Ortho effects in the dissociation of ionized *N*-chlorophenyl- and *N*-bromophenyl-2-aminobenzamidines: intramolecular aromatic substitution with cyclization to protonated 2-(2-aminophenyl)-1*H*-benzimidazoles

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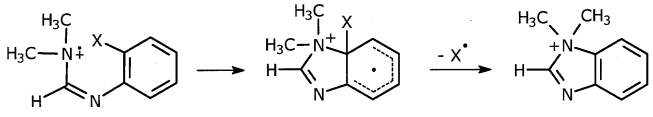
Electron ionization (70 eV) mass spectra, double-stage (MS^2) 10 eV collision-induced dissociation (CID) product-ion mass spectra of molecular ions and triple-stage (MS^3) sequential product-ion mass spectra of major fragment ions are reported for the parent *N*-phenyl and the isomeric *ortho*-, *meta*- and *para*-*N*-chlorophenyl- and *N*-bromophenyl-2-aminobenzamidines. Dissociation is greatly influenced by an *ortho* effect that favors the loss of *ortho* H atoms and particularly the loss of the *ortho* halogen substituents. Dissociation occurs via a two-step intramolecular aromatic substitution reaction and a distonic-ion intermediate inhibits scrambling of ring hydrogens thus favoring the loss of the *ortho* substituents. The *ortho* isomers form an abundant and diagnostic $[M - X]^+$ fragment ion (X = Cl, Br) and are easily distinguished. Protonated 2-(1*H*-benzimidazol-2-yl)-phenylammonium ions are likely formed; they dissociate mainly by NH_3 loss upon CID and react readily with pyridine by proton transfer.

Keywords: *ortho* effect, benzamidines, intramolecular aromatic substitution, pentaquadrupole mass spectrometry, MS/MS, MS/MS/MS, gas-phase ion chemistry

Introduction

The *ortho* effect is one of the diagnostically most important processes in electron ionization mass spectrometry.[1,2] It operates for vicinally-substituted aromatic compounds and provides a foremost example of the influence of structural details of a compound on its mass spectrum.[3] Grützmacher and co-workers[4-7] investigated the mechanism of the *ortho* effect which operates for ionized *N*,*N*-dimethyl-*N*´-phenylformamidines and established that the vicinal X group is eliminated via a two-step intramolecular aromatic substitution reaction. A distonic-ion intermediate was found to govern the reaction outcome by inhibiting the scrambling of ring hydrogens thus favoring the loss of H atoms or substituents at the *ortho* position. The final product was characterized as the cyclic *N*,*N*-dimethyl-1*H*-benzimidazol-1-ium ion (Scheme 1).[7]

Amidines, the dinitrogen analogs of carboxylic acids and esters, display a rich chemistry conferred by their unique structure and diverse electronic and binding properties.[8] Many amidines are biologically active[9,10] and their pharmaceutical properties depend heavily on their structures and configurations. Amidines also display a distinct coordina-



Scheme 1.

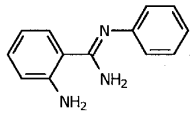
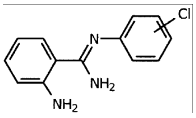
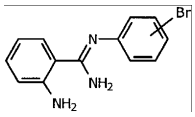
tion chemistry,[11] are highly basic[12,13] and participate as the key intermediates in the synthesis of important heterocyclic compounds.[10,14]

Here, we report that a strong *ortho* effect, analogous to that observed for *N´*-phenylformamidines,[4-7] is observed in the 70 eV electron ionization (EI) mass spectra of the isomeric *ortho*-, *meta*- and *para*-*N*-chlorophenyl- and *N*-bromophenyl-2-aminobenzamidines, as well as (and more obviously) in the 10 eV collision-induced dissociation (CID) product-ion mass spectra of their molecular ions. MS^3 experiments have been applied to investigate the structures of these *ortho*-effect product ions.

Experimental

The parent *N*-phenyl and the isomeric *N*-chlorophenyl- and *N*-bromophenyl-2-aminobenzamidines were prepared as reported.[14,15] The 70 eV EI mass spectra were recorded using an EBE Autospec (Micromass, UK) mass spectrometer. The double- (MS^2) and triple-stage (MS^3) mass spectrometric experiments[16,17] were performed using an Extrel (Pittsburgh, PA, USA) pentaquadrupole (Q1q2Q3q4Q5) mass spectrometer described in detail elsewhere.[18] For the MS^2 experiments, ions were formed by 70 eV EI, mass-selected by Q1 and further dissociated by 10 eV collisions

Table 1. Major fragment ions [*m/z* and relative abundances (%)] in the 70 eV EI mass spectra of the parent *N*-phenyl and the isomeric *N*-chlorophenyl- and *N*-bromophenyl-2-aminobenzamidines.

									
m/z	parent benzamidine	*m/z*	*ortho*	*meta*	*para*	*m/z*	*ortho*	*meta*	*para*
211	47	247	22	16	16	291	24	55	45
210	**18**	246	17	18	12	290	11	26	18
209	1	245	65	50	51	289	23	57	44
194	21	**244**	**12**	**25**	**8**	**288**	**6**	**18**	**9**
193	7	230	13	8	8	274	7	12	10
167	3	228	30	27	26	272	7	12	10
166	2	**210**	**39**	**0**	**0**	**210**	**58**	**2**	**0**
119	42	209	12	3	2	209	11	2	3
118	13	193	7	2	2	193	12	2	2
106	6	192	8	2	3	192	6	2	3
105	7	129	33	30	32	173	57	38	52
102	4	127	100	90	100	171	57	38	55
93	100	119	85	100	80	119	100	100	100
92	23	118	36	28	44	118	47	30	25
91	10	105	10	25	7	105	16	23	23
77	21	92	34	50	29	92	55	58	55
66	14	91	24	25	25	91	50	38	25
65	23	75	12	26	16	76	25	25	25
64	5	65	25	52	28	65	72	46	63
51	13	52	7	8	7				

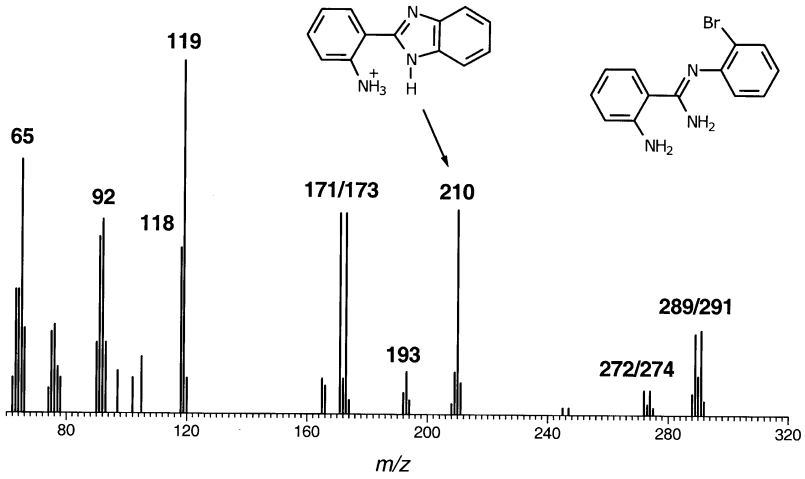


Figure 1. 70 eV EI mass spectrum of *N*-2-bromophenyl-2-aminobenzamidine. Note the abundant fragment ion of *m/z* 210, which is diagnostic for the *ortho* isomers.

with argon. To record the product-ion mass spectra, Q5 was scanned while operating Q3 in the broadband RF-only mode. For the MS^3 experiments, a fragment ion of interest formed in q_2 was mass-selected by Q3 and further dissociated by 10 eV collisions with argon in q4 or reacted with pyridine by near 1 eV collisions in q4, while scanning Q5 to record the spectrum. The 10 eV and near 1 eV collision energies were taken as the voltage difference between the ion source and the collision quadrupole.

Results and discussion

EI-MS

The 70 eV EI mass spectrum of the parent *N*-phenyl-2-aminobenzamidine (Table 1) displays an $[M - H]^+$ fragment ion of *m/z* 210 of relatively high abundance, which indicates, therefore, that H atom loss from $M^{+\cdot}$ is energetically favorable. Other abundant fragments are those of *m/z* 194 (loss of NH_3), *m/z* 119 (loss of $PhNH^{\cdot}$) and *m/z* 93 (ionized aniline).

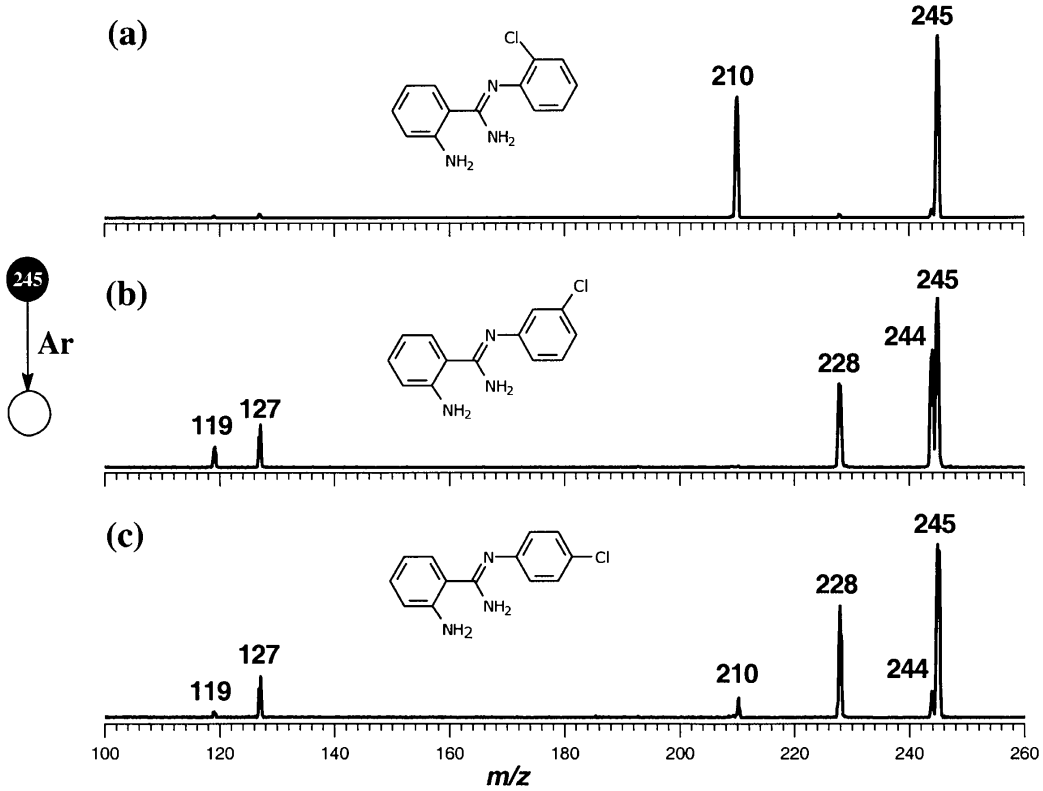


Figure 2. Double-stage (MS^2) 10 eV CID product-ion mass spectrum of the molecular ion of (a) *N*-(2-chlorophenyl)-, (b) *N*-(3-chlorophenyl)- and (c) *N*-(4-chlorophenyl)-2-aminobenzamidine.

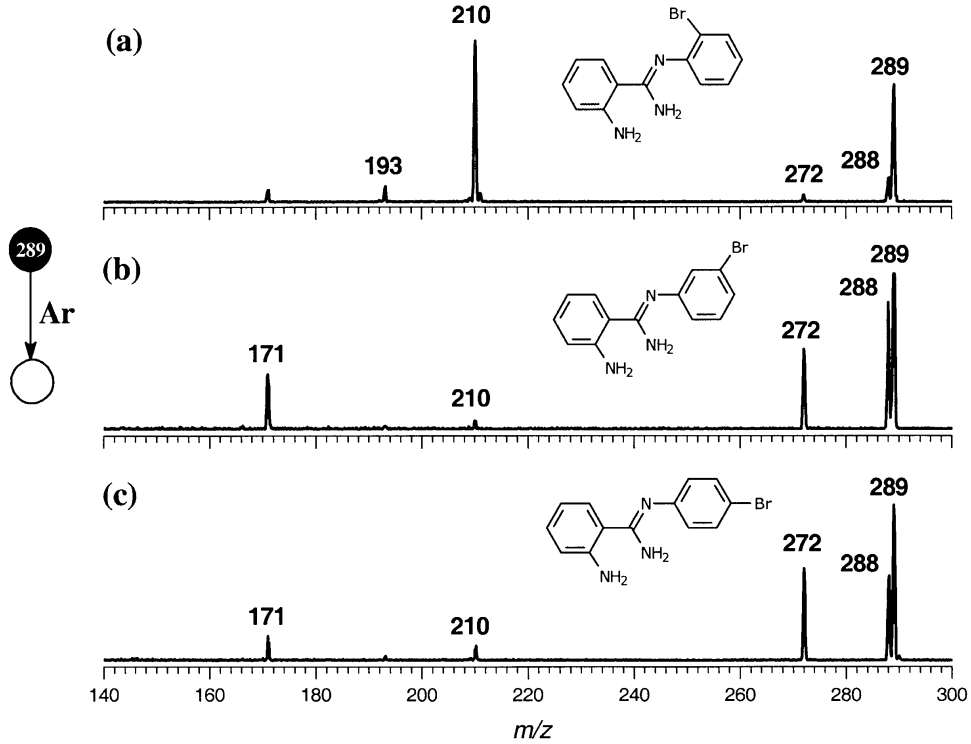


Figure 3. Double-stage (MS^2) 10 eV CID product-ion mass spectrum of the molecular ion of (a) *N*-(2-bromophenyl)-, (b) *N*-(3-bromophenyl)-, and (c) *N*-(4-bromophenyl)-2-aminobenzamidine.

H-atom loss is also favored for all halogenated isomers, particularly for the *meta* isomers [to give *m/z* 244 for the chlorine isomers and *m/z* 288 for the bromine isomers; (Table 1)]. But, by far the most structurally diagnostic fragment ion is $[M - X]^+$ with *m/z* 210, which is formed abundantly and nearly exclusively for the *ortho* isomers (Table 1), as exemplified in Figure 1 by the 70 eV EI mass spectrum of the *N*-(2-bromophenyl)-2- aminobenzamidine.

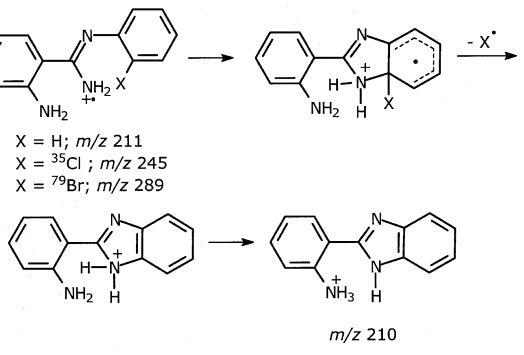
MS²

The *ortho* effect is even more prominent when molecular ions are mass-selected and dissociated by 10 eV collisions with argon (Figures 2 and 3). The *ortho* isomers dissociate nearly exclusively to *m/z* 210 by halogen atom loss [Figures 2(a) and 3(a)]. Just as for the related *N´*-phenylformamidines,[4-7] this strong *ortho* effect likely operates via a two-step intramolecular aromatic substitution that proceeds through a distonicion intermediate (Scheme 2). In such an intermediate, the quaternary ammonium center carries the positive charge whereas the unpaired electron is delocalized.[19] This intermediate inhibits scrambling of ring hydrogens,[7] thus favoring the loss of the *ortho* halogen substituent. The *2-(1H*-benzimidazol-2-yl)phenyl- ammonium ion, an *N*-protonated form of the aromatic 2-(2-aminophenyl)-1*H*-benzimidazole, is likely formed after intramolecular proton transfer to the amino group.

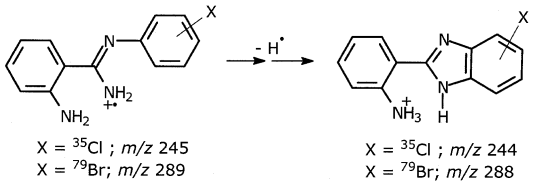
The molecular ions of the *meta* and *para* isomers [Figures 2(b) and (c) and 3(b) and (c)] also dissociate distinctively by 10 eV CID. H-atom loss forms *m/z* 244 and 288, respectively, and this dissociation is particularly favored for the *meta* isomers. Likely, *ortho* H atoms (Scheme 3) are eliminated in a process similar to that depicted in Scheme 2. But, for the *meta* and *para* isomers, other dissociations compete favorably: for example, NH_3 loss (to give *m/z* 228 and 272, respectively) and $C_7H_6N_2$ loss (to give *m/z* 127 and 171, respectively).

MS³

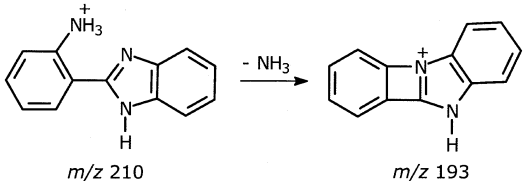
Figure 4 displays the triple-stage CID product-ion mass spectrum of the $[M - Cl]^+$ ion from ionized *N*-(2-chlorophenyl)-2-aminobenzamide. Consistent with the proposed 2-(1*H*-benzimidazol-2-yl)phenylammonium ion structure, it dissociates mainly by NH_3 loss to an ion of *m/z* 193 (Scheme 4). The $[M - Br]^+$ ion of *m/z* 210 from ionized



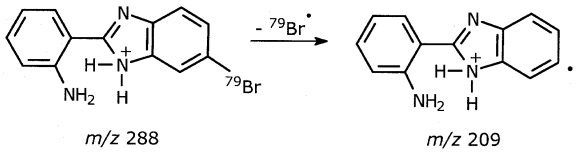
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

N-(2-bromophenyl)-2-aminobenzamide displays a nearly identical spectrum (not shown).

Figure 5 displays the sequential product-ion mass spectrum of the $[M - H]^+$ ion from ionized *N*-(4-bromophenyl)-2-aminobenzamide. If *ortho* H atoms are indeed lost, a halogen-substituted 2-(1*H*-benzimidazol-2-yl)phenylammonium ion should be formed (Scheme 3). In contrast with *m/z* 210 (Figure 4), that dissociates extensively by NH_3 loss, *m/z* 288 [Figure 4(b)] dissociates extensively by $^{79}Br^{\cdot}$ loss (Scheme 5). The $[M - H]^+$ ion of *m/z* 244 from ionized *N*-(4-chlorophenyl)-2-aminobenzamide also dissociates preferentially to *m/z* 209 by $^{35}Cl^{\cdot}$ loss (spectrum not shown).

Reactions with pyridine

Figure 6 displays the sequential product-ion mass spectrum from the reaction with pyridine of the $[M - Cl]^+$ ion formed by CID of ionized *N*-(2-chlorophenyl)-2-amino-

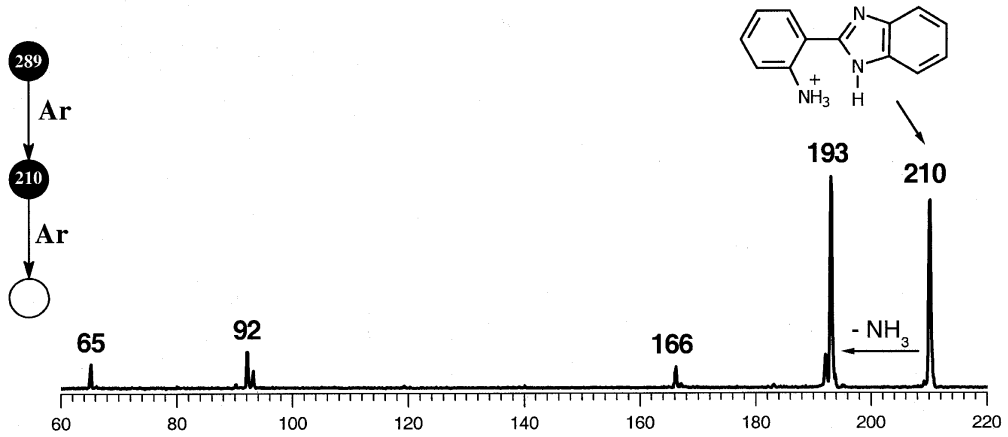


Figure 4. Triple-stage (MS^3) 10 eV CID sequential product-ion mass spectrum of the $[M - Cl]^+$ fragment of *m/z* 210 from ionized *N*-(2-chlorophenyl)-2-aminobenzamidine.

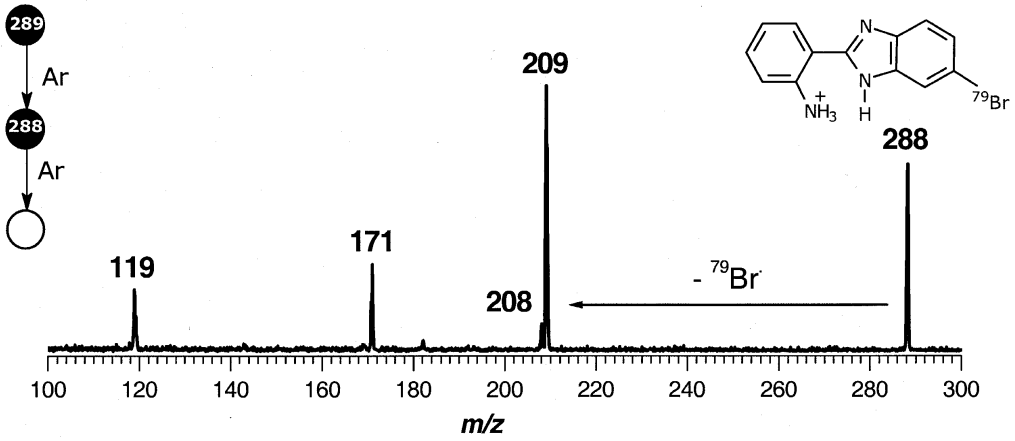


Figure 5. Triple-stage (MS^3) 10 eV CID sequential product-ion mass spectrum of the $[M - H]^+$ fragment of *m/z* 288 from ionized *N*-(4-bromophenyl)-2-aminobenzamidine.

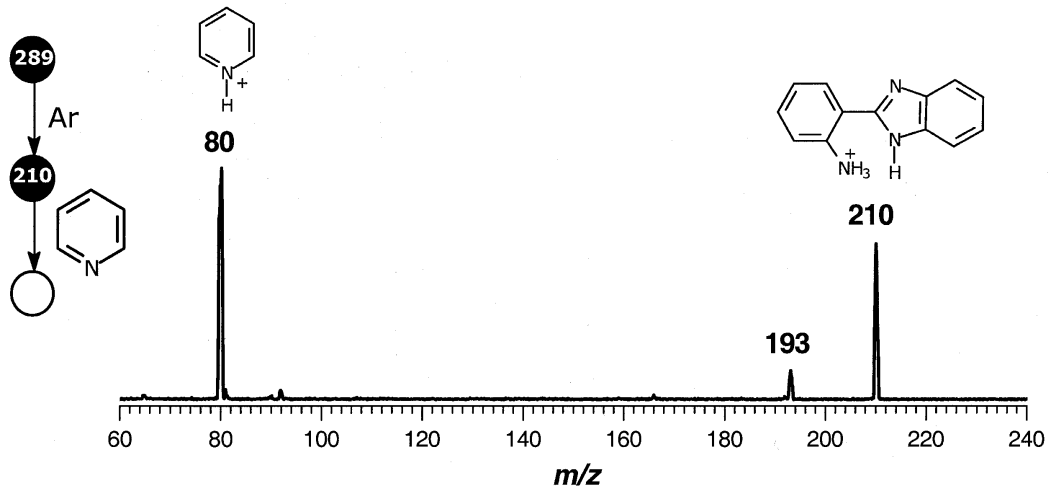
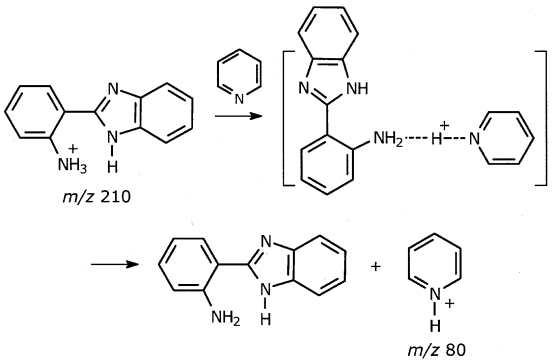


Figure 6. Triple-stage (MS^3) product-ion mass spectrum from the reaction with pyridine of the $[M–Cl]^+$ fragment ion of *m/z* 210 from 10 eV CID of ionized *N*-(2-chlorophenyl)-2-aminobenzamidine.

benzamidine. The putative protonated 2-(2-aminophenyl)-1*H*-benzimidazole ion (Scheme 2) should readily transfer a proton to pyridine, a stronger base. The spectrum of Figure 6 shows that proton transfer occurs readily, likely via the intermediacy of a proton-bound heterodimer. Both protonated pyridine of *m/z* 80 and the neutral (and, therefore, undetectable) 2-(2-aminophenyl)-1*H*-benzimidazole (Scheme 6) are likely formed. The $[M – Br]^+$ ion formed by CID of ionized *N*-(2-bromophenyl)-2-aminobenzamidine reacts similarly with pyridine (spectrum not shown).

Conclusion

Dissociation of ionized *N*-phenyl and isomeric *ortho*-, *meta*- and *para*-*N*-chlorophenyl- and *N*-bromophenyl-2-aminobenzamidines is largely governed by an *ortho* effect. The *ortho*–halogen isomers are, therefore, easily distinguished because they form an abundant and diagnostic fragment ion of *m/z* 210. Dissociation occurs via a two-step intramolecular aromatic substitution reaction and a distonic-ion intermediate inhibits scrambling of ring hydrogens, thus favoring the loss of the *ortho* substituents. Stable 2-(1*H*-benzimidazol-2-yl)phenylammonium ions amino-protonated forms of 2-(2-aminophenyl)-1*H*-benzimidazoles are likely formed. Consistent with the proposed structures, the $[M – X]^+$ ions from the *ortho* isomers dissociate predominantly by NH_3 loss and react readily with pyridine by proton transfer.



Scheme 6.

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