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Protonation Susceptibility and Fragmentation Capability of Functional Groups in Chemical Ionization Mass Spectrometry of Simple Bifunctional Compounds. Semi-quantitative Interpretation of Spectra

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Positive-ion, methane-mediated chemical ionization mass spectra were measured for simple bifunctional aromatic compounds of the type *m*-$XCH_2C_6H_4CH_2Y$, where X = NH_2 and $N(CH_3)_2$, and Y = OH and OCH_3. Essentially only three peaks of ions, $[MH]^+$, $[MH - XH]^+$ and $[MH - YH]^+$, have appeared for each compound. Since the two functional groups XCH_2- and YCH_2- do not interact with each other after protonation or after fragmentation, they are assumed to be protonated and to undergo fragmentations independently. The relative protonation susceptibility and fraction of fragmenting $[MH]^+$ can be estimated for each functional group in these compounds. A semi-quantitative interpretation of the observed spectra is presented.

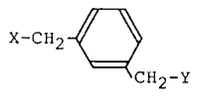
INTRODUCTION

In recent years, positive-ion chemical ionization mass spectrometry (CIMS)[1–3] has increased in importance because the molecular protonated ion of $[MH]^+$ formed in CIMS has, at least formally, been recognized as a molecular ionic species in secondary ion mass spectrometry (SIMS)[4] and fast atom bombardment (FAB)[5] spectra. The $[MH]^+$ ion has a crucial role in interpreting the behaviour of a given compound, and a detailed knowledge concerning the structure of $[MH]^+$ and the reactivity of each functional group is required for analysing observed spectra. As a part of our recent series of studies,[6–8] the aim of this work is to evaluate in a semi-quantitative manner the trend of bond fission of the functional groups in $[MH]^+$ ions by using simple bifunctional aromatic compounds of the type *m*-$XCH_2C_6H_4CH_2Y$.

EXPERIMENTAL

Syntheses of compounds

We have synthesized four test compounds, **1–4**. *m*-Cyanotoluene was oxidized with chromium trioxide in a mixture of acetic anhydride and acetic acid[9] and the resulting *m*-cyanobenzaldiacetate was hydrolysed to give *m*-cyanobenzaldehyde, which was then reduced with sodium borohydride in ethanol to afford *m*-cyanobenzyl alcohol. Diborane reduction of the cyano group of the alcohol in tetrahydrofuran (THF) gave *m*-aminomethylbenzyl alcohol (**1**). Treatment of **1** with formaldehyde and formic acid yielded the corresponding *N*,*N*-dimethyl compound **2**.



Compound	X	Y
1	NH_2	OH
2	$N(CH_3)_2$	OH
3	NH_2	OCH_3
4	$N(CH_3)_2$	OCH_3

Methylation of *m*-cyanobenzyl alcohol with methyl iodide and sodium hydride in THF gave *m*-cyanobenzyl methyl ether, the cyano group of which was reduced with diborane in THF to afford *m*-aminomethylbenzyl methyl ether (**3**). Methylation of **3** with formaldehyde and formic acid gave the corresponding *N*,*N*-dimethyl compound (**4**).

Compounds **1–4** were purified as their crystalline hydrochlorides, and the structures were confirmed by ^1H and ^{13}C NMR spectra. Supplementary information on the detailed synthetic procedures is available on request.

Mass spectra

Conventional CI mass spectra were measured with a Shimadzu LKB 9000A mass spectrometer and GCMS-

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Table 1. Conventional methane CI mass spectra of 1–4

Compound			Relative abundance (%)			
No.	X	Y	$[MH]^+$	$[MH-XH]^+$	$[MH-YH]^+$	Total
1	NH_2	OH	6	41	53	100
2	$N(CH_3)_2$	OH	29	8	63	100
3	NH_2	OCH_3	8	49	43	100
4	$N(CH_3)_2$	OCH_3	36	11	53	100

Table 2. Corrected relative abundances of ions (methane CI)

Compound			Relative abundance (%)			
No.	X	Y	$[MH]^+$	$[MH-XH]^+$	$[MH-YH]^+$	Total
1	NH_2	OH	6	41	53	100
2	$N(CH_3)_2$	OH	24	7	53	84
3	NH_2	OCH_3	7	41	36	84
4	$N(CH_3)_2$	OCH_3	24	7	36	67

PAC-90 computer system. The source pressure was checked with an MKS Baratron manometer, Type 221A. The spectra were recorded at a source temperature of 230 °C and an accelerating voltage of 3.5 kV. The total emission current was 120 μA and the electron energy 150 eV. Solid samples of the hydrochlorides of **1–4** were introduced directly from a solid insertion probe.

Methane CI mass spectra of **1–4** are given in Table 1. Essentially only three peaks of ions appeared for each compound: $[MH]^+$, $[MH-XH]^+$ and $[MH-YH]^+$.

RESULTS AND DISCUSSION

Corrected relative abundance of ions

In CIMS the abundance of fragment ions from a given compound is considered to be related both to the extent of initial protonation and to the fraction of the fragmenting $[MH]^+$. For particularly selected series of compounds we can assume that these two quantities are defined if the structure of the fragmenting functional group is fixed. In fact, our previous work[6–8] suggested that in the present type of compounds the relative extent of initial protonation on one functional group and the extent of fragmentation of this protonated group depend only on the structure of the group concerned and are independent of other functional groups within the molecule.

Accordingly, one can estimate the normalized relative abundance of each ion from the spectral data in Table 1. For example, the relative abundance of the $[MH-NH_3]^+$ ion of **1** was 41%, and if we take this compound as an arbitrary standard, the value of 41% should also be applicable as a corrected relative abundance to the $[MH-NH_3]^+$ ion of **3**, because these two compounds have a common NH_2 group. Similar treatment of the data in Table 1 leads to the corrected relative abundance of each ion, as shown in Table 2.

The relative peak intensity ratios of the $[MH]^+$, $[MH-XH]^+$ and $[MH-YH]^+$ ions for the respective compounds are, of course, the same as those in Table 1, but the total relative abundance of the ions is not necessarily 100%. Therefore, the values in Table 2 roughly reflect the actual relative abundances of ions formed in the ion source.

General tendency in protonation and fragmentation

The total abundances of ions shown in Table 2 represent the efficiency of the initial protonation of each compound. The data indicate that **1** (no *N*- or *O*-methyl group) is protonated most effectively and **4** (fully methylated) least favorably. This means that the methyl group on NH_2 and/or OH group prevents the protonation. This result is consistent with that for the corresponding *para* derivatives.[6]

The abundance of $[MH]^+$ appears to be constant if the X group (N-containing function group) is the same, as for **1** and **3** and for **2** and **4**. This result suggests that the stable non-fragmenting $[MH]^+$ has the attached proton on the nitrogen-containing functional groups. This also agrees with the data for the collisionally induced dissociation (CID) spectra of $[MH]^+$ of the *para*-substituted compounds.[6]

Our previous results[6,10] of deuterium-labelling experiments showed that the attached proton from the reactant ion is not mobile in $[MH]^+$ ions and that the protonation of one functional group causes bond weakening around that group. Consequently, all the $[MX-XH]^+$ ions are assumed to be formed only from the X-protonated $[MH]^+$, whereas all the $[MH-YH]^+$ ions are formed only from the Y-protonated $[MH]^+$. Some of the X-protonated $[MH]^+$ ions do not have sufficient energy to fragment and are observed as $[MH]^+$ in the mass spectrum, whereas all the Y-protonated $[MH]^+$ ions of these compounds are sufficiently energized to afford the $[MH-YH]^+$ ion. One can then calculate the relative extent of protonation for each functional group under methane CI conditions: initial X-protonation corresponds to the sum of the abundances of observed $[MH]^+$ and $[MH-XH]^+$ ions, and Y-protonation is equivalent to the abundance of the $[MH-YH]^+$ ion. Thus, the following result was obtained: OH (53) > NH_2 (47–48) > OCH_3 (36) > $N(CH_3)_2$ (31). This is regarded as representing the relative proton-accepting ability of these functional groups in the compounds under the applied methane CI conditions.

Although this order is again in agreement with that for the previously reported *para* derivatives,[6] the order is not related to the proton affinities (*PA*) of these functional groups, since the estimated *PA* values for this

type of compounds are OH 789, NH_2 907, OCH_3 822 and $N(CH_3)_2$ 954 kJ mol^{-1}.[6] The order rather seems to reflect the inhibitory effect of protonation by the methyl group. In this respect, it should be noted that a new parameter, protonation susceptibility (*PS*), which is independent of the well known *PA*, has recently been proposed[11] for evaluating the relative proton-accepting ability of functional groups in CIMS.

The above values of proton-accepting ability (*PS*) of each functional group are slightly different from those for the corresponding *para* derivatives.[6] The differences are small, however, and it is not obvious whether they are simply experimental deviations or represent a real trend that might be ascribed in part to the difference in protonation cross-sections between *meta*- and *para*-substituted compounds.

From the data in Table 2, the fraction of fragmenting $[MH]^+$ in initially formed X-protonated $[MH]^+$ ions can also be calculated: NH_2 86% and $N(CH_3)_2$ 23%. The corresponding fraction for the *para* derivatives are NH_2 95% and $N(CH_3)_2$ 59–66%.[6] The reason for this discrepancy between the *meta*- and *para*-substituted compounds is not clear. One possible explanation is that the remaining YCH_2–group in $[MH - XH]^+$ ions would slightly stabilize the positive charge from *para* but not from *meta* positions, and thus the [MH – XH] fragmentation in *para* compounds could be facilitated to some extent.

On the other hand, all of the Y-protonated $[MH]^+$ ions can fragment to give $[MH - YH]^+$ ions, as discussed above, and the fraction of fragmenting $[MH]^+$ in total Y-protonation is 100% for both *meta* and *para* compounds. It should be noted that the C—O (C—Y) bond is usually cleaved much more easily than the C—N (C—X) bond. For instance, thermochemically estimated[12] minimum critical energies for cleavage of a single bond between benzyl and protonated functional groups are OH 16, OCH_3 63, NH_2 146 and $N(CH_3)_2$ 220 kJ mol^{-1}. Accordingly, the similar stabilization of the positive charge by the XCH_2–group in $[MH - YH]^+$ ions as described above would not effectively be operative.

Semi-quantitative analysis of fragmentations

Since in the compounds examined here the two functional groups XCH_2– and YCH_2– do not interact strongly with each other after protonation or after fragmentation, these functional groups can be protonated and can undergo fragmentations independently under the applied methane CI conditions. Consequently, we can summarize our data as shown in Table 3.

Consider, for example, NH_2 and OCH_3 groups. The initial, total protonation ratio (*PS* ratio) of NH_2 and OCH_3 is 48:36; 14% of initially formed, amino-protonated $[MH]^+$ ions can remain as non-fragmenting $[MH]^+$ ions, whereas 86% of them fragment to give $[MH - NH_3]^+$ ions. On the other hand, all (100%) methoxy-protonated $[MH]^+$ ions can fragment and none remain as $[MH]^+$ ions. This leads to the observed relative abundances of the ions from **3**, i.e. $[MH]^+ : [MH - NH_3]^+ : [MH - CH_3OH]^+ = 7 : 41 : 36$, as seen in Table 2.

CONCLUSION

This work clearly demonstrates the importance and usefulness of two parameters, the protonation susceptibility (*PS*) and the fraction of fragmenting $[MH]^+$ ions, for analysing observed CI spectra. The discrepancy between the order of *PA* and the order of *PS* is not unexpected because the ordinary *PA* corresponds to the proton-accepting ability of functional groups under equilibrium conditions, whereas the relative *PS* is regarded as a measure of proton-accepting ability that obviously involves kinetic factors such as protonation cross-sections. In view of the unimolecular decomposition of $[MH]^+$ ions, the fraction of fragmenting $[MH]^+$ ions would be affected by the internal energy distributions of $[MH]^+$ ions.[11] Therefore, the figures in Table 3 are presumably variable with the ion source conditions such as temperature and/or pressure and, of course, with the kind of reactant ions employed.

For structurally similar compounds, however, one would be able to predict methane CI mass spectra by using these two parameters, the protonation susceptibility and the fraction of fragmenting $[MH]^+$. It is expected that the present approach would shed some light on understanding gas-phase ion chemistry under CI conditions in a mass spectrometer. Further work is continuing to develop these analyses.

Table 3. Summary of intensity correlation of compounds 1–4

Functional group	Relative protonation susceptibility	Fraction of $[MH]^+$ (%)		Observed abundance of ions (%)	
OH	53	Non-fragmenting	0	0	$[MH]^+$
		Fragmenting	100	53	$[MH - H_2O]^+$
NH_2	48	Non-fragmenting	14	7	$[MH]^+$
		Fragmenting	86	41	$[MH - NH_3]^+$
OCH_3	36	Non-fragmenting	0	0	$[MH]^+$
		Fragmenting	100	36	$[MH - CH_3OH]^+$
$N(CH_3)_2$	31	Non-fragmenting	77	24	$[MH]^+$
		Fragmenting	23	7	$[MH - NH(CH_3)_2]^+$

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