

Substituent Effects in the Fragmentation of Acetanilides

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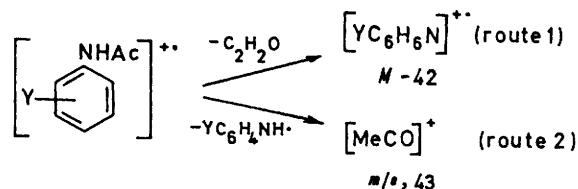
The mass spectra of a series of *meta*- and *para*-substituted acetanilides have been examined. Substituent effects have been used to provide information about the mechanism of the competing fragmentations and of the structures of the ions involved. The correlation of substituent effects with ionization potential and appearance potential measurements and with $\Delta(\text{A.P.} - \text{I.P.})$ values suggests that the fragmentation of *meta*-substituted acetanilides proceeds through an excited state.

NUMEROUS attempts have been made to use the effect of substituents on the relative abundances of daughter and parent ions as a measure of the relative rate of fragmentation of organic ions in a mass spectrometer. Correlations between $\log Z/Z_0$ and substituent constants (σ or σ^+), where $Z = [A]^+/[M]^+$ for the fragmentation $[M]^{+\bullet} \rightarrow [A]^{+\bullet} + N$ for a substituted compound whereas Z_0 is the corresponding value for the unsubstituted reference compound, have been used to provide information about the mechanism of the process and structure of the ions involved.¹ Recently, however, attention has been drawn to various defects in the simple kinetic approach and the complex variety of the ways in which a substituent may influence Z/Z_0 has been clearly enumerated.²⁻⁴ Another approach to this problem has been to assume that the experimentally determined value of A.P. - I.P. is a reasonable measure of the activation energy and to attempt to correlate this with substituent constants (*e.g.*, for the fragmentation of trifluoro-amides⁵). An attempt has also been made to determine the relative importance of the energies of the ground states and transition states for the frag-

mentation of pairs of *meta*- and *para*-substituted benzyl phenyl ethers.⁶

The publication by Shapiro and Tomer⁷ of a study of substituent effects on the fragmentation of acetanilides and phenyl acetates prompts us to report our more detailed observations on the former series of compounds. These provide experimental confirmation of some of Shapiro and Tomer's predictions and are considered in the light of the recent developments outlined above.

Two of the principal ions in the spectra of substituted acetanilides are $[M - \text{C}_2\text{H}_2\text{O}]^+$ and $[\text{MeCO}]^+$. The loss of keten arises from a rearrangement, whilst the



SCHEME 1

formation of the acetyl cation is a simple cleavage process as shown in Scheme 1. We have carried out a

¹ Cf. M. M. Bursey, *Org. Mass Spectroscopy*, 1968, **1**, 31.

² I. Howe and D. H. Williams, *J. Amer. Chem. Soc.*, 1968, **90**, 5461.

³ F. W. McLafferty, *Chem. Comm.*, 1968, 956.

⁴ R. G. Cooke, I. Howe, and D. H. Williams, *Org. Mass Spectrometry*, 1969, **2**, 137.

⁵ R. A. W. Johnstone and D. W. Payling, *Chem. Comm.*, 1968, 601.

⁶ P. Brown, *J. Amer. Chem. Soc.*, 1968, **90**, 4459, 4461.

⁷ R. H. Shapiro and K. B. Tomer, *Org. Mass Spectrometry*, 1969, **2**, 579.

detailed study of substituent effects on the mass spectra of substituted acetanilides to provide further information about (1) the effect of substituents on the two competing fragmentation pathways and (2) the possible structure of the daughter ion in the rearrangement process.

RESULTS AND DISCUSSION

The relative abundances of the two principal ions in the compounds (1)–(12) at various energies are shown in Table 1. Our values of Z_1 and Z_2 for the compounds studied by Shapiro and Tomer are in reasonable accord with their data. Table 1 shows that, in all the acet-

TABLE 1

Ratios of Z_1^+ ($= [M - C_2H_2O]^+ / [M]^+$) and Z_2^+ ($= [MeCO]^+ / [M]^+$) in the spectra of substituted acetanilides ($Y \cdot C_6H_4 \cdot NHAc$)

Cmpd. no.	Y	70 ev		50 ev		20 ev		16 ev	
		Z_1	Z_2	Z_1	Z_2	Z_1	Z_2	Z_1	Z_2
(1) *	<i>p</i> -NO ₂	1.94	2.11	1.97	2.20	1.46	0.35	0.91	—
(2) *	<i>m</i> -NO ₂	2.31	1.96	2.32	2.59	1.73	0.36	0.91	—
(3)	<i>p</i> -CO ₂ H	2.39	1.24	2.22	1.26	1.48	0.15	0.77	—
(4)	<i>p</i> -Br	2.72	0.67	2.72	0.72	1.68	0.13	0.94	—
(5)	<i>m</i> -Br	2.64	0.98	2.70	1.24	1.47	0.14	0.65	0.01
(6) *	<i>p</i> -Cl	3.67	0.94	3.48	0.92	1.62	0.10	0.55	—
(7) *	<i>m</i> -Cl	2.97	0.87	2.91	0.89	1.50	0.11	0.55	—
(8) *	H	3.00	0.65	2.66	0.63	1.41	0.04	0.59	—
(9) *	<i>p</i> -Me	1.97	0.39	1.93	0.39	1.05	0.02	0.44	—
(10) *	<i>m</i> -Me	2.57	0.48	2.40	0.50	1.31	0.04	0.52	—
(11) *	<i>p</i> -OMe	0.99	0.38	0.98	0.32	0.59	0.01	0.25	—
(12) *	<i>m</i> -OMe	1.61	0.66	1.44	0.62	0.88	0.03	0.29	—

* Also studied by Shapiro and Tomer.⁷ † Average of three determinations.

anilides studied, the $[M - C_2H_2O]^+$ ion is much more prominent at low energies than the $[MeCO]^+$ ion. This is consistent with the general observation⁸ that rearrangement processes will have lower activation energies and frequency factors than single-bond cleavages and will therefore be more prevalent in low-voltage spectra. Two important factors influencing the Z_1 and Z_2 values are the ionization potentials of the M^+ ions and the appearance potentials of the rearrangement fragment ions. These have been measured and are recorded in Table 2.

TABLE 2

Ionization potentials and appearance potentials of the $[M - 42]^+$ ion in the mass spectrum of substituted acetanilides $Y \cdot C_6H_4 \cdot NHAc$

Cmpd. no.	Y	I.P. (± 0.2 ev)	A.P. (± 0.2 ev)	A.P. - I.P. (± 0.4 ev)
(1)	<i>p</i> -NO ₂	9.05	10.44	1.39
(2)	<i>m</i> -NO ₂	8.84	10.49	1.65
(3)	<i>p</i> -CO ₂ H	8.70	10.58	1.88
(4)	<i>p</i> -Br	8.42	10.58	2.16
(5)	<i>m</i> -Br	8.56	10.62	2.06
(6)	<i>p</i> -Cl	8.31	10.60	2.29
(7)	<i>m</i> -Cl	8.65	10.90	2.25
(8)	H	8.61	10.76	2.15
(9)	<i>p</i> -Me	8.24	10.62	2.38
(10)	<i>m</i> -Me	8.29	10.85	2.56
(11)	<i>p</i> -OMe	8.10	10.68	2.58
(12)	<i>m</i> -OMe	7.96	10.68	2.72

The ionization potentials of substituted acetanilides correlate reasonably well with σ^+ values. Electron-

releasing groups lower the ionization potential whilst electron-withdrawing groups raise it. Similar effects of substituents on ionization potentials have been reported for substituted benzenes.⁹

The daughter:parent ratios at 50 ev for the simple cleavage process (route 2) of *para*-substituted acetanilides correlate reasonably well with σ^+ values (Figure 1, $\rho = +0.7$). The effect of substituents is as expected since electron-withdrawing substituents will both weaken the C-N bond and, by raising the ionization potential of the ring, will favour charge localization in the side-chain. Both these effects will facilitate cleavage leading to the formation of the acetyl cation. The corresponding plot of $\log Z_2/Z_0$ against σ^+ for *meta*-substituents shows considerable scatter (see later).

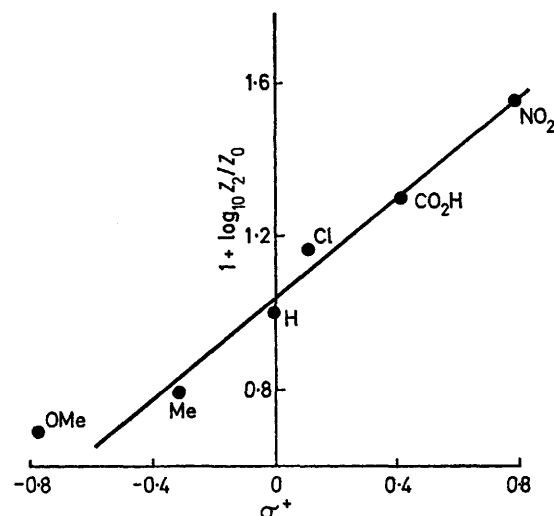
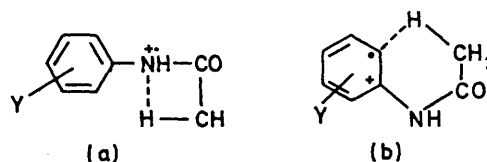


FIGURE 1 Variation of $\log_{10} Z_2/Z_0$ with σ^+ in the mass spectra of some *para*-substituted acetanilides at 50 ev; $\rho = 0.70$

The rearrangement (route 1) could occur *via* either a four- or a six-membered transition state, (a) or (b).



Shapiro and Tomer analysed their data⁷ in terms of the average relative rates of the two competing fragmentations, which showed only a small variation with change of substituent for acetanilides although a much larger change was noted for phenyl acetates. Our data for substituent effects in Table 1 are expressed in terms of the relative abundance of daughter and parent ions. At low ionizing voltages (16 ev), $\log Z_1/Z_0$ for *para*-substituents correlates well with σ^+ (Figure 2, $\rho = 0.4$), whereas the data for *meta*-substituents again shows a certain amount of scatter.

⁸ D. H. Williams and R. G. Cooks, *Chem. Comm.*, 1968, 663.

⁹ G. F. Crable and G. L. Kearns, *J. Phys. Chem.*, 1962, **66**, 436.

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Electron-withdrawing substituents appear strongly to enhance the formation of the rearranged product, *i.e.*, the reaction is facilitated by increased positive charge at the reaction site, an effect which is opposite from

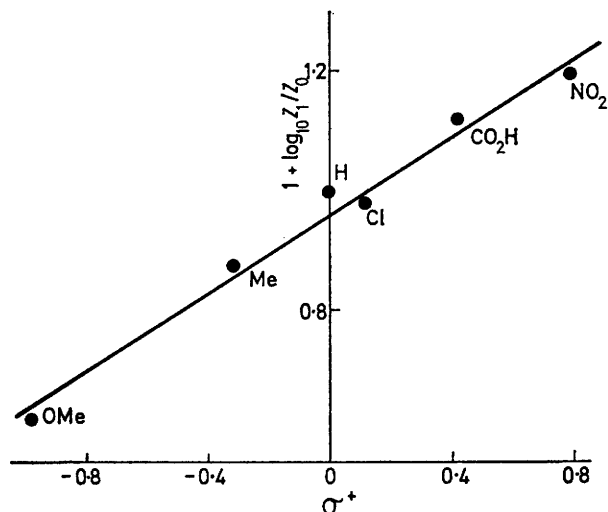


FIGURE 2 Variation of $\log_{10} Z_1/Z_0$ with σ^+ in the mass spectra of some *para*-substituted acetanilides at 16 eV; $\rho = 0.44$

that expected for the migration of a proton. If Shapiro and Tomer's data are used in Figure 2 a similar value of ρ (+0.4) is obtained.

The effect of substituents is therefore similar for both the molecular rearrangement and the simple cleavage processes. A study of the rearrangement at higher ionizing electron energies further illustrates the dependence of competitive fragmentations on activation energies and frequency factors. A plot of $\log Z_1/Z_0$ against σ^+ for *para*-substituents has the peculiar form indicated in Figure 3. We have established that electron-withdrawing substituents facilitate both the rearrangement and cleavage reactions. The observed values of Z_1 for such substituents at 50 eV will be much lower than predicted because the higher frequency factor for the cleavage reaction leads to the predominance of this mechanism. A linear correlation is observed with electron-donating substituents at 50 eV ($\rho = 0.7$). The weakly electron-withdrawing substituent effect of chlorine accounts for its position at a maximum on the plot. The anomalous behaviour by strongly electron-withdrawing groups is further illustrated by the dependence of Z_1 on eV (Figure 4), which shows that the values of Z_1 for *p*-nitro- and *p*-CO₂H substituents actually 'cross over' those of electron-releasing groups in the 18–20 eV region. The similarity of the ρ values at 50 eV obtained for both the rearrangement and the simple cleavage (+0.7) suggests that bond-fission is more important than bond-formation in the rearrangement process. It is difficult, however, to disentangle the effect of the substituent on activation energy from

other factors which may influence Z/Z_0 .¹⁰ Indeed Johnstone and his co-workers¹¹ have suggested that correlations between values of $\log Z/Z_0$ with σ^+ arise because of the correlation of the ionization potential with σ^+ rather than being characteristic of the reaction type. In the present case therefore it is probably unwise to attach too much importance to the correlation of $\log Z_1/Z_0$ with σ^+ .

Some information about the structure of the ion $[Y \cdot C_6H_5N]^+$ formed by the rearrangement loss of C_2H_2O can be deduced from $Z_m:Z_p$ ratios, where Z_m and Z_p are the values for corresponding *meta*- and *para*-isomers. Our data for these ratios in Table 3 are in reasonable accord with those of Shapiro and Tomer.

Our data show only a slight random variation of $Z_m:Z_p$ with substituent. For both the rearrangement

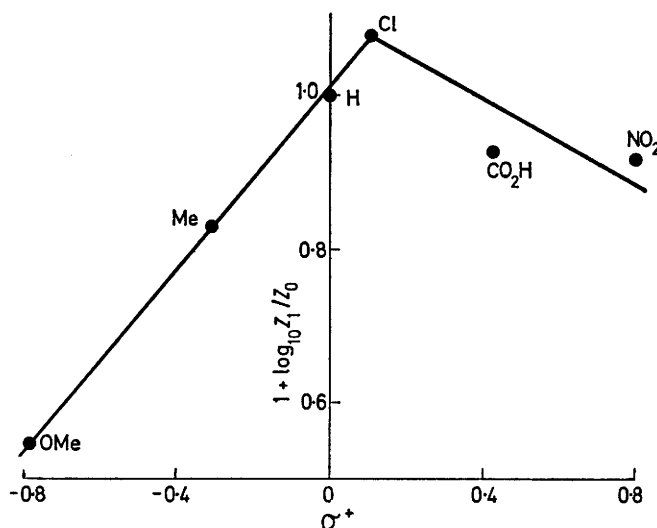


FIGURE 3 Variation of $\log_{10} Z_1/Z_0$ with σ^+ in the mass spectra of some *para*-substituted acetanilides at 50 eV

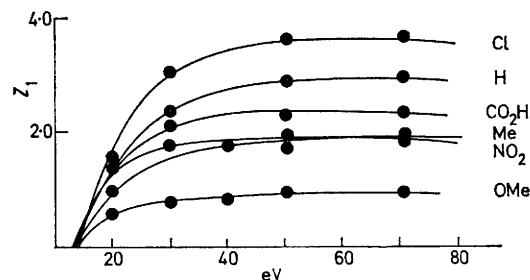


FIGURE 4 Variation of Z_1 with eV for the rearrangement process of acetanilides

and cleavage processes this ratio shows a somewhat greater dependence on ionizing potential for the methoxy-group than for other substituents.

The absence of a substituent effect on $Z_m:Z_p$ ratios can arise because of loss of positional identity of the substituent before fragmentation. Shapiro and Tomer ruled out this possibility for acetanilides because in the

¹⁰ I. Howe, D. H. Williams, D. G. I. Kingston, and H. F. Tannenbaum, *J. Chem. Soc. (B)*, 1969, 432.

¹¹ T. W. Bentley, R. A. W. Johnstone, and D. W. Payling, *J. Amer. Chem. Soc.*, 1969, **91**, 3978.

case of some substituents, *e.g.*, OMe, the $[M - C_2H_2O]^+$ ions for the *meta*- and *para*-isomers undergo different secondary fragmentations. In the case of nitro-compounds, the loss of NO from the $[M - C_2H_2O]^+$ ion was found to be greater for *para*- than *meta*-substituents. This could, in principle, occur from a common

TABLE 3

Z_m/Z_p Values for substituted acetanilides $Y \cdot C_6H_4 \cdot NHAc$

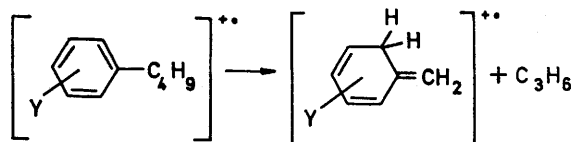
(a) $M^+ - 42$ Rearrangement

Y	50 ev	40 ev	30 ev	20 ev	18 ev	17 ev	16 ev	15 ev	14 ev
NO ₂	0.82	1.20	1.22	1.14	1.04	0.99	0.96	0.97	0.82
Cl	0.84	0.91	0.85	0.93	0.98	0.88	1.00	0.85	0.67
MeO	1.47	1.73	1.82	1.54	1.35	1.28	1.21	0.92	0.75
Me	1.24	1.34	1.23	1.25	1.16	1.15	1.18	1.08	1.11

(b) $M^+ - 43$ Cleavage

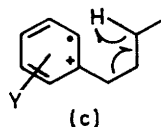
Y	70 ev	50 ev	40 ev	30 ev	20 ev
NO ₂	1.00	1.04	1.04	1.04	1.00
Cl	0.97	0.99	1.04	0.97	1.03
Me	1.11	1.14	1.20	1.18	1.44
MeO	—	1.41	1.82	2.01	2.01

structure if such a structure had different energy distributions depending on whether this ion was derived from a *meta*- or *para*-substituted precursor molecular ion. This unlikely occurrence is ruled out by our data because both the activation energies (A.P. — I.P.) and ionization potentials (Table 2) are almost identical for *meta*- and *para*-isomers. Another rearrangement which has been studied recently is the $M - 42$ reaction of *n*-butylbenzenes¹² (Scheme 2). The values of Z_m



SCHEME 2

and Z_p for this reaction are very different (Z_m/Z_p varies by a factor of 10 for a range of substituents) and suggest quite a different mechanism to that postulated for the rearrangement of acetanilides and phenetoles. In support of a McLafferty rearrangement involving hydrogen transfer to the ring (c), Nicoletti and Lightner observed that $\log Z/Z_0$ correlated well with σ or σ^+ for *meta*-substituted substituents treated as *para* to the reaction site (*i.e.*, using σ_p^+ values). Similar plots,

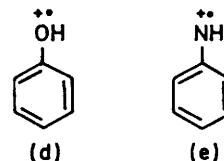


(c)

however, with *para*-substituents showed a considerable scatter. Such observations probably provide further indirect confirmation that in the rearrangement of acetanilides and phenetoles no disruption of the aromatic ring occurs.

¹² R. Nicoletti and D. A. Lightner, *J. Amer. Chem. Soc.*, 1968, **90**, 2997.

A detailed study of the 75 ev mass spectra of *meta*- and *para*-substituted phenyl ethyl ethers shows Z_m/Z_p values which are also approximately unity.¹³ At low voltages, however, weak substituent effects are observed.¹⁴ Loss of positional identity has in any case been ruled out since different metastable ion characteristics were obtained for the fragmentation of the *meta*- and *para*-isomers. The most abundant ion in the mass spectrum of phenyl ethyl ether is considered to have the structure of the molecular ion of phenol (d). It



seems reasonable to suppose that the $[M - C_2H_2O]^+$ ion in the spectra of acetanilides has the ionized aniline structure (e) which is isoelectronic with (d).

According to Brown,⁶ for processes with identical transition-state energies for each isomer, the ratio $Z_p : Z_m$ should be effectively constant over a wide energy range from 70 ev down to the threshold energy for the process, and its magnitude will be determined by the relative activation energies. In terms of this simple treatment, the values of $Z_p : Z_m$ observed suggest that the rearrangements of *meta*- and *para*-substituted acetanilides have similar activation energies, identical ground-state energies, and identical transition-state energies. This is consistent with the data in Table 2

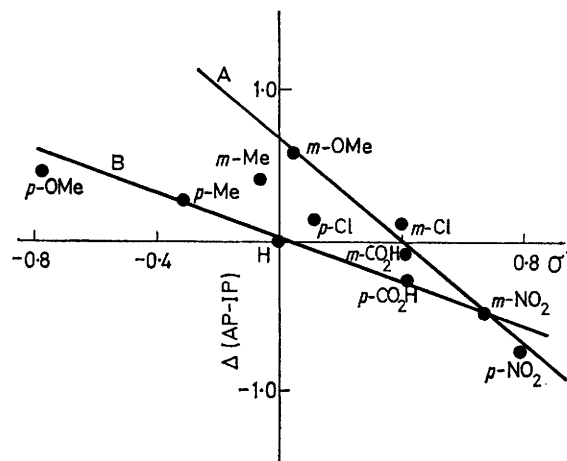


FIGURE 5 Variation of $\Delta(\text{A.P.} - \text{I.P.})$ with σ^+ for the rearrangement (route 1) of *meta*- and *para*-substituted acetanilides; A, *meta*; B, *para*

which show that the quantities I.P., A.P., and (A.P. — I.P.) are approximately identical within experimental error. It seems likely therefore that the identical $Z_m : Z_p$ ratios arise from similar energy distributions in the molecular ions of the *meta*- and *para*-isomers.

¹³ F. W. McLafferty, M. M. Bursey, and S. M. Kimball, *J. Amer. Chem. Soc.*, 1966, **88**, 5022.

¹⁴ F. W. McLafferty and L. J. Schiff, *Org. Mass Spectrometry*, 1969, **2**, 757.

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Shapiro and Tomer thought that such a similarity would be highly coincidental.

Another formal possibility which should be examined is that one isomer, probably the *meta*, fragments in an excited state and gives values of Z_1/Z_0 which are fortuitously similar to those for the fragmentation of the *para*-isomer which fragments *via* its ground state. If the differences in activation energies, $\Delta(\text{A.P.} - \text{I.P.})$, for both the simple cleavage and the rearrangement are

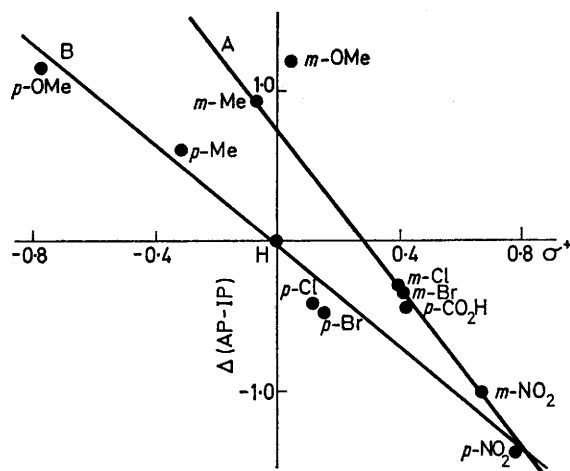
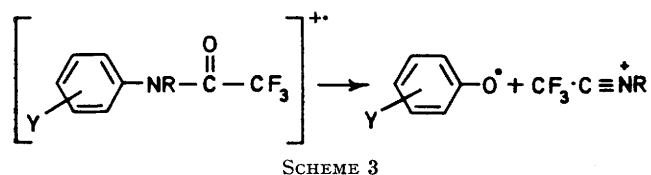


FIGURE 6 Variation of $\Delta(\text{A.P.} - \text{I.P.})$ with σ^+ for the simple cleavage (route 2) of *meta*- and *para*-substituted acetanilides; A, *meta*; B, *para*

plotted against σ^+ substituent constants, linear correlations are obtained (Figures 5 and 6). In both cases, however, the data for *meta*- and *para*-substituents fall on different lines. Johnstone and Payling have recently



reported a similar observation⁵ for the rearrangement of trifluoroamides (Scheme 3). Such behaviour is

¹⁵ E. L. Wehry and L. B. Rogers, *J. Amer. Chem. Soc.*, 1965, **87**, 4234.

characteristic of excited-state reactions of aromatic compounds for which *meta*-substituents show enhanced resonance effects in the excited state.¹⁵ This suggests that a similar situation exists in the rearrangement of substituted acetanilides and that reactions of *meta*-isomers proceed through an electronically excited state. This is not inconsistent with our earlier conclusion that the *meta*- and *para*-isomers have similar energy distributions in the molecular ion.

Values of Z_m/Z_p near unity were also observed for the loss of ethylene from ethyl phenyl ethers¹⁴ and a plot of $\Delta(\text{A.P.} - \text{I.P.})$ against σ^+ will therefore show distinct lines for *meta*- and *para*-substituents. This appears to be a further illustration of a system in which the *meta*-isomer reacts *via* an excited state.

A Referee has pointed out the dangers of using the value of A.P. - I.P. as a measure of vibrational activation energy. We consider, however, as did Johnstone and Payling⁵ and Baldwin and Loudon,¹⁶ that useful information can be derived from the empirical correlation of substituent effects with this quantity, and that such a correlation avoids many of the objections which have been properly levelled at the simple kinetic approach.

EXPERIMENTAL

The acetanilides were either purified commercial samples or were prepared by acetylation of the appropriate acid.

The mass spectra were obtained on an AEI MS 12 mass spectrometer operated with an ion source temperature of $100^\circ \pm 10^\circ \text{C}$ and an ionizing electron beam of 70 eV (unless otherwise stated) with a 20 μA trap current. No change in total ion current was observed during the measurement of spectra. Samples were introduced by a direct-insertion probe and pressure changes during any one scan were not allowed to exceed 1%. Appearance potentials and ionization potentials were determined by the method of Lossing *et al.*¹⁷

We thank the S.R.C. for a studentship (to A. A. G.) and Mr. E. Potter for technical assistance.

[9/1882 Received, November 5th, 1969]

¹⁶ M. A. Baldwin and A. G. Loudon, *Org. Mass. Spectrometry*, 1969, **2**, 549.

¹⁷ F. P. Lossing, A. W. Tickner, and W. A. Bryce, *J. Chem. Phys.*, 1951, **19**, 1254.