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Fragmentation Selectivity in Electron Impact Ionization Mass Spectra of Substituted Dimethoxybenzenes

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Several 1-X-substituted-3-methoxy-4-trideuteromethoxybenzenes were synthesized and their electron impact ionization mass spectra were measured with an ionizing energy of 20 eV. From the peak intensity ratio of $[M - CD_3]$ and $[M - CH_3]$ the fragmentation-directing ability of the substituent X was evaluated. The most powerful group was found to be NH_2, which expelled a methoxy methyl group only from its *para* position. The CH_3 group and four halogen atoms, F, Cl, Br and I, exerted a moderate effect. Electron-withdrawing groups such as NO_2, CHO and CN had only a little influence on the fragmentation selectivity. These results were interpreted in terms of the effect of X on the distribution of both the unpaired electron and the positive charge in the molecular ion.

INTRODUCTION

During the past decade, extensive studies have been made of the substituent effect in the fragmentation of aromatic compounds under electron impact ionization.[1] In connection with the study of the relationship between fragmentation and the electronic state of the molecular ion, we have also reported substituent effects in butylbenzenes[2] and benzyl acetates.[3]

It is instructive that a very distinctive selectivity was found in fragmentations of *p*- and *m*-aminobutylbenzenes: the *p*-amino compound virtually exhibited only the $[M - 43]^+$ ion, whereas the *m*-amino compound gave the $[M - 42]^+$ ion almost exclusively (see Table 1).[2] This result can be explained in terms of the distribution of an unpaired electron that causes these fragmentations in the molecular ion.[2] One might argue that these two fragmentations are in different categories: the $[M - 43]^+$ ion corresponds to a simple cleavage at the benzylic C—C bond, whereas the $[M - 42]^+$ ion involves a hydrogen rearrangement from the butyl chain.

In this study, we selected substituted dimethoxybenzenes as test compounds. Unsubstituted 1,2-dimethoxybenzene has been known to afford a strong $[M - CH_3]$ peak because of the stable fragment ion with an *o*-quinoid structure.[4] When we introduce a substituent on the bezene nucleus, either one of the two methoxy methyl groups would be eliminated, and the fragmentation is regarded as a simple cleavage reaction whichever methyl group is lost. To discriminate between the two methoxy methyl groups, we synthesized 1-X-substituted-3-methoxy-4-trideuteromethoxybenzenes (**1–10**), and their mass spectra were measured at a low ionizing energy of 20 eV.

The substituent effect on the similar $[M - CH_3]^+$ fragmentations of simple anisole derivatives has already been reported.[5,6] Effects on the ionization energy and appearance energy[7,8] or on kinetic energy release[9,10] with substituents of anisoles have also been reported. In all these studies the results for different compounds were compared, and this may well involve some factors other than the effect of the substituent itself.

One of the main drawbacks of using these monosubstituted anisoles is that the fragmenting methoxy group itself is the positive charge-stabilizing substituent. Thus, the effect of a given substituent and the effect of the methoxy group are either additive or competitive according to their relative positions in the benzene nucleus. With the present test compounds (**1–10**), the influence of two methoxy groups is intramolecularly cancelled, and the fragmentations to be compared occur from each common molecular ion. Therefore, the effect of the substituent is expected to be revealed more clearly.

Table 1. Fragmentation selectivity in butylbenzene and aminobutylbenzenes[2]

Compound	Fragmentation (%) [M − 43]	[M − 42]
H[a]	32	68
p-NH_2	99	1
m-NH_2	4	96

[a] Unsubstituted butylbenzene.

EXPERIMENTAL

Syntheses of compounds

Detailed synthetic procedures for compounds **1–10** are available on request. The structures of these compounds and those of synthetic intermediates were confirmed by

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^1H and ^{13}C NMR and IR spectra and the purity was checked by thin-layer chromatography and/or gas chromatography/mass spectrometry. The samples of **6–9** for mass spectral measurement were purified by preparative gas chromatography.

3-Methoxy-4-trideuteromethoxynitrobenzene (**1**) was prepared by methylation with hexadeuterodimethyl sulphate of 2-methoxy-4-nitrophenolate, which was obtained from the alkaline hydrolysis[11] of 2-methoxy-4-nitroaniline with aqueous sodium hydroxide. Recrystallization from ethanol afforded **1** as pale yellow plates, m.p. 97 °C (3,4-dimethoxy-nitrobenzene, m.p. 96 °C[12a]).

Catalytic reduction of the nitro group of **1** with hydrogen at atmospheric pressure in the presence of PtO_2 in ethanol yielded 3-methoxy-4-trideuteromethoxyaniline (**10**), m.p. 88 °C, after recrystallization from ethanol containing a small amount of hexane (3,4-dimethoxyaniline, m.p. 85–86 °C[12b]).

Methylation of vanillin (3-methoxy-4-hydroxybenzaldehyde)[13] with hexadeuterodimethyl sulphate gave 3-methoxy-4-trideuteromethoxybenzaldehyde (**2**), m.p. 40–42 °C (3,4-dimethoxybenzaldehyde, m.p. 44–45 °C[12c,13]).

The oxime of **2** (m.p. 92–93 °C) was refluxed with acetic anhydride[14] for 2 h and the resulting nitrile was recrystallized from ethanol to yield 3-methoxy-4-trideuteromethoxybenzonitrile (**3**) as colourless needles, m.p. 69–70 °C (3,4-dimethoxybenzonitrile, m.p. 67–68 °C[12c,14]).

1-Methoxy-2-trideuteromethoxybenzene (**4**) was obtained by methylation of *o*-methoxyphehol with hexadeuterodimethyl sulphate. M.p. 23–24 °C (dimethoxybenzene, m.p. 23 °C[12c]).

The Clemmensen reduction of vanillin[15] afforded 3-methoxy-4-hydroxytoluene, which was then methylated with trideuteromethyl iodide in hexamethylphosphoramide (HMPA)[16] to give 3-methoxy-4-trideuteromethoxytoluene (**5**) as a colourless liquid, b.p. 118 °C/25 mmHg (3,4-dimethoxytoluene, b.p. 116–117 °C/23 mmHg[12d]).

Nitration of *m*-fluoroanisole (3-methoxyfluorobenzene) with fuming nitric acid in acetic anhydride gave 3-methoxy-4-nitrofluorobenzene, m.p. 49–50 °C (lit. m.p. 52 °C[12e]) in 41% yield. Catalytic reduction of the nitro group with H_2/PtO_2, followed by diazotization and acid hydrolysis, afforded 3-methoxy-4-hydroxyfluorobenzene, the hydroxyl group of which was methylated with trideuteromethyl iodide in HMPA[16] to give 3-methoxy-4-trideuteromethoxyfluorobenzene (**6**).

The Sandmeyer reaction of diazotized **10** with copper(I) chloride gave 3-methoxy-4-trideuteromethoxychlorobenzene (**7**). Similarly, 3-methoxy-4-trideuteromethoxybromobenzene (**8**) and 3-methoxy-4-trideuteromethoxyiodobenzene (**9**) were prepared.

Measurement of mass spectra

Electron impact ionization mass spectra were measured by a Hitachi RMU-6 mass spectrometer with an all-glass heated inlet system at 150 °C. The spectra were recorded at a source temperature of 230 °C and an accelerating voltage of 1.75–2.0 kV. The total emission current was 80 μA. In order to avoid successive secondary fragmentations, all spectra were measured at ionizing electron energy of 20 eV. Even at this low energy, some of the compounds showed extra peaks due to $[M - CH_3 - 28]$ or $[M - CD_3 - 28]$, and in that case intensities of these peaks were added to those of the respective $[M - CH_3]$ or $[M - CD_3]$ peaks.

RESULTS AND DISCUSSION

In the mass spectra of compounds **1–10**, two peaks of $[M - CH_3]$ and $[M - CD_3]$, among others, appeared. We define the fragmentation selectivity (k_p/k_m) as

$$k_p/k_m = \frac{[M - CD_3]k_H/k_D}{[M - CH_3]}$$

where $[M - CH_3]$ and $[M - CD_3]$ denote the observed peak intensities corresponding to the respective fragmentations. The term k_H/k_D is for correction of the secondary isotope effect between CH_3 and CD_3 eliminations, and was evaluated as 1.25 from the spectrum of 1-methoxy-2-trideuteromethoxybenzene (**4**) at an ionizing energy of 20 eV.

From the results in Table 2, it is evident that the amino group exhibited a remarkable selectivity in this series of compounds, as in the aminobutylbenzenes mentioned above.[2] Thus, from compound **10**, only the CD_3 group was eliminated from the C(4)-methoxy group. A weakly electron-donating CH_3 substituent showed a moderate selectivity. Four halogens, F, Cl, Br and I, all showed a similar trend but the selectivity is larger than that of CH_3. It is worth noting that the F atom has a tendency to expel the methoxy methyl group mainly from its *para* position, although it is considered to be the most electronegative atom among the four halogens in solution chemistry.

On the other hand, the effect of electron-withdrawing substituents such as NO_2, CHO and CN appears to be weak. Although the tendency of the fragmentation is reversed by NH_2 and NO_2 groups, as expected, even the powerful electron-withdrawing NO_2 has only a small influence on the selectivity of fragmentation.

Table 2. Fragmentation selectivity in 1-X-substituted 3,4-dimethoxybenzenes

Compound No.	X	k_p/k_m	Elimination of methoxy methyl group from C(4) (*p*)	C(3) (*m*)
1	NO_2	0.64	39%	61%
2	CHO	0.82	45	55
3	CN	1.04	51	49
4	H	1.00	50	50
5	CH_3	2.59	$72._2$	$27._8$
6	F	5.19	$83._8$	$16._2$
7	Cl	4.62	$82._2$	$17._8$
8	Br	3.75	79	21
9	I	4.50	$81._8$	$18._2$
10	NH_2		100	0

The fragmentation-directing ability of a substituent that has lone-pair electrons can be simply accounted for by assuming the stabilizing effect of the transition state through a *para* quinoid-like structure. On the other hand, the above results can be qualitatively interpreted in terms of electron distributions in the molecular ion.

In terms of ordinary molecular orbital theory, the electron distribution in the molecular ion of unsubstituted 1,2-dimethoxybenzene is symmetrical because of its symmetrical structure. The influence of any extra substituents is regarded as a perturbation that causes a redistribution of electrons. Hence one can depict *two extreme* distributions of an unpaired electron in the molecular ion of 1-X-substituted-3-methoxy-4-trideuteromethoxybenzenes (Fig. 1). The unpaired electron would spread over the shaded carbon atoms of the benzene nucleus, in addition to being distributed either on the substituent X or one of the two methoxy oxygen atoms. The positive charge, on the other hand, would locate on the other unshaded carbon atoms and, of course, either on X or one of the two oxygen atoms. If the structure of the molecular ion is represented as *a*, we can expect exclusive elimination of CD_3 from the C(4)-methoxy group through the ordinary re-pairing of electrons, whereas if it is *b*, CH_3 would be expelled preferentially from C(3).

When the substituent X is NH_2, this group can stabilize the positive charge much more effectively than it stabilizes the unpaired electron, and therefore the structure of the molecular ion is assumed to be *a* because the charge-stabilizing substituent X (NH_2) is directly bound to one of the positively charged carbon atoms of the benzene nucleus. In this structure, one (at C(3)) of the two methoxy groups would also act as a positive charge-stabilizing substituent. This distribution of the unpaired electron would be responsible for a very high probability of bond cleavage in the C(4)-methoxy group, thus causing a very high fragmentation selectivity.

Even the halogen atoms would stabilize the positive charge in the molecular ion, and this would lead to enhanced selectivity, as observed. In this case, however, the selectivity is not very pronounced. Moreover, the four halogens do not fit the expected order, and it is not clear at present whether this is a real trend or simply experimental deviations.

When the substituent X is an electron-withdrawing group such as NO_2, the substituent does not stabilize the positive charge but may stabilize the unpaired electron. The structure of the molecular ion would then be approximated as *b*, which suggests the elimination of CH_3 from the C(3)-methoxy group. In this case, however, the unpaired electron density on C(3) would be low because a large proportion of it is attracted by the X substituent. Accordingly, facile CH_3 elimination is not expected, and this is reflected by the low reactivity and the low fragmentation selectivity. In fact, the peak intensity ratio $([M - CD_3] + [M - CH_3]) \times 100$ *vs.* $[M]^{+\cdot}$ is 16 for **1** but 60 for **10**, which indicates the low reactivity of **1** *vs.* **10**.

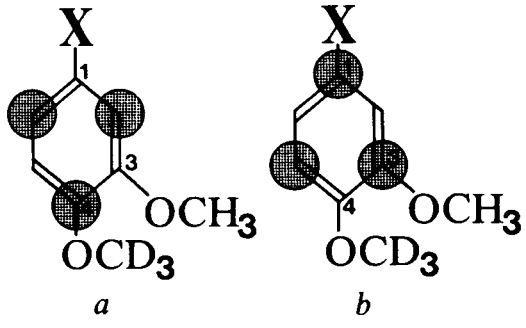

Figure 1. Schematic representation of two extreme distributions of the unpaired electron in the molecular ion. The shaded carbon atoms show the area on which a fraction of the unpaired electron distributes.

CONCLUSION

This work has clearly demonstrated that electron-donating substituents strongly affect the distribution of both the unpaired electron and the positive charge on the molecular ion, and thus exhibit several characteristics in fragmentations, one of which is the high fragmentation selectivity discussed. Even halogen atoms behave as an electron-donating substituents in positive ion mass spectrometry.

On the other hand, the effect of electron-withdrawing substituents appears to be mild and, consequently, relatively low fragmentation selectivity and low reactivity were observed.

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