen atom, but substitution onto the aromatic ring dominates. Ring $CO^{•+}$ substitution most likely occurs at the para position, based on comparison with the para-substituted model ion and with the information provided below on the site of $CO^{•+}$ substitution in anisole.

Previous studies of alkylation of aniline show that reaction can occur either at the ring[1d,2c] or at the nitrogen atom.[1e,2d] Differences in experimental conditions, including operation under thermodynamically vs kinetically controlled conditions,[34] provide a reason

(34) Brodbelt, J. S.; Wysocki, V. H.; Cooks, R. G. *Org. Mass Spectrom.* **1988**, *23*, 54 and references therein.

(35) Liauw, W. G.; Lin, M. S.; Harrison, A. G. *Org. Mass Spectrom.* **1981**, *16*, 383.

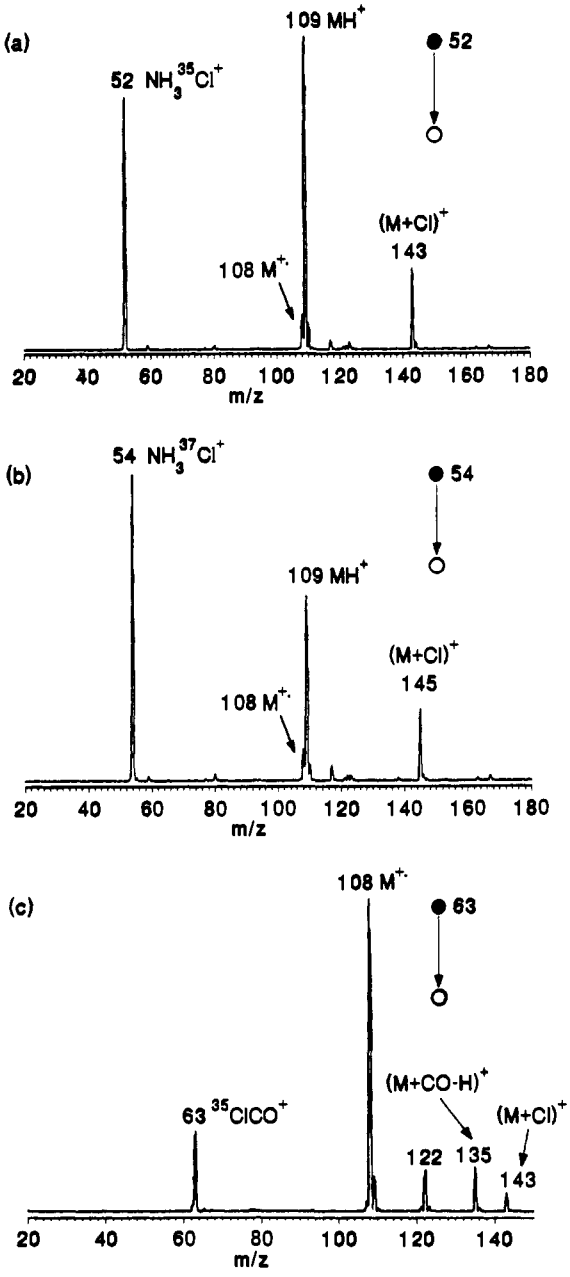


Figure 4. Ion/molecule reaction product ion spectra obtained for reactions of (a) $NH_3{}^{35}Cl^+$, m/z 52, (b) $NH_3{}^{37}Cl^+$, m/z 54, and (c) $^{35}ClC{\equiv}O^+$, m/z 63, with anisole.

for the difference observed in sites of protonation (discussed above) and alkylation. The thermochemically favored site of protonation of aniline is the nitrogen atom,[1c] whereas the high-pressure (>300 Torr) radiolytic experiments are generally believed to occur under kinetic control and to give ring protonation.[7,12c]

Radiolytic experiments have shown that the relatively soft electrophiles, e.g., the alkylation reagent ions,[8b] add at the nitrogen or at the ring carbons with equal preference but that hard electrophiles such as acetyl[8a] and benzoyl[12b] preferably add at the nitrogen atom. The explanation proposed is that harder electrophiles are more selective toward the most electron-rich site of aniline, the nitrogen atom. The favored position of addition to the benzene ring is the ortho position for alkylating reagents[8b] and the para position for acetyl and benzoyl ions.[8a,12b] The preference for the para product for the hard electrophiles acetyl

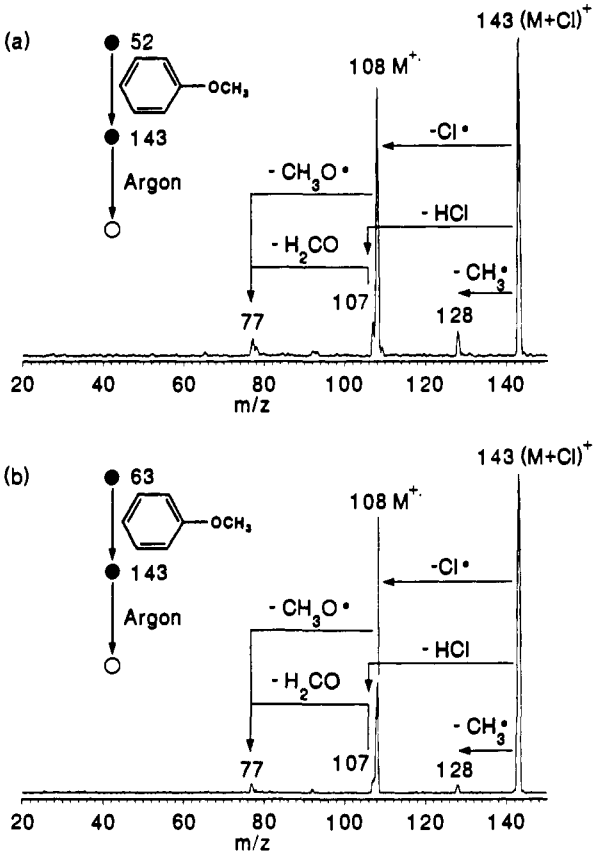


Figure 5. MS/MS/MS sequential product ion spectra for the reaction of (a) $NH_3{}^{35}Cl^+$ ion or (b) $^{35}ClC{\equiv}O^+$ ion with anisole in Q2 with Q3 mass selection of the product $(M + Cl)^+$, m/z 143, and subsequent dissociation using 10-eV collisions in Q4.

and benzoyl occurs because during the attack at the ortho site strong electrostatic attraction between the reagent and the nitrogen atom causes bonding mostly at the nitrogen atom. Therefore, only in the case of para attack can the ring addition product be formed. In contrast to this, soft electrophiles (alkylating reagents) are not subject to such strong electrostatic forces and can add at either the ortho position or at the nitrogen atom.

Thermodynamic control is difficult to achieve in a conventional chemical ionization source,[2c,39,40] and the present measurements were not made under equilibrium conditions. The change in fragmentation routes of 2- and 4-chloroanilines as the chemical ionization gas was changed demonstrates that the reactions occurred under kinetic control. The results on Cl^+ addition are consistent with the above radiolytic experiments for aniline if NH_3Cl^+ and $ClCO^+$ are accepted to be hard electrophiles. As such, they are expected to react mainly at nitrogen and at the C_4 position. On the other hand, the Cl^+ addition product at nitrogen is not favored (Table III) and is apparently not observed. For the case of $CO^{\bullet+}$ substitution, reactions at the ring and at nitrogen both apparently lead to stable products as both are observed, although ring substitution dominates due to the greater product stability evident from resonance stabilization and charge delocalization (see eqs 4 and 5).

Anisole. Anisole reacts with $NH_3{}^{35}Cl^+$ by two main routes, proton transfer and Cl^+ transfer, producing the ions MH^+, m/z 109, and $(M + Cl)^+$, m/z 143, respectively (Figure 4a). Minor reaction channels are charge exchange and further reaction of protonated anisole with neutral anisole to form the proton-bound dimer. Figure 4b shows the MS/MS product ion spectrum obtained for the reaction of $NH_3{}^{37}Cl^+$ with anisole. Note the quantitative shift in the Cl^+ addition peak from m/z 143 to 145. The selection of different isotopic forms of the reagent ion provides

(36) Thölmann, D.; Grützmacher, H.-F. *J. Am. Chem. Soc.* **1991**, *113*, 3281.
(37) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A*, 2nd ed.; Plenum Press: New York, 1984.
(38) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 240.
(39) Harrison, A. G. *Chemical Ionization Mass Spectrometry*, CRC Press: Boca Raton, FL, 1983.
(40) Nakata, H. *Org. Mass Spectrom.* **1992**, *27*, 686.

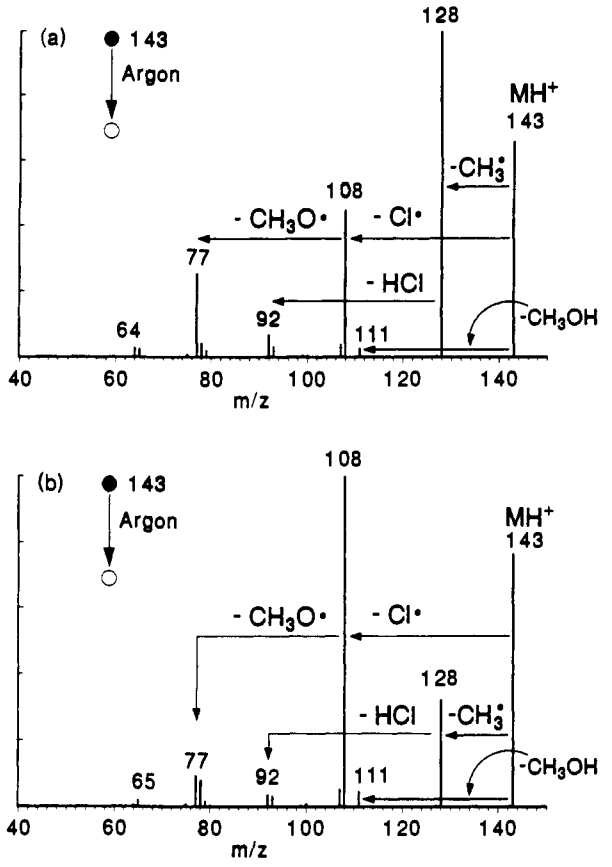


Figure 6. MS/MS product ion spectra of MH^+ ions of (a) 2-chloroanisole and (b) 4-chloroanisole ionized by methane chemical ionization. Collision energy 20 eV, argon collision gas pressure 1 mTorr.

a convenient check into which ion/molecule reaction products contain chlorine and also checks on the quality of the data. Reactions between the $ClC{\equiv}O^+$ ion and anisole (Figure 4c) proceed by three main channels, Cl^+ addition, $CO^{\bullet+}$ substitution, and charge exchange, to produce the ions $(M + Cl)^+$, $(M + CO - H)^+$, and $M^{\bullet+}$ at m/z 143, 135, and 108, respectively.

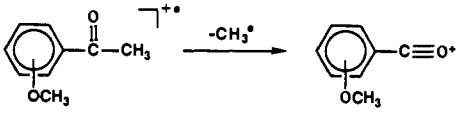
The structure of the Cl^+ addition product generated from both of the reactant ions NH_3Cl^+ and $ClC{\equiv}O^+$ was studied by recording sequential product ion spectra (Figure 5) and comparing these to the MS/MS product spectra (Figure 6) of the protonated reference compounds 2- and 4-chloroanisole. As seen in Figure 5, the sequential product ion spectra for both the reactant ions NH_3Cl^+ and $ClC{\equiv}O^+$ are very similar, suggesting that Cl^+ addition occurs at the same positions for either reagent ion.

The reference compounds 2- and 4-chloroanisole are easily distinguished upon ionization by chemical ionization using methane or isobutane. The third reagent gas, ammonia, did not protonate these compounds. The MS/MS product spectra of MH^+ ions of 2- and 4-chloroanisole produced by methane CI (Figure 6) show more fragmentation than the MH^+ ions produced by isobutane CI, but the two isomers are easily distinguished using either CI gas. On the other hand, the spectrum of 3-chloroanisole is not significantly different from that of the para isomer. The most probable site of protonation of these model compounds is the ring, since anisole itself is known to be protonated on the ring.[1a] The two main fragmentation routes of the MH^+ ions, common to both 2- and 4-chloroanisole, are the loss of a methyl radical or chlorine radical, producing product ions which correspond to ionized chlorophenol at m/z 128 and anisole at m/z 108, respectively. The ion m/z 128 fragments further by the loss of a chlorine radical or by the loss of HCl, giving the product ions at m/z 93 and 92, respectively. Further fragmentation of the ion at m/z 108 proceeds by the loss of methoxy radical or neutral formaldehyde (CH_2O), producing the phenyl ion $C_6H_5^+$ at m/z 77 and the molecular ion of benzene at m/z 78, respectively. The different abundances of methyl radical and chlorine radical loss products from 2- and 4-chloroanisole can again be attributed to the ortho effect, which is effective for 2-chloroanisole and assists the elimination of methyl radical. The favored loss of methyl radical in 2-chloroanisole was reported earlier in a study in which fragmentation of chloroanisoles was studied under chemical ionization conditions.[35]

Comparison of the sequential product ion spectrum for the Cl^+ addition product with the MS/MS product ion spectra of the MH^+ ions of the reference compounds suggests that the major site of Cl^+ addition is the para position (see Figures 5 and 6). The sequential product ion spectrum for $(M + Cl)^+$ shows favored loss of chlorine radical over the loss of methyl radical, a feature characteristic of fragmentation of protonated 4-chloroanisole. Of course, minor contributions of ortho and oxygen-bonded Cl^+ addition products cannot be excluded. The lack of a reference compound chlorinated on the oxygen atom hinders examination of the extent to which Cl^+ addition occurs at the ring substituent. Nevertheless, this is not expected to be significant since the AM1 calculations (Table III) show the C_4 site to have the largest Cl^+ affinity. They also show a very low Cl^+ affinity value for attachment at the oxygen.

Chlorination of aniline at the meta position is extremely unlikely on the basis of the AM1 calculations (Table III). This is not the case for chlorination of anisole, and the model ion protonated *m*-chloroanisole was therefore generated by chemical ionization and its MS/MS spectrum recorded. This was done using isobutane and ammonia and a variety of collision gas pressures and energies. Product spectra were also performed in Q2 and Q4 of the pentaquadrupole, as well as in the triple quadrupole. These experiments, done simultaneously for the ortho, meta, and para isomers, showed that the three isomers could always be distinguished; the meta isomer displaying the most abundant ion at m/z 111 is assigned to the loss of CH_3OH. However, the meta and para isomers gave spectra which were similar enough that the occurrence of meta substitution by NH_3Cl^+ and $ClCO^+$ cannot be excluded.

A sequential product ion spectrum was also recorded for the $CO^{\bullet+}$ substitution product ion, m/z 135, and compared to the product spectra of model ions (Figures 7a–d) formed as a result of methyl loss from ionized 2- and 4-methoxyacetophenone (eq 6). The main fragmentation route for the $CO^{\bullet+}$ substitution ion



(6)

(Figure 7e) is the loss of CO, producing the ion at m/z 107. The m/z 107 ion fragments further by methyl radical loss, CO loss, or CH_2O loss to produce product ions at m/z 92, 79, and 77, respectively. The 4-isomer model ion also yields these fragments with similar relative abundances in an MS/MS product spectrum recorded at 5–10-eV collision energies. At these collision energies the 2-isomer model ion yields a much lower abundance of m/z 107 in addition to new fragments appearing at m/z 120 and 105 due to methyl and H_2CO loss. The model ion fragmentation indicates that $CO^{\bullet+}$ substitution occurs mostly at the para position with little or no ortho or oxygen addition.

The positional selectivity in favor of the para position as the site for reaction of anisole is also observed for nitration[10a] and benzoylation.[12b] On the other hand, radiolytic studies show that alkylation[7a] and acetylation[12a] of anisole occur preferably at the ortho position. Hence, the current data as well as previous results are consistent in showing that cationic additions occur at the ring of anisole, the favored ring position depending on the cationic species.

Styrene. Styrene was the third compound studied having an activating, ortho-/para-directing substituent. It reacts with NH_3Cl^+ and $ClC{\equiv}O^+$ reagent ions by routes similar to those of aniline and anisole. Reaction of styrene with NH_3Cl^+ produced the Cl^+ addition product at m/z 139 and protonated styrene at m/z 105 as the principal products. Reactions of $ClC{\equiv}O^+$ with styrene yielded the Cl^+ addition product at m/z 139 and the $CO^{\bullet+}$ substitution product at m/z 131 as the main products.

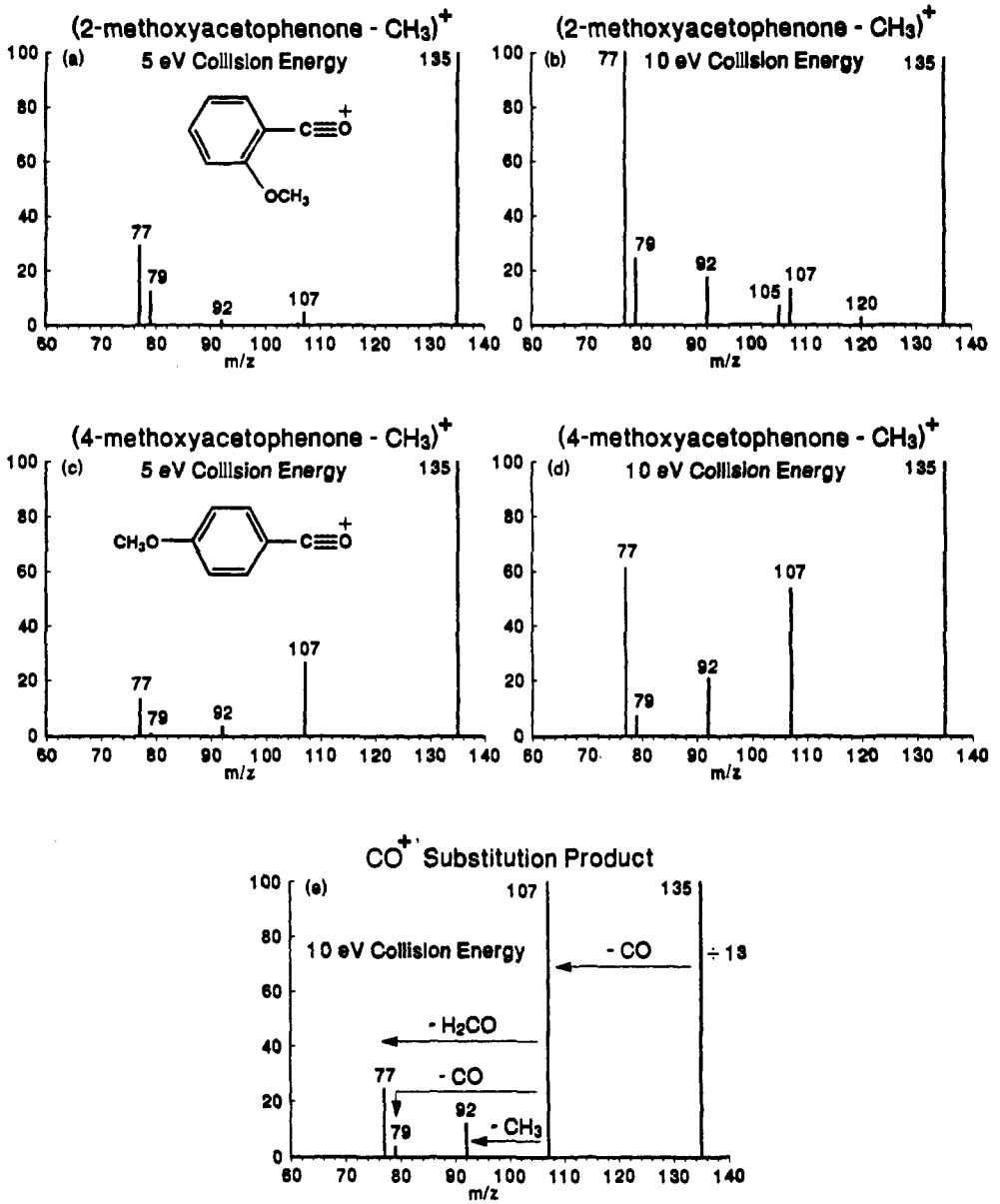


Figure 7. (a–d) MS/MS product spectra displaying fragmentation of model ions for $CO^{\cdot+}$ substitution, m/z 135, formed by methyl loss upon EI ionization of 2- and 4-methoxyacetophenone for comparison to (e) an MS^3 sequential product ion spectrum of the $CO^{\cdot+}$ substitution product.

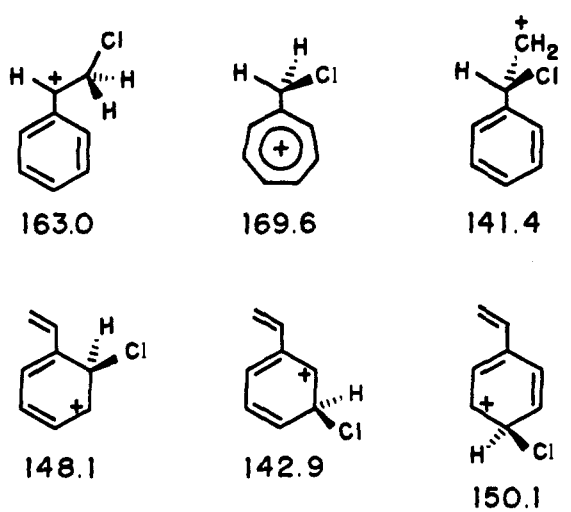
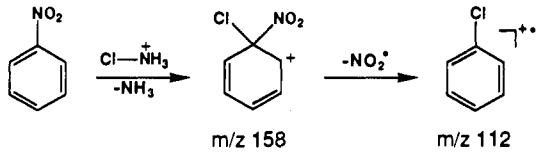


Figure 8. Structures of the ionic products of Cl^+ addition to the different sites of styrene and to the exocyclic carbon of 1,3,5-cycloheptatriene-7-methylene used in the AM1 Cl^+ affinity calculations and the respective values obtained (in Kcal/mol).

The structure of the Cl^+ addition product for styrene was investigated by recording a sequential product ion mass spectrum. This spectrum showed product ions at m/z 103 and 77. The former is formed by HCl elimination from the chlorinated precursor, and the latter probably arises by C_2H_2 loss from m/z 103. These fragmentation processes are easily rationalized by assuming Cl^+ addition at the vinyl group. Addition to the vinyl group is also supported by AM1 calculations (Table III and Figure 8), which show the carbon β to the ring to have the largest Cl^+ affinity. If the β-carbon adduct is assumed to rearrange to the CH_2Cl-substituted tropylium ion, reaction at the β-carbon is even more exothermic. Figure 8 illustrates the structures used in the AM1 calculations and shows the values of Cl^+ affinities for reaction at the different sites of styrene and for the exocyclic carbon of 1,3,5-cycloheptatriene-7-methylene (tropylium rearrangement).

Chlorobenzene. The results obtained for chlorobenzene show that even this deactivated compound reacts with NH_3Cl^+ and $ClC{\equiv}O^+$ and forms products which incorporate Cl^+ (by addition) and $CO^{\cdot+}$ (by substitution). Also, NH_3Cl^+ protonates chlorobenzene to produce the MH^+ ion at m/z 113 which reacts with the neutral molecules present to yield the proton-bound dimer. $ClC{\equiv}O^+$ ions react by charge exchange, with secondary reactions occurring between the ionized chlorobenzene and the neutrals.

Scheme III



The structure of the $(M + Cl)^+$ addition product of chlorobenzene was studied by collecting sequential product ion spectra (MS^3). MS/MS product spectra of MH^+ ions of 1,2-, 1,3-, and 1,4-dichlorobenzene were also acquired in an attempt to confirm the site of Cl^+ addition, but the MS/MS product ion spectra of the MH^+ (m/z 147) ions of the different isomers of dichlorobenzene did not show significant differences. The main fragmentation route of each of the protonated dichlorobenzenes was the loss of neutral HCl, producing the product ion at m/z 111, a process which also dominated the product ion spectra of the ion/molecule reaction product. The results obtained do not establish the site of chlorine cation addition to chlorobenzene, but they do suggest that the Cl^+ addition product generated upon reaction with NH_3Cl^+ or $ClC{\equiv}O^+$ has the structure of protonated dichlorobenzene, viz. that ring addition occurs. The para and ortho positions are the most likely sites of addition as these sites show the highest chlorine cation affinities (Table III) as calculated by the AM1 method.

The structure of the $CO^{\bullet+}$ substitution product was also studied by recording the sequential product ion spectrum. The only product ion observed, m/z 111, is formed by CO loss. This fragmentation route is observed for the $CO^{\bullet+}$ substitution products of aniline, anisole, and benzene (see above) and suggests that the $CO^{\bullet+}$ addition process occurs by the same mechanism for all the aromatic compounds, i.e., that the main position of $CO^{\bullet+}$ substitution is the ring. Several gas-phase studies pertaining to electrophilic reactions of chlorobenzene also show that ring reaction is usually favored. Mass spectrometric studies of protonation[1a,g] and radiolytic studies of nitration,[10a] alkylation,[7a] and bromination and iodination[11] all indicate reaction at the ring. The latter results also show that the positional selectivity of electrophilic attack is low.

Nitrobenzene. The only aromatic compound with a strongly deactivating substituent group examined in this study was nitrobenzene. Ion/molecule reactions of nitrobenzene with NH_3Cl^+ result in protonation, producing MH^+ at m/z 124 and some minor products due to reactions of protonated nitrobenzene with neutral nitrobenzene. No Cl^+ addition product was observed using NH_3Cl^+, and reaction with $ClC{\equiv}O^+$ produced only trace amounts of the Cl^+ addition product at m/z 158 (^{35}Cl) and 160 (^{37}Cl).

Although the product spectrum recorded for the reactions of NH_3Cl^+ with nitrobenzene fails to show Cl^+ addition, an interesting product corresponded to the molecular ion of chlorobenzene. This product ion, m/z 112, was also observed to occur for $^{35}ClC{\equiv}O^+$, and its mass increased by two when using $^{37}ClC{\equiv}O^+$. Clearly, this product is the result of substitution of $NO_2^{\bullet}$ by Cl^+, and the reaction is therefore analogous to the substitution of $H^{\bullet}$ for $CO^{\bullet+}$ discussed above. The mechanism may involve initial binding of the chlorine cation at the ipso position followed by NO_2 radical loss (Scheme III). Results presented in the literature show that ipso attack is not uncommon in electrophilic[11b,8c] and nucleophilic[36] gas-phase reactions. The fact that the carbon atom in the ipso position has the highest total π-electron density in nitrobenzene[37] also favors ipso attack. An alternative but less likely mechanism given the semiempirical MO calculations (Table III) is one in which the reagent ion binds to an oxygen atom of the nitro group and by subsequent rearrangement the Cl^+ ion attacks the ipso position, followed by loss of an NO_2 radical. This kind of rearrangement has been observed during fragmentation of alkylated nitrophenols studied under high-energy collisions.[1b]

Conclusion

Electrophilic aromatic Cl^+ addition to benzene and the substituted benzenes listed in Table I occurs with NH_3Cl^+ and $ClC{\equiv}O^+$. These reagent ions are generated by protonation of monochloramine using membrane introduction mass spectrometry and electron ionization from acetyl chloride, respectively. The NH_3Cl^+ reagent ion also protonates the aromatic compounds, while $ClC{\equiv}O^+$ causes $CO^{\bullet+}$ substitution for a hydrogen atom.

The structures of the ion/molecule reaction products, including the position of chlorine cation addition, were determined by collecting sequential product ion mass spectra on the ion/molecule reaction products. MS/MS product ion spectra of the MH^+ ions of chlorinated reference compounds were recorded to assist in the analysis of the positional selectivity of Cl^+ addition. The positional selectivity was generally observed to follow the trend expected considering the directing nature of the substituents. The results obtained show that NH_3Cl^+ and $ClC{\equiv}O^+$ add Cl^+ principally at the para position of aniline. For the other aromatic compounds, the site of addition could not be decided as confidently although ring substitution clearly occurs in all cases except styrene. The experimental and theoretical results strongly suggest that Cl^+ addition occurs mainly at the β-carbon for styrene. Nitrobenzene, the least reactive compound, yielded only traces of Cl^+ addition and no $CO^{\bullet+}$ substitution product. Nitrobenzene, however, did undergo substitution of $NO_2^{\bullet}$ by Cl^+ in analogy to the substitution of $H^{\bullet}$ by $CO^{\bullet+}$ seen with the activated substrates. In cases in which the site of Cl^+ addition could be determined, results were obtained by AM1 calculations which show the experimentally preferred sites as having the highest Cl^+ affinity values. This evidence for the reliability of the AM1 calculations allows this method to be used with confidence to predict the preferred sites for other cases. For instance, the experimental evidence combined with the AM1 predictions strongly suggest that Cl^+ addition occurs at the β-carbon of styrene. Ring $CO^{\bullet+}$ substitution was most often observed; however, substituent substitution was also observable for aniline and is proposed to be the main product for styrene.

The site of electrophilic attack for aromatic compounds occurring under kinetically controlled conditions has often been explained on the basis of Klopman's reactivity model. This model states that for soft electrophiles the reaction is controlled by bonding between the atoms carrying the highest charge density in frontier orbitals and for hard electrophiles the reaction is controlled by attractive electrostatic interactions between the centers of the two reagents with the highest charge.[41] This model has been successfully used to explain the positional selectivity observed in reactions of five-membered heteroarenes with various electrophiles[9] and also in reactions of aniline with various electrophiles[8a] studied using radiolytic methods. The results obtained in the present study are also in agreement with Klopman's theory if the assumption is made that NH_3Cl^+ and $ClC{\equiv}O^+$ are relatively hard electrophiles.

This study demonstrates the advantages of the combination of a direct insertion membrane probe and a pentaquadrupole mass spectrometer in the investigation of ion/molecule reactions. The use of the membrane for sample introduction allows reactions of highly reactive species, which are available only in aqueous solutions, to be studied easily. The pentaquadrupole provides convenient MS^3 capabilities to study structures of the ion/molecule reaction products.

Other possible chlorine cation addition reagent ions of interest for future work are protonated hypochlorous acid (H_2OCl^+), protonated organic chloramines (RNH_3Cl^+), and the $ClSO^+$ ion produced from thionyl chloride ($SOCl_2$) by EI. The $ClSO^+$ ion may display another interesting reaction route, namely an $SO^{\bullet+}$ substitution channel, analogous to the $CO^{\bullet+}$ substitution reaction of $ClCO^+$.

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(41) (a) Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223. (b) Pearson, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 8440. (c) Pearson, R. G. *J. Org. Chem.* **1989**, *54*, 1423.