ponents by TLC on silica gel (hexane/ethyl acetate, 1:1): **5a** (R_f 0.15) and **3a** (R_f 0.26). The two were separated by flash column chromatography on silica gel (10 g of Merck silica gel 60, 230–400 mesh), with hexane/ethyl acetate (1:1) as eluent, to give 74 mg (20%) of **3a** and 210 mg (61%) of **5a** as a crystalline solid: mp 165.0–166.0 °C ^{1}H NMR δ 1.68 (d, 1 H, J = 13.0 Hz), 1.74 (d, 1 H, J = 13.0 Hz), 1.90 (d, 2 H, J = 12.0 Hz), 2.0–2.2 (m, 4 H), 2.4–2.6 (m, 4 H), 7.0 (br s, 2 H, exchangeable with D_2O); ^{13}C NMR δ 180.51, 86.83, 54.70, 50.26, 46.14, 35.48, 33.34; IR 3600–3000, 1720 cm^{-1}; MS, m/e (relative intensity) 182 (M^+, 1.9), 164 (63.4), 136 (72.6), 95 (100.0); exact mass calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0975.

Direct Preparation of 5a from 3b. In order to check that both methods for preparing **5a** gave the same ratio of **5a** to **3a**, a solution of 13 mg (0.066 mmol) of **3b** in 1 mL of methanol and 0.5 mL of 5% aqueous sodium hydroxide was stirred at room temperature for 1.5 h. Following the workup described above, 11 mg (92%) of a mixture of **5a** and **3a** was isolated. The acids were dissolved in 5 mL of diethyl ether and converted to their corresponding methyl esters by treatment with diazomethane to give **5b** (75%) and **3b** (25%) by gas chromatographic analysis. Hydrolysis of **5b** to **5a** and **3a** followed by esterification to **5b** and **3b** as described above gave the identical 3:1 (**5b**:**3b**) ratio.

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Registry No. **3a**, 87801-59-0; **3b**, 87801-60-3; **3b**-d_2, 87801-61-4; **3b**-d_3, 87801-62-5; **3b**-d_6, 87801-63-6; **4a**, 87801-64-7; **4b**, 87801-65-8; **5a**, 87801-66-9; **5b**, 87801-67-0; **6**, 21933-00-6; **7**, 87801-68-1; **11**, 770-15-0; **16**, 21898-84-0; **17**, 87860-03-5; **18**, 87860-04-6; **19**, 87801-69-2.

Supplementary Material Available: Coordinates for the MM2-optimized chair–chair and chair–boat conformations of **3b** and chair–chair conformation of **4b** and the vicinal coupling constants computed at these geometries (4 pages). Ordering information is given on any current masthead page.

Site of Gas-Phase Cation Attachment. Protonation, Methylation, and Ethylation of Aniline, Phenol, and Thiophenol

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Attachment of gaseous cations (H^+, CH_3^+, and $C_2H_5^+$) to aniline, phenol, and thiophenol can be effected by using chemical ionization and the products characterized by mass spectrometry/mass spectrometry (MS/MS). Data taken at both low and high collision energies give consistent results, although individual MS/MS spectra show the expected strong dependence upon collision energy. The site of reaction is inferred from characteristic fragmentations of the mass-selected adduct ions. In the case of alkylation, direct comparison is made of the MS/MS spectra of the ion/molecule reaction products and spectra of model compounds representative of the isomeric structures under consideration. In the case of protonation, deuterium-labeling data were obtained. The results for alkylation show competitive ring and substituent reaction, with phenol reacting largely on the ring in contradistinction with the behavior of aniline and thiophenol. Protonation of phenol appears to occur exclusively on the ring, and this is also the favored site for aniline, although some N-protonation is evident from the spectra. The difference between aniline and phenol, and that between alkylation and protonation, is consistent with expected trends in thermodynamic stability.

Introduction

The combination of mass spectrometry/mass spectrometry (MS/MS)[1] with chemical ionization[2] provides a proven capability for ion characterization, in conjunction with a means of carrying out ion/molecule reactions. This combination early[3] yielded surprising information on competitive protonation of substituents in disubstituted aromatic compounds, with nitro and cyano groups being much more readily protonated than a methoxyl substituent. Thermodynamic data[4] from ion cyclotron resonance spectroscopy confirms that the order of product ion stabilities matches the observed order of reactivity.

The present enquiry into the site of alkylation and protonation is prompted, first, by an interest in intrinsic molecular properties such as proton affinity.[5] Second, there is interest in the effect of site of protonation on characteristic ionic fragmentations.[6] Third, it is important to be able to characterize chemical-ionization behavior under kinetic control and to distinguish it from that which occurs under thermodynamic control. In addition to equilibrium data from high-pressure mass spectrometry,[7] ion cyclotron resonance spectroscopy,[8] and the flowing

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afterglow method,[9] other information on site of protonation is available. Chemical-ionization fragmentation behavior,[10] deuterium-exchange experiments,[11] and cluster ion reactions[12] have all been used to infer the preferential site of protonation of particular substrates. Also, theoretical studies[13] and core ionization energies[14] are suggestive of the site of chemical bonding.

Among the compounds in which the site of protonation has been examined, aniline and phenol are two of the more thoroughly investigated cases. The consensus from experiments done under equilibrium conditions appears to be that aniline is protonated on the nitrogen atom in the gas phase.[15] despite results from molecular orbital calculations that show N-protonation to be favored by only 1–3 kcal/mol.[8a] Indeed, one recent calculation indicates essentially no difference in proton affinity between the heteroatom and the ortho and para positions, while another predicts a 5 kcal/mol[13c] difference in the proton affinities of the two sites and finds a minimum to exist in the electrostatic potential surface of the molecule over the aromatic ring. In light of these findings, one might expect competitive protonation at the two types of basic sites in aniline and a substantial substituent effect on the extent of protonation of each.[8b]

There is similar uncertainty over the site of protonation in phenol. The suggestion that protonation occurs on the aromatic ring has been advanced from results obtained by deuterium exchange,[16] from ion stability,[17] and from calculations,[4] while chemical-ionization clustering experiments with water as the reagent gas are indicative of oxygen protonation[18] although this may apply only to the solvated ions.[17] Still another study, based on core ionization energies, reports that protonation may occur competitively between the aromatic ring and the oxygen substituent.[19] This uncertainty concerning the site of protonation in phenol makes this system also worthy of further examination.

In addition to the protonation of gaseous aromatic molecules, the reactions of these molecules with other cations are of interest since they may relate to traditional solution-phase reactions such as Friedel–Crafts alkylation. Ethylation has been used to crudely model protonation in CIMS/MS studies by Kruger et al.,[3] Maquestiau et al.,[20] and Flammang et al.[21] This procedure is facilitated by the ease with which ethylation can be accomplished under conditions of chemical ionization with use of methane reagent gas.[22,23] Ambiguities that complicate the interpretation of the MS/MS spectra of protonated compounds (possibility of hydrogen migration and the dearth of structurally unambiguous fragmentation reactions) are reduced for the ethylated analogues. Methylation is preferable to ethylation as an analogue for protonation because the structurally uninformative low-energy pathway of ethylene elimination is precluded. For some disubstituted aromatics[3] it is known that ethylation and protonation behave analogously. However, such correspondence cannot be assumed in the cases of aniline and phenol, in which ring–substituent affinity differences may be small. The experimental data for ethylation of aniline and phenol under chemical-ionization conditions have been interpreted in terms of predominant ring ethylation in both cases.[20,21] At considerably higher pressures, radiolysis procedures have been used to generate methyl cation sources (e.g., the dimethylfluoronium ion),[24] and the methylation of phenol[25] and aniline[26] has been investigated. These experiments, which are not carried out at thermodynamic equilibrium, show largely substituent methylation in the case of phenol and ring methylation in aniline.

Experimental Section

Experiments were performed on two MS/MS instruments, operating at very different collision energies. The first, a mass-analyzed ion kinetic energy spectrometer (MIKES),[27] is a sector instrument of reversed geometry, viz., magnetic followed by electric sector. The second is a commercial triple quadrupole instrument (Finnigan-MAT).[28] MS/MS spectra were obtained by setting the first mass analyzer (magnetic sector or quadrupole) to pass only ions of the desired mass-to-charge ratio to the collision region of the instrument. These ions were then collisionally dissociated and their daughter ions monitored via a scan of the second mass analyzer (electric sector or quadrupole). All MS/MS spectra were acquired with the instruments under computer control. No correction is made for unimolecular contributions, which are typically very small for chemical ionization under the conditions used.

Typical operating conditions for the MIKE spectrometer were as follows: source pressure, ca. 0.3 torr as measured by a capacitance manometer; electron ionizing energy, 500 eV; and ion accelerating potential, 7 kV. Reagent gases included isobutane for protonation, deuterium for deuteration, methane and ethyl bromide for ethylation, and methyl fluoride and methyl chloride for methylation. Variation of the methylating (or ethylating) reagent gas resulted in no observable differences in the MS/MS spectra of the alkylated substrates in the high-energy spectra. All reagents were obtained commercially and used without further

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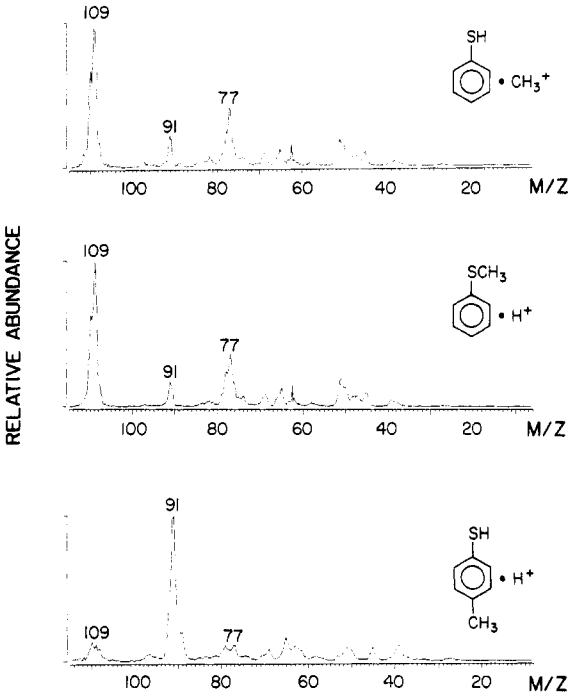


Figure 1. Fragment-ion spectra recorded for collision-induced dissociation of methylated thiophenol (top) and for two model ions representative of substituent (middle) and ring-alkylation products (bottom): 7-keV collisions, MIKE spectrometer, precursor ion m/z 125.

purification. All MS/MS spectra were recorded with air as collision gas at an indicated pressure of 2×10^{-5} torr (2–3-torr estimated collision cell pressure, corresponding to single collision conditions).

Operating conditions for the triple quadrupole spectrometer were as follows: source pressure, ca. 0.3 torr; electron ionizing energy, 70 eV; and ion axial (kinetic) energy, ca. 20 eV as determined by the offset potential of the collision quadrupole with respect to the ion source. All other offset and lens potentials were set to maximize total ion intensity. Argon was used as collision gas at a pressure of ca. 2 mtorr, viz., under multiple collision conditions. Unit mass resolution is achieved in all low-energy MS/MS spectra.

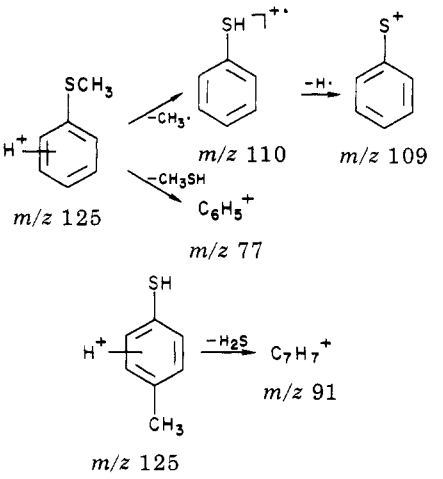
Aniline, phenol, and thiophenol were introduced into the ion sources via direct insertion probes. Spectra were recorded after the initial surge in sample pressure. All experiments were performed in duplicate, and all data are reproducible to ±10% relative intensity.

Results and Discussion

The order of presentation is as follows. Methylation of thiophenol is discussed first since this simple case provides evidence for the validity of the experimental method. Methylation and ethylation of aniline and methylation and ethylation of phenol are then treated in turn. Since both alkylating agents give rather similar results, this form of presentation allows differences associated with changes in the substrate to be highlighted. Protonation is discussed last, both because the results are more difficult to interpret and becuase they appear to be significantly different from the results of alkylation.

Methylated Thiophenol. The MS/MS spectrum given in Figure 1 displays the fragment ions arising by dissociation, at high collision energy, of the adduct between thiophenol and the methyl ion. Shown for comparison are the spectra of two ions having skeletal structures that serve to model substituent and ring methylation, protonated thioanisole, and protonated *p*-methylthiophenol, respectively. All three precursor ions have the same formula, and the similarity between the spectra of methylated thiophenol and protonated thioanisole is compelling evidence, in view of the structural diagnostic capabilities of MS/MS, that these two precursors have the same structure (or mixture of structures). Note that no assumption is made regarding the site of protonation in the reference ions. The objective here and in the following discussion of alkylation of phenol and aniline is to characterize the *skeletal* structure of the alkylated ion. It is well-known that skeletal rearrangement in mass spectrometry is far less facile than hydrogen rearrangement, and the results of Figure 1 indicate that the Ar–S–C and C–Ar–S structures are readily distinguishable, even though the presence of m/z 91 in protonated thioanisole is indicative of a small contribution from skeletal rearrangement.

Scheme I



The nature of the fragmentations observed for the two model compounds provides direct support for the ability to specify skeletal structure by this method, even if the site of protonation is unknown. The major fragmentations of protonated thioanisole are loss of $CH_3\cdot$ and CH_4 to give m/z 110 and 109, respectively, and formation of m/z 77, presumably the phenyl cation. By contrast, there is only one dominant dissociation channel for the *p*-methylthiophenol isomer, and this yields m/z 91, presumably the benzyl or tropylium cation. Not only are these reactions precisely those expected, given the structures of the neutral precursors, but the same types of reactions occur in the cases of the alkylated anilines and phenols and have similar origins. The reactions are rationalized in Scheme I.

In summary, thiophenol is exclusively methylated at the heteroatom. If any ring methylation occurs, it is estimated to be less than 10%. The use of the para isomer as a model for ring methylation is justified by the fact that the various ring isomers give very similar spectra. The alternatives not explicitly tested are (i) ipso methylation, which can be ruled out for all substrates on the basis of a high enthalpy, and (ii) formation of a π-complex. This latter alternative is considered unlikely because it should lead to regeneration of starting materials on dissociation and hence the observation of CH_3^+ or, possibly via charge exchange, C_6H_5–$SH^+\cdot$. The latter ion is indeed present at m/z 110, but it does not dominate the spectrum in the way that is often observed for the products of loosely bound ions.

Methylated Aniline. Figure 2 displays low collision energy data for aniline that are analogous to those shown for thiophenol in Figure 1. Aromatic ring and nitrogen methylation are modeled by protonated *p*-toluidine and protonated *N*-methylaniline, respectively. Selection of the para isomer of toluidine to represent ring methylation is arbitrary. The three ring isomeric compounds give similar

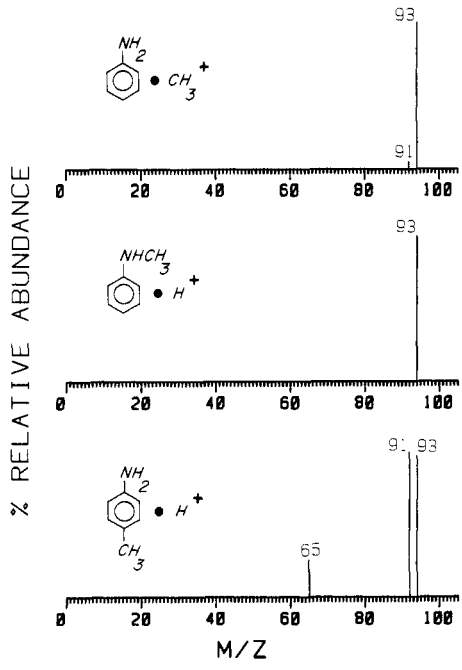


Figure 2. Fragment-ion spectra recorded for collision-induced dissociation of methylated aniline (m/z 108, top) and for ions that model substituent methylation (middle) and ring methylation (bottom): 20-eV collisions, triple quadrupole, precursor ion m/z 108.

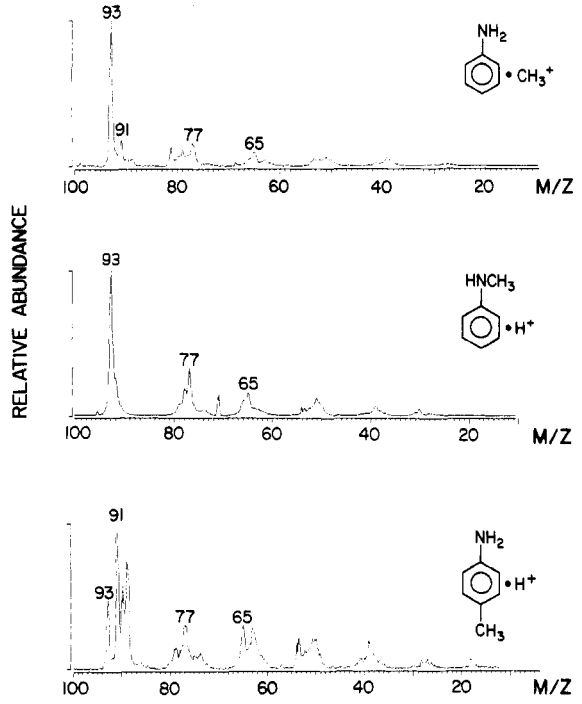


Figure 3. Fragment-ion spectra recorded for collision-induced dissociation of methylated aniline (top) and for ions that model substituent methylation (middle) and ring methylation (bottom): 7000-eV collisions, MIKE spectrometer, precursor ion m/z 108.

spectra, and the question of the specific site of ring substitution is not addressed. Again, protonation of these model substrates may occur at different or multiple sites within the molecule, but the pertinent structural information is contained within the spatial arrangement of the carbon–heteroatom skeleton.

In order to confidently distinguish between structurally isomeric ions and hence to structurally characterize a gas-phase alkylation product containing mixed structures, the two fragmentation spectra should possess characteristic differences. This criterion is satisfied for the isomeric methylanilines (Figure 2) by the appearance of the fragment ion at m/z 91 (assigned as $C_7H_7^+$) for the ring-methylated species, and the complete absence of this ion in the spectrum of the substituent-methylated compound. This particular ion is produced by the elimination of ammonia from the parent ion, a typical reaction of a primary aromatic amine.

Considering that 91^+ is the base peak in the MS/MS spectrum of protonated *p*-toluidine (Figure 2, bottom) and that the gas-phase methylation product displays relatively little of this fragment ion (Figure 2, top), it is clear that only a relatively small percentage of the methylated aniline ions being sampled have the *p*-toluidine skeletal structure. Only if there were overwhelming effects due to differences in ion internal energy could the data of Figure 2 yield any conclusion but that substituent methylation is dominant. The absence of significant internal energy effects on MS/MS spectra is the basis for ion structural studies by this method.[29] Confirmation that structural differences underlie the spectral dissimilarities seen in Figure 2 comes from measuring the same spectra on a different instrument at high collision energy. The results of these experiments are shown in Figure 3. Although the high collision energy spectra display poorer resolution and more extensive fragmentation than those of the low collision energy spectra, the salient feature remains the same, viz., the structurally diagnostic $C_7H_7^+$ (m/z 91) fragment ion is the base peak in the spectrum of *p*-toluidine, but it only occurs to a slight extent in the spectrum of the methylated product. Some ring methylation occurs, but the results confirm overwhelming methylation at the nitrogen substituent. In fact, by treatment of the CID spectrum of the ion/molecule reaction product as a linear combination of the spectra of the two model compounds, relative contributions on the order of 4:1 can be derived for *N*-methylaniline and *p*-toluidine structures, respectively. It should be emphasized, however, that quantitative values such as these are intended only to highlight the trends established by the spectral data taken at both low and high collision energy.

Ethylated Aniline. The ethylation of aniline was performed to observe the effect of the increased size of the alkyl substituent and, if possible, to substantiate the results of the methylation reaction. As before, the dissociation spectrum of the gas-phase alkylation product produced on low-energy collision is compared directly to those of appropriate model compounds (supplementary data). Once again, the models (protonated *N*-ethylaniline and *p*-ethylaniline) were chosen to represent the two possible sites of interaction of the ethyl cation with the substrate molecule. No consideration is given to the specific site on the aromatic ring that participates in the reaction since only the distinction between substitutent and ring alkylation can be made reliably. It is apparent from the data that the ethylated aniline spectrum closely resembles the *N*-ethylaniline spectrum, suggesting that substituent ethylation predominates. In both spectra, the primary fragment ion is m/z 93, which results from loss of $C_2H_5\cdot$ from the parent ion, m/z 122. This is in contrast to the daughter spectrum of protonated *p*-ethylaniline, which loses not only $C_2H_5\cdot$ but also $CH_3\cdot$ to give the peak at m/z 107 and has intense fragment ions at m/z 77 ($C_6H_5^+$) and 79 (presumably $C_5H_5N^+$).

The high energy collision spectrum of the gas-phase ethylated product has also been compared with those of the appropriate model compounds (supplementary data).

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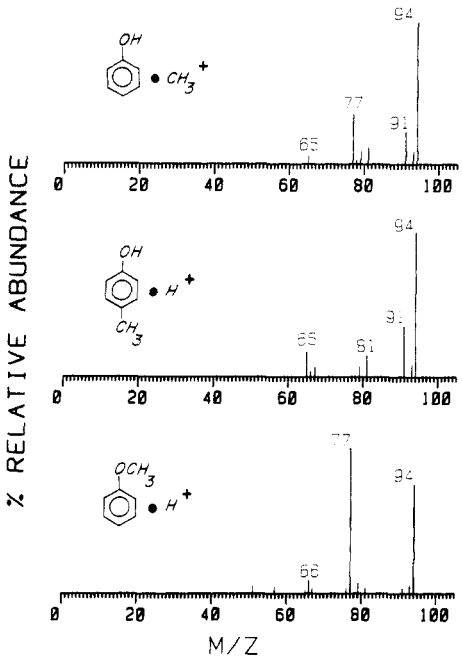

Figure 4. MS/MS spectra showing fragments due to dissociation of methylated phenol (top), protonated *p*-cresol (middle), and protonated anisole: 20-eV collisions, triple quadrupole, precursor ion m/z 109.

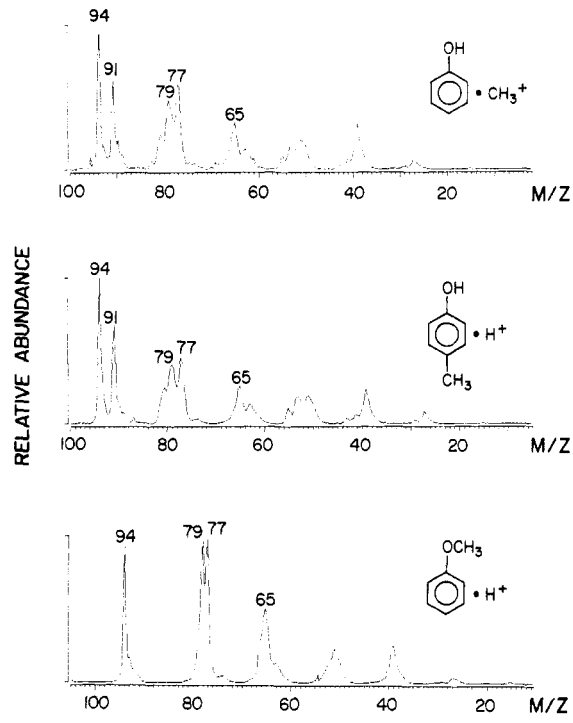

Figure 5. MS/MS spectra showing fragments due to dissociation of methylated phenol (top), protonated *p*-cresol (middle) and protonated anisole (bottom): 7000-eV collisions, MIKE spectrometer, precursor ion m/z 109.

Close examination of the spectra of the model systems reveals a less ideal situation than was encountered for low-energy collisions, in that there are no dominant fragment ions that are unique to just one of the structures. However, loss of a C_1 fragment (to give m/z 106, 105, 104, and 103) is characteristic of the ring-ethylated structure, while loss of a C_2 fragment, especially loss of an ethyl radical to give m/z 93, characterizes the N-ethylated compound. By utilization of the same linear combination approach used for the methylation results, it is evident that the ion/molecule reaction product contains contributions from both structures. Estimated values for the relative contribution of the *N*-ethylaniline to *p*-ethylaniline structures correspond to a ratio of 4:1. The experimental error in these estimates is significant, but it is clear that both methylation and ethylation of aniline occur preferentially at the heteroatom and to approximately the same degree.

A final point deserving discussion is the anomalous intensity of the fragment ion at m/z 94 in the high-energy dissociation spectrum of the ethylation product. This particular ion corresponds to loss of neutral ethylene and apparently does not readily arise from protonated *N*-ethylaniline. This intense fragment ion has been shown to be due to a metastable ion dissociation in experiments done over a range of collision gas pressures. Ready fragmentation of this ion could be due to its existing as a weakly bound ion/molecule complex, for example, a proton-bound dimer of aniline and ethylene. Such noncovalent structures can have high cross sections for fragmentation in MS/MS.[30]

Methylated Phenol. The relative degree of gas-phase methylation at each of the basic sites in phenol is determined through comparison of the daughter ion spectra of the ion/molecule reaction product with those of two model systems, protonated *p*-cresol (the ortho and meta isomers give similar spectra) and protonated anisole. Examination of the triple quadrupole spectra (Figure 4) reveals the existence of unambiguous fragment ions in the critical high-mass region of the spectra of each of the model systems. The appearance of the ion at m/z 91 ($C_7H_7^+$), due to loss of water, in the *p*-cresol spectrum (Figure 4, center) clearly indicates the presence of the methyl substituent on the benzene ring. The same fragment is not observed in the spectrum of protonated anisole, rather loss of methanol yields the ion at m/z 77 (phenyl cation) as base peak. The relative intensities of these characteristic fragment ions in the spectrum of methylated phenol suggest that the degree of ring methylation exceeds substituent methylation. This result contrasts with that observed for aniline. However, the m/z 77 ion is not the best ion to choose to quantitatively differentiate the two isomeric forms. This is because of the observation of a variation in the intensity of this ion with respect to a constant m/z 91 to m/z 94 ratio upon varying methyl fluoride reagent gas pressures. (This result will be discussed below.) Even when this process is excluded, deconvolution of the spectrum of the methylated compound yields relative contributions for ring and oxygen methylation of approximately 4:1.

The identical experiment was performed on the sector instrument (high collision energy), and the results are shown in Figure 5. Again, a noticeable feature of these spectra is the increased amount of fragmentation relative to the quadrupole data. This makes it easy to recognize that alkylation occurs almost quantitatively on the ring in the population studied. Detailed analysis of the spectra of the model systems show the same structurally significant fragment ions as in the low-energy spectra, once again allowing a deconvolution of the alkylation product spectrum into the relative contributions of its two components. The values arrived at by this procedure find the contribution of protonated *p*-cresol relative to protonated anisole to be on the order of 10:1. Although the values generated from the two experiments differ, the trend of the data is clear. Phenol displays a preference for methyl cation at-

(30) (a) S. A. McLuckey, D. Cameron, and R. G. Cooks, *J. Am. Chem. Soc.*, **103**, 1313 (1980); (b) L. G. Wright, S. A. McLuckey, R. G. Cooks, and K. V. Wood, *Int. J. Mass Spectrom. Ion Phys.*, **42**, 115 (1982).

tachment to the aromatic ring, in contrast to the behavior of aniline.

Ethylated Phenol. The MS/MS specra of ethylated phenol and reference ions that exemplify the Ar–O–C_2 and the C_2–Ar–O skeletal structures have been recorded (supplementary material). The data are taken with the MIKE spectrometer. Loss of a C_1 unit is characteristic of the ring-ethyl structure just as for aniline, and this is clearly the dominant process. An estimate can be made of at least 10:1 contribution of the ring-ethylated structure relative to the O-ethylated structure. These values are similar to those obtained for the methylation of phenol, just as methylation and ethylation of aniline gave similar results.

Protonated Aniline. Abundant loss of ammonia (NH_3), m/z 77, is typical of protonated primary amines[31] in chemical ionization. Although suggestive of protonation on the nitrogen atom, this elimination is not necessarily unique to that process. For example, protonation on the ring of cyclohexanol[32] has been demonstrated to be partially responsible for the loss of water from that ion. Loss of ammonia from protonated aniline could also occur via 1,2-elimination of the substituent and an ortho ring proton.

The daughter-ion spectrum of protonated aniline (supplementary material) does not yield unambiguous information pertaining to the location of the ionizing proton. However, loss of H· from the protonated molecule is replaced by H·/D· loss in deuterated aniline in a ratio of 4:1. Complete statistical scrambling would lead to a H·/D· loss ratio of 7:1, substituent reaction without involving the ring protons in H/D exchange would lead to a ratio of 2:1, while ring substitution with complete scrambling requires a ratio of 5:1. In light of these values, the experimental results are indicative of a 4:1 contribution of ring reaction relative to reaction at nitrogen. The loss of H·(D·) from the doubly charged ion shows similar behavior, again excluding a predominantly substituent interaction. (This different, presumably higher energy process justifies the implicit assumption of negligible kinetic isotope effects.)

The elimination of ammonia from protonated aniline can be similarly analyzed. Complete randomization of hydrogen and deuterium would yield an NH_3/NH_2D ratio of 1.6:1, substituent deuteration without randomization would yield exclusively NH_2D loss, while ring deuteration with accompanying ring atom scrambling would give NH_3 and NH_2D loss in the ratio of 5:1. The NH_3/NH_2D ratio found (after accounting for the contribution of $M^{+\cdot} - H - NH_3$) is approximately 3:1, which corresponds to a relative ring/substituent ratio of nearly 8:1. This is somewhat higher than was determined with the loss of H·/D·, but it confirms a substantial amount of ring protonation.

Protonated Phenol. Protonated and deuterated phenol[33] as well as ring-deuterated forms (phenol-*2,4,6-d_3*) and phenol-*ring-d_5* were investigated. As in the case of aniline, daughter-ion spectra do not yield unambiguous information pertaining to the location of the ionizing proton. Conclusions from these high-energy studies are that (i) ring protonation occurs and (ii) there is no evidence that O-protonation occurs, although it cannot be excluded. If protonation were to occur solely on the oxygen atom, with no subsequent rearrangement, exclusive loss of H_2O would be expected for protonated phenol-d_3 and -d_5, while deuterated phenol should lose only HDO. Low-energy spectra *also* show mixtures of H_2O and HDO loss. The data are consistent with bonding at the ring as the predominant process.

Table I. Sites of Protonation and Alkylation[a]

process	thiophenol	aniline	phenol
methylation	S only	S > R 4:1	S < R 1:6
ethylation		S > R 4:1	S < R 1:6
protonation		S < R 1:6	R

[a] R = ring, S = substituent.

Table II. Methylation of Phenol

P of CH_3F, mtorr	m/z 91:m/z 94	P of CH_3F, mtorr	m/z 91:m/z 94
0.17	0.19	0.54	0.22
0.27	0.20	0.79	0.21
0.36	0.20		

Conclusion

Alkylation of phenol and aniline in the gas phase under chemical-ionization conditions occurs both at the heteroatom and on the ring as measured by MS/MS product analysis. These results and those for protonation and for methylation of thiophenol are summarized in Table I. The main conclusions are as follows. (i) As expected, the nitrogen substituent is more likely than oxygen to be alkylated, while the sulfur analogue shows exclusive heteroatom alkylation. (ii) Protonation appears to occur largely on the ring, even for aniline where ring alkylation is a minor process. The first conclusion is in agreement with trends displayed in the available gas-phase (proton) affinity data (see Introduction). The second conclusion is readily explained in terms of polarizability. Because alkyl groups are much more polarizable than the proton, they allow effective charge delocalization to occur upon heteroatom substitution. This is not the case for the proton, for which resonance delocalization after ring protonation is the only effective means of charge dispersal.

Different trends might have been expected if kinetic factors controlled the ion structure examined; hard/soft acid/base concepts might lead one to expect alkylation on the ring and protonation at the heteroatom. These experiments are not done under chemical equilibrium conditions, but the results do appear to reflect thermodynamic control rather than kinetic control. This could occur by alkyl transfer in a collision between the alkylated species and the corresponding neutral species. Additional evidence for the approach to equilibrium comes from (i) data taken at reduced chemical-ionization source pressure and (ii) the apparent lack of a dependence on the type of reaction used to generate the ions under investigation. The effect of chemical-ionization source pressure was studied with use of methyl fluoride for the methylation of phenol. The $91^+/94^+$ ratio was constant for all reagent gas pressures studied, as seen in Table II. Furthermore, the relative abundance of the other fragment ions were constant as well, except that at long times after the phenol was admitted into the source a large, reproducible increase in the m/z 77 ion was observed. Further evidence that the ionization reaction occurs under conditions approaching thermodynamic control comes from the fact that identical MS/MS fragmentation patterns were obtained with use of a variety of different ionizing reagent gases to obtain

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(32) C. Fenselau, M. M. Green, and I. Jardine, *Org. Mass Spectrom.*, **14**, 326 (1979).

(33) D. Cameron, Ph.D. Thesis, Purdue University, West Lafayette, IN, 1979.

a given alkylated or protonated species. Examples include ethyl bromide $(C_2H_5)_2Br^+$ and methane $C_2H_5^+$ for ethylation, methyl fluoride $(CH_3)_2F^+$ and methyl chloride $(CH_3)_2Cl^+$ for methylation, and isobutane $C_4H_9^+$, methane CH_5^+, and hydrogen H_3^+ for protonation.

Our conclusions are in broad agreement with those of theoretical calculations, including the similar basicities of ring and substituent sites in aniline. There is less agreement with an earlier study[21] on the ethylation of phenol although we interpret the corresponding aniline results rather differently than these authors. (Our high collision energy aniline data were further confirmed by use of a VG Instruments ZAB reverse-geometry mass spectrometer.) It should also be noted that our results for methylation of phenol and aniline are quite different from those obtained[25,26] under nonequilibrium conditions at much higher pressures. These authors found predominant substituent methylation for phenol and a substantial degree of ring alkylation for aniline. Although the reasons for these differences are not fully understood, the short reaction times, and quenching associated with the higher pressures used, could result in kinetically controlled processes. Key features of the present results, which are representative of chemical-ionization conditions, are the contrasting behavior of aniline and phenol on the one hand and the contrasting results obtained for protonation and alkylation on the other. The data are self-consistent, and agreement between the high- and low-energy MS/MS data is good.

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Registry No. Aniline, 62-53-3; phenol, 108-95-2; thiophenol, 108-98-5; thioanisole (protonated), 77421-01-3; *p*-methylbenzenethiol (protonated), 87728-89-0; *p*-toluidine (protonated), 17112-11-7; *N*-methylaniline (protonated), 17456-49-4; *N*-ethylaniline (protonated), 23388-60-5; *p*-ethylaniline (protonated), 41265-89-8; *o*-cresol (protonated), 58142-00-0; *m*-cresol (protonated), 37396-35-3; anisole (protonated), 18223-09-1; *p*-ethylphenol (protonated), 87728-90-3; phenetole (protonated), 87728-91-4.

Supplementary Material Available: Figures showing MS/MS spectra for collision-induced dissociation of ethylated aniline, spectra of fragment ions produced on collision-induced dissociation of ethylated phenol and ions formed by protonation of *p*-ethylphenol and phenetole, spectra of fragment ions from protonated and deuterated aniline, and daughter-ion spectra of protonated aniline (6 pages). Ordering information is given on any current masthead page.

Selenium-Stabilized Carbocations. Formation of 2-(Phenylseleno)allyl Cations and Their Reactions with Furan, Pyrrole, and Thiophene

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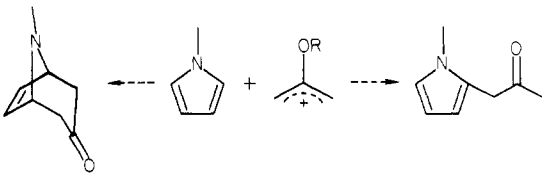
β-Bromovinyl selenides I (R_1 = H, CH_3, C_2H_5; R_2 = H, CH_3; R_3 = H, CH_3) have been prepared in excellent yields from allenes and benzeneselenenyl bromide. On treatment with silver perchlorate in nitromethane at −15 °C and in the presence of a weak base, these β-bromovinyl selenides reacted smoothly with electron-rich aromatic molecules such as furan, *N*-methylpyrrole, thiophene, or 1,3,5-trimethoxybenzene to give electrophilic substitution products exclusively and in good yields (60–70%). From this and from the systematic absence of [4 + 3 → 7] cycloaddition products it is tentatively concluded that the actual reactive species might be III rather than allylic cation II. It has also been shown that the substitution products can be efficiently deselenated by the use of tri-*n*-butyltin hydride at reflux in benzene and in the presence of azobis(isobutyronitrile) (AIBN).

Allyl cations substituted at position 2 are interesting reactive intermediates from both synthetic and theoretical points of view. The synthetic usefulness of these species arises primarily from their ability to undergo [4 + 3 → 7] cycloadditions,[1-3] thus providing a new entry to the class of seven-membered-ring compounds including the bicyclic ones. It is known, however, for the 2-oxyallyl[4-6] and the 2-[(trimethylsilyl)oxy]allyl[3] species that in the case of their reactions with aromatic molecules such as furan or pyrrole, substantial competition exists between the two major pathways, i.e., cycloaddition and electrophilic substitution (eq 1). A number of factors have been shown to affect



(1)

R = metal, alkyl, $Si(CH_3)_3$

this competition, the most important ones being (i) the specific electronic nature of the cationic species,[4b,5a,6,7] (ii) the substitution pattern of the aromatic reagent,[4b,5,6,8] and (iii) the reaction medium.[3]

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