Kinetic and Thermodynamic Effects on Intramolecular Aromatic Substitution in *meta* and *para* Substituted Benzalacetones†

Bernd Schaldach,‡ Barbara Grotemeyer, Jürgen Grotemeyer and Hans-Friedrich Grützmacher

Fakultät für Chemie, Universität Bielefeld, Universitätsstraße, D-4800 Bielefeld 1, West Germany

***meta* and *para* substituted benzalacetones lose the substituents after electron impact in a multi-step intramolecular aromatic substitution. The differences in the relative abundances of the benzopyrylium ions thus formed are not determined by the activation energies for the substituent losses but depend on a delicate balance between the thermodynamic stability of the intermediates involved and the rates of several H-shifts within the intermediates (kinetic stability). The consequences for the analytical utility of intramolecular aromatic substitution are discussed briefly.**

INTRODUCTION

Intramolecular aromatic substitution is a well-known mass spectrometric fragmentation reaction which often leads to diagnostically important peaks of high intensity in the mass spectra of certain aromatic compounds. However, the understanding of this reaction is still limited, so that predictions concerning the distinction of *ortho*, *meta* and *para* substituted isomers cannot be made reliably. For example, *N*-phenylformamidines,[2] 2-stilbazoles,[3] 1-phenyl-1-pyridylethylenes[4] and benzalacetonesemicarbazones[5] specifically lose the *ortho* substituents, thus permitting the differentiation of the *ortho* from the *meta* and *para* isomers with certainty. On the other hand, benzalmalonates,[6] benzylidenecyclohexanones[7] or benzalacetones[8] also lose a chloro substituent from the *meta* and *para* positions, making it difficult to distinguish between the isomers without reference mass spectra. The three chloro substituted phenylbutadiene[9] and cinnamaldehyde[10] isomers show identical mass spectra and cannot be distinguished at all by this means. Methyl substituted cinnamic acids[11] lose the CH_3 group from the *meta* and *para* positions even more abundantly than from the *ortho* position. Clearly, if intramolecular aromatic substitution is to serve its purpose in analytical chemistry, much more has to be known about the factors which influence the outcome of the reaction in each special case.

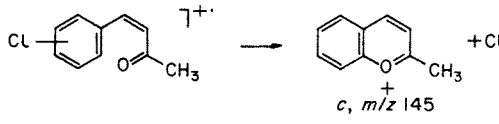
In this communication some thermochemical results obtained from *meta* and *para* substituted benzalacetones are reported, and compared with those obtained from the *ortho* isomers[12,13] in order to detect the correlation between the thermochemistry of substituent loss and the differences in the 70 eV mass spectra of positional isomers of aromatic compounds.

† See Ref. 1.

‡ Author to whom correspondence should be addressed.

RESULTS AND DISCUSSION

It has been shown previously that molecular ions $[M]^{+\cdot}$ of *o*-, *m*- and *p*-chlorobenzalacetones lose the Cl atom and form stable 2-methylbenzopyrylium ions *c*[12] (Eqn (1)). The rate of this reaction is much faster in

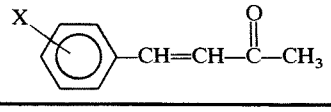


(1)

the case of *ortho* substitution than with the loss of Cl from the *meta* or *para* positions. This deceleration has been shown to be caused by a reduction of the frequency factors for Cl loss which decrease from $\nu = 10^9\,s^{-1}$ (*o*-Cl) to $\nu = 7\times10^7\,s^{-1}$ (*m*-Cl).[12] The critical energies $\varepsilon_f^{\neq}$ are 0.5 eV in both cases. Thus, the change in the reaction rate is not caused by a variation of the critical energy but is determined by the details of the mechanism of reaction (1). In order to ascertain whether the relative rates of substituent losses from isomeric benzalacetones are generally independent of the critical energies, compounds with X = Br, I, CH_3 and CF_3 have been studied. In all cases ions *c* are formed by the loss of the substituent.[14]

Table 1 gives the ratios of the intensities of *c* and

Table 1. Relative intensity ratios [*c*]:[M]$^{+\cdot}$ as a function of the position of the substituent X for



	Position		
X	o-	m-	p-
Cl	1	0.06	0.05
Br	1	0.14	0.10
I	1	0.013	0.10
CH_3	1	0.63	0.71
CF_3	1	0.37	0.27

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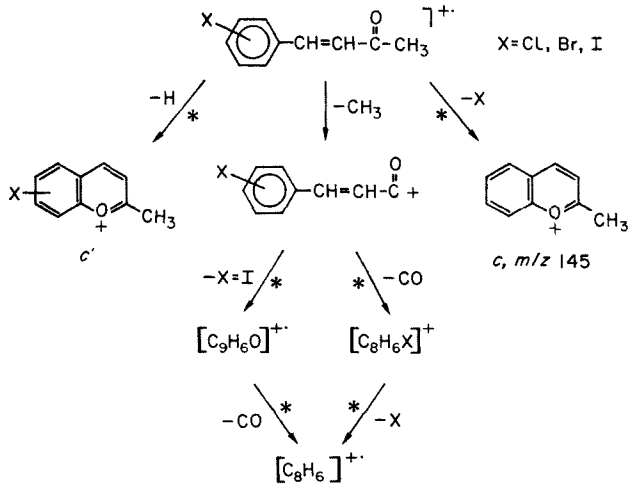
Table 2. Ionization energies *I*(M) and critical energies[a] $\varepsilon_f^{\neq}$ for competing reactions of molecular ions of substituted benzalacetones

X	*I*(M)	$\varepsilon_f^{\neq}$ [M−X]$^+$	[M−H]$^+$	[M−CH$_3$]$^+$
H	8.8	0.6	0.6	1.6
o-Cl	8.8	0.5	—[b]	1.9
m-Cl	8.9	0.5	0.8	1.5
p-Cl	8.7	0.8	0.7	1.8
o-Br	8.7	0.5	—[b]	2.1
m-Br	8.9	0.4	—[c]	1.7
p-Br	8.9	0.7	—[c]	1.7
o-I	8.6	0.3	—[b]	—[c]
m-I	8.7	0.3	—[c]	—[c]
p-I	8.4	0.6	—[c]	—[c]
o-CH$_3$[d]	8.5	0.6	0.9	0.9
m-CH$_3$[d]	8.6	0.9	0.8	2.1
p-CH$_3$[d]	8.5	0.8	0.9	2.1
o-CF$_3$	9.0	0.6	0.7	1.3
m-CF$_3$	9.1	0.1	0.5	1.3
p-CF$_3$	9.1	0.2	—[c]	1.1

[a] $\varepsilon_f^{\neq} = A(\text{ion}) - I(\text{M})$.
[b] No [M—H]$^+$ > 0.5%
[c] Not determined.
[d] Deuterated compounds, see Table 3.

$[M]^{+\cdot}$ ions in the 70 eV mass spectra. These ratios serve to illustrate the changes in rate for a given set of isomers. This procedure is justified in the case of the benzalacetones because (i) ions *c* do not decompose further significantly and (ii) the depletion of $[M]^{+\cdot}$ ions due to competing reactions is assumed not to alter significantly within a set of positional isomers, the activation energies being similar for the competing processes, viz. loss of CH_3 and H from $[M]^{+\cdot}$ (see Table 2). Therefore, the changes in the rates of the substituent losses within a series of isomers are reflected by the variations of the intensity ratio [*c*]/$[M]^{+\cdot}$ in the 70 eV mass spectra of the benzalacetones (see Fig. 1).

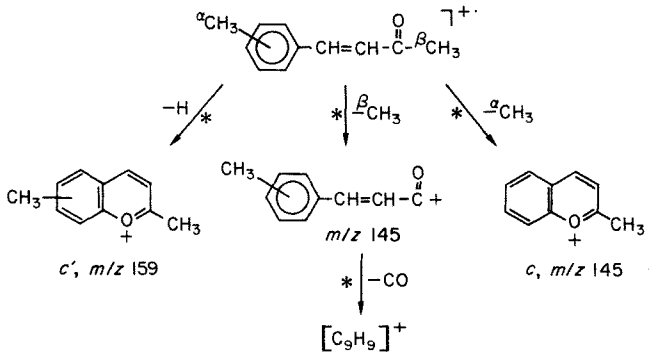
The fragmentations leading to the most prominent peaks in the 70 eV mass spectra of the halogen substituted benzalacetones are shown in Scheme 1.



Scheme 1. Fragmentations leading to the most prominent peaks in the 70 eV mass spectra of the halogen substituted benzalacetones.

Like the chlorobenzalacetones, the bromo and iodo derivatives lose the *ortho* substituent much faster than the corresponding *meta* and *para* compounds (Table 1). The critical energies $\varepsilon_f^{\neq}$ for the substituent losses are the same for each *ortho* and *meta* pair of isomers, however, and rise only slightly in the case of the *para* compounds (Table 2). For all nine halogenobenzalacetones $\varepsilon_f^{\neq}$ covers a narrow range of values, viz. $\varepsilon_f^{\neq} = 0.5 \pm 0.2$ eV. This result shows clearly that the critical energies for the losses of the halogen substituents do not determine the differences in the rate of this intramolecular aromatic substitution.

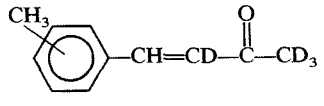
In contrast to the halogenated benzalacetones, the three methyl substituted isomers exhibit nearly identical mass spectra (Fig. 1). The main peaks result from the fragmentations shown in Scheme 2. In order to



Scheme 2. Fragmentations leading to the main peaks in the 70 eV mass spectra of CH_3 substituted benzalacetones.

distinguish between CH_3 loss from the phenyl ring and from the acyl group, deuterium labelled methylbenzalacetones have been studied. The 70 eV mass spectra show (Table 3) that both CH_3 groups are lost from the molecular ion in approximately equal amounts in all three cases. The ratios *c* : $[M]^{+\cdot}$ (Table 1) show that the rates for the loss of CH_3 are nearly independent of the position of the substituent at the phenyl ring, in contrast to the halogenobenzalacetones. The critical energies for CH_3 loss from the phenyl ring of the deuterated isomers fall into the narrow range of 0.75 ± 0.15 eV (Table 2). However, the magnitudes of $\varepsilon_f^{\neq}$ for CH_3 loss and loss of Cl are

Table 3. Partial 70 eV mass spectra[a] (%B) of



	m/z	o-	m-	p-
$[M]^+$	164	25	40	32
$[M-H]^+$	163[b]	13	23	22
$[M-CH_3]^+$	149	100	100	95
$[M-CD_3]^+$	146	87	80	100
$[M-COCD_3]^+$	118	66	83	94
	117	35	25	22
	116	96	91	82
	115	29	23	20

[a] Uncorrected.
[b] [M−D] < 0.1%.

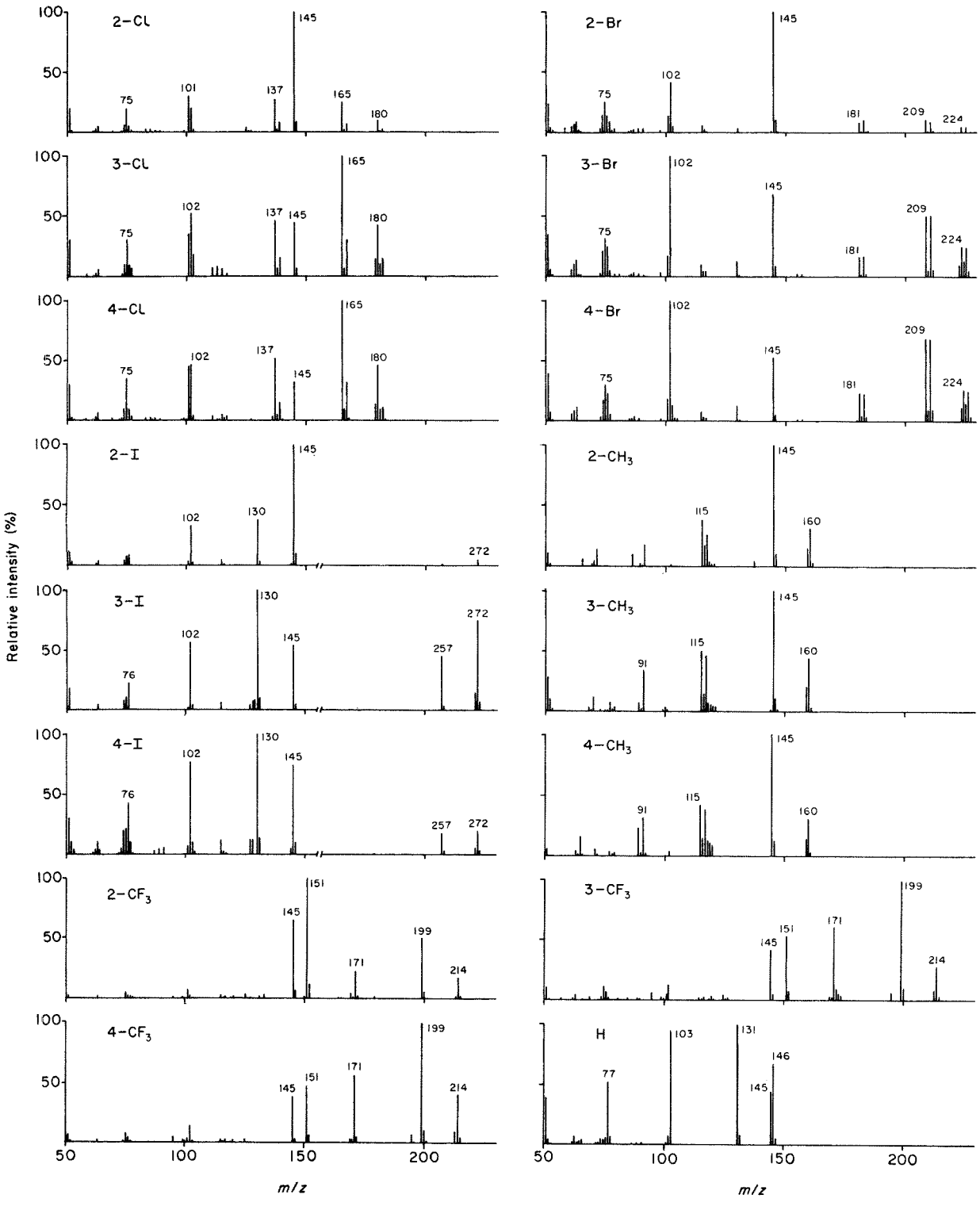
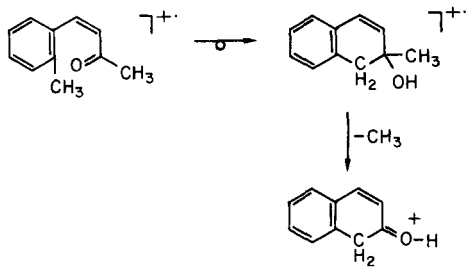


Figure 1. 70 eV mass spectra of substituted benzalacetones.

similar, although both sets of positional isomers exhibit different variations in the dependence of the rate of substituent loss on its position. This shows clearly that in both series of compounds other factors besides $\varepsilon_f^{\neq}$ must strongly influence the rate of the intramolecular substitution.

The critical energies for the losses of CD_3 from the sidechain are much higher for the *meta* and *para* isomers than for *o*-methylbenzalacetone (Table 2). This result is supported by the occurrence of abundant metastable peaks for both CH_3 and CD_3 loss in case of the *ortho* substituted isomer. The metastable peaks for CH_3 elimination from the *meta* and *para* isomers remain large but those for CD_3 loss are drastically reduced, however, (Fig. 2). Probably the loss of the terminal CD_3 group from the molecular ions of the *ortho* isomer occurs via a special mechanism ('hidden *ortho* effect', Scheme 3).[15]

The molecular ions of the three trifluoromethylbenzalacetones decompose mainly by losses of CH_3 and



Scheme 3. Tentative mechanism for the loss of the terminal CH_3 group in the molecular ion of *o*-methylbenzalacetone.

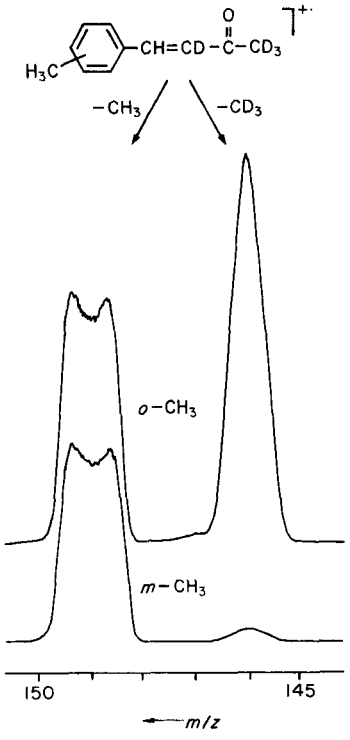
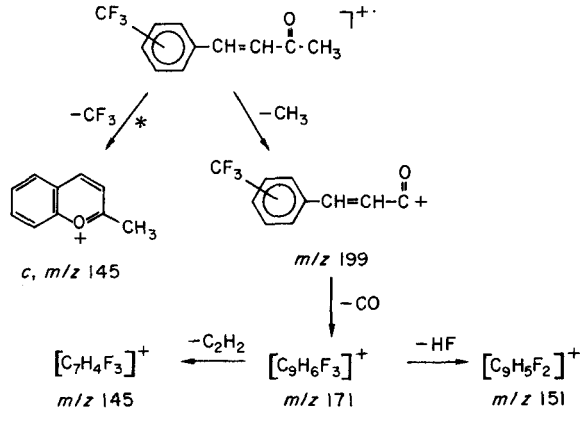


Figure 2. Metastable peaks for the loss of CH_3 and CD_3 from deuterated *o*- and *m*-methylbenzalacetones.

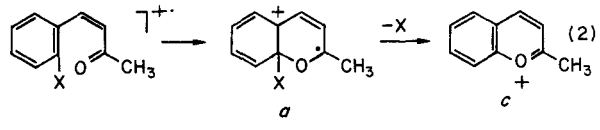


Scheme 4. Fragmentations leading to the main peaks in the 70 eV mass spectra of CF_3 substituted benzalacetones.

CF_3 (Scheme 4). The loss of CH_3 is followed by successive eliminations of CO and HF or C_2H_2. The peaks at *m/z* 145 are doublets composed of ions *c* as the major component and of $[C_7H_4F_3]^+$ ions, with the intensity ratios 5:1, 3:1 and 4:1 for *ortho*, *meta* and *para* substitution, respectively. The ratios $c:[M]^{+\cdot}$, corrected for the $[C_7H_4F_3]^+$ contribution (Table 1), indicate a decrease in the rate of the substituent loss in the order $o > m \geqslant p$. However, the effect is far less pronounced than in the case of the halogen substituted benzalacetones.

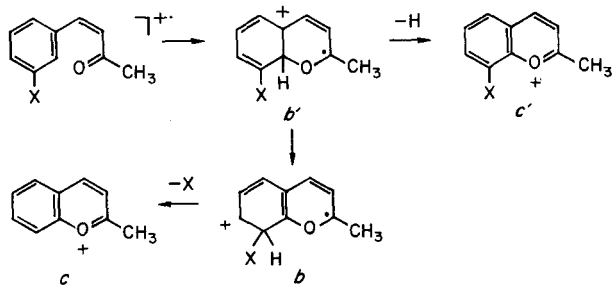
The critical energies for CF_3 loss from the *meta* and *para* substituted benzalacetones are remarkably low compared with the value for the *ortho* isomer (Table 2). This result is supported by a larger kinetic energy release for CF_3 loss from the *ortho* compound[14] as compared with the *meta* and *para* isomers, and may reflect a steric effect for the *ortho* CF_3 group. The order of $\varepsilon_f^{\neq}$ for CF_3 loss is the reverse of the order of the rates for this reaction. Thus, there is obviously no connection between $\varepsilon_f^{\neq}$ and the reaction rates, in accord with the results obtained with the halogeno- and methylbenzalacetones.

In the case of the *ortho* substituted benzalacetones, the independence of $\varepsilon_f^{\neq}$ for substituent loss on the dissociation energy D(C—X) has been taken as evidence for a two-step mechanism (Eqn (2)).[13] The first



step determines the activation energy by the formation of a cyclic intermediate *a* with sufficient excitation energy to break the (C—X) bond in the second step. In the case of *m*- and *p*-chlorobenzalacetone, it has been proposed[12] that several 1,2-H or 1,3-H migrations follow the cyclization step until the intermediate *b'* has rearranged into a reactive configuration *b* (Scheme 5). Within this reaction sequence it is obviously not the formation of *a* or *b'* (Eqn (2) and Scheme 5) which determines the relative probability of the substituent loss but the lifetimes of these intermediates and the rates of their further decomposition to *c*.

Considering only the forward direction of the reaction, the lifetime of *a* depends on the height of the energy barrier for the dissociation into *c* and X. For *b'* (Scheme 5) there are two reaction channels open, dissociation into *c'* and H or isomerization by 1,2-H



Scheme 5. Mechanism for the loss of substituents from *meta* and *para* substituted benzalacetones, exemplified by the *meta* isomer.

shifts. Similarly, the intermediate *b* either decomposes to product ion *c* and X, or isomerizes again by 1,2-H shifts. If the energy barriers for loss of X from *a* and *b* are similar and large relative to the critical energy for the H-migration, this energy barrier will be rate-determining and the rate of formation of *c* from *a* and *b* will be similar. In this case the mass spectra of the positional isomers of the substituted benzalacetones will also be very similar. On the other hand, if the energy barrier for the dissociation of *a* and *b'* respectively, is smaller than the critical energy for H-migration in *b'* and *b*, the rate-determining step for the formation of *c* from the initially formed intermediate *b'* will be the isomerization to the reactive configuration *b*, while *a* decomposes much more easily. Therefore, in this case the mass spectra of the positional isomers of the substituted benzalacetones will be different, the intensity of ions *c* decreasing in the order *ortho* ≫ *meta* > *para* isomer. It is seen immediately that the nature of the substituent and the dissociation energy of the corresponding C—X bond determines which of the two situations exists in a series of isomeric benzalacetones.

Thus, intermediate *a* is obviously much less stable with X = I than with X = CH_3, which also holds for intermediates *b*. However, the rates of the H-migrations must be much slower than the rate of decomposition of *a* or *b* in the case of X = I, whereas the opposite is true in the case of X = CH_3. These arguments are supported by a calculation of the heats of formation of the intermediates involved (see Appendix). As a result of the assumptions made in these calculations, the values obtained are somewhat uncertain. However, the conclusions are in good agreement with the arguments given above. The results are summarized in Fig. 3.

According to Fig. 3 the intermediates *a* (Eqn (2)) with X = Br and I are unstable thermodynamically, and for X = Cl the decomposition of *a* into *c* and Cl is approximately thermoneutral. Therefore, an attack of the carbonyl oxygen at the *ortho* position with X = Cl, Br and I leads to an intermediate which is neither thermodynamically nor kinetically stable. An attack at the unsubstituted *ortho* position leads to an intermediate analogous to *b'* (Scheme 5), which is only kinetically stable. However, the 70 eV mass spectra of the *o*-chloro-, bromo- and iodobenzalacetones show that an attack at the unsubstituted position is not an important pathway. The *m*- and *p*-chloro-, bromo- and iodobenzalacetones form intermediates *b'* which are unstable thermodynamically but which are kinetically stable, because several 1,2-H shifts have to follow the cyclization before a reactive configuration *b* is reached. Thus, the rate of the substituent loss is drastically reduced as compared with the *ortho* substituted isomers. This must mean that the rates of the 1,2-H shifts are much slower than the rate of decomposition of *a* with X at the *ortho* position.

With the substituents X = CF_3, CH_3 and H the intermediate *a* becomes increasingly stable thermodynamically. In the case of X = CF_3 the moderate decrease of the reaction rate in the order *o* > *m* ≳ *p* indicates that the rates of the 1,2-H shifts become comparable to the rate of decomposition of *a*. In the

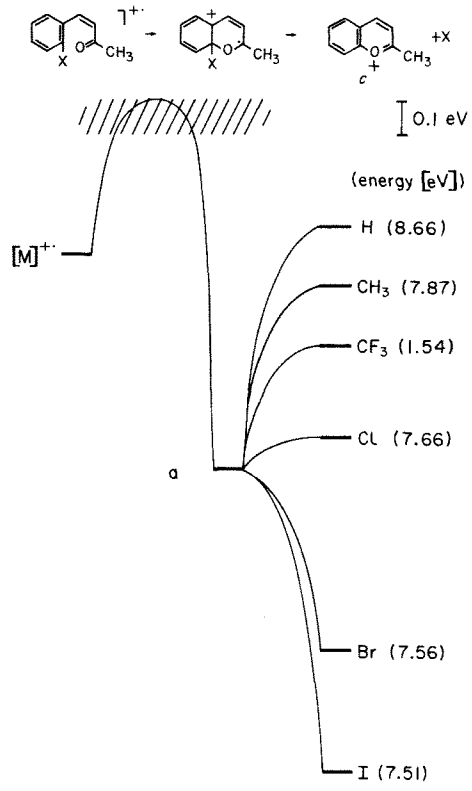


Figure 3. Thermochemistry of the formation and decomposition of intermediates *a* from the molecular ions of substituted benzalacetones. The individual values for ΔH_f can be obtained by taking the energy level of the products, given in parentheses, and applying the scale, given by the bar.

case of X = CH_3 the rate of decomposition of *a* is obviously slow compared with the rates of the 1,2-H shifts. Therefore, the three CH_3 substituted benzalacetones lose the substituents in nearly equal amounts. The molecular ions of the unsubstituted benzalacetone also lose the H-atom from each position of the phenyl ring with equal probability. This was observed some years ago employing deuterated benzalacetones.[16]

Thus, in the case of substituted benzalacetones the rate determining factor for the loss of the substituent from the molecular ions via intramolecular aromatic substitution turns out to be the stability of the reaction intermediates *a* and *b'* towards fragmentation into ion *c* and the substituent X·, and the rate of hydrogen migrations in this intermediate. Only if the rate for the loss of the substituent X is large because of the thermodynamic instability of *a*, will the mass spectrum of the *ortho* isomer exhibit a much larger peak for $[M—X]^+$ ions than the *meta* and *para* isomers. Otherwise the intermediate *b'* isomerizes quickly before fragmentation and the differences between the $[M—X]^+$ ion intensities in the mass spectra of the positional isomers become smaller or disappear. It is likely that this delicate balance between the rate of substituent loss and rate of hydrogen migration in a reaction intermediate also governs the intensity effects in the mass spectra of the positional isomers of other compounds which are known to lose their substituents in a two-step intramolecular substitution reaction. In each series of compounds this balance depends on the thermodynamic stability of the intermediates *and* on

the rate of hydrogen migration. The different behaviour of the various compounds, as discussed in the introduction, shows that *both* are probably very different in different systems.

EXPERIMENTAL

The 70 eV mass spectra were obtained on a Varian MAT 311A mass spectrometer with 70 eV electron energy, 3 mA emission current, 150 °C source temperature, 10^{-6} Torr source pressure. Liquids and solids were introduced via the heated inlet system (T = 150 °C) and via the direct insertion probe, respectively. The ionization efficiency curves were determined on a Vacuum Generators MM 12B mass spectrometer as described previously[12] with CH_3I as internal standard. The ionization and appearance energies were obtained using the semilog plot procedure[17] with a reproducibility of ±0.05 eV and ±0.1 eV, respectively.

The benzalacetones were prepared by the aldol condensation of the respective benzaldehydes with acetone analogous to the procedures reported in the literature.[12,13]

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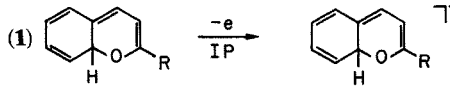
APPENDIX

The heat of formation of the intermediate *a* was obtained according to Eqn (3) (R = CH_3). The values for $\Delta H_f(\mathbf{1})$ and $I(1)$ were calculated with MINDO/3.



(3)

Because of the program capacity the calculation was performed on **1** (R = H) and the additional CH_3 group was accounted for by increments. The results are: $\Delta H_f(\mathbf{1}, R = H) = +102.1$ kJ mol^{-1}, $I(\mathbf{1}, R = H) = 7.74$ eV. Substituting R = H by R = CH_3 lowers $\Delta H_f(\mathbf{1}, R = H)$ by 42.7 kJ mol^{-1} (Benson's increments[18]) and $I(\mathbf{1})$ by *c.* 0.5 eV (viz. I(furan) − I(methylfuran) = 0.5 eV.[19] Combining these values gives $\Delta H_f(a) = 7.86$ eV. The reliability of the MINDO/3 calculation was checked by comparing the calculated $\Delta H_f(\mathbf{1}, R = H)$ with a value obtained from Benson's increments,[18] i.e. $\Delta H_f(\mathbf{1}, R = H) = +87.0$ kJ mol^{-1}. In the next step the same effect of X on $\Delta H_f(a)$ as on $\Delta H_f([M]^{+\cdot})$ is assumed which leads to an approximately constant exothermicity of the cyclization step of *c.* 0.7 eV (Fig. 3). The $\Delta H_f([M]^{+\cdot})$ values were calculated from the I(M)s and the ΔH_f of the neutral benzalacetones.[13]