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PERSPECTIVE

Intra- and Intermolecular Reactions of Aromatic Radical Cations: an Account of Mechanistic Concepts and Methods in Mass Spectrometry

Hans-Friedrich Grützmacher
Lehrstuhl I für Organische Chemie der Fakultät für Chemie, Universität Bielefeld, P.O.B. 10 01 31, D-33 501 Bielefeld, Germany

Investigations in the authors's laboratory in Bielefeld and elsewhere on the mechanism of the intramolecular and intermolecular aromatic substitution via radical cations are reviewed with the aim of presenting an example for the development of mass spectrometric methods and concepts for the study of the mechanisms of gaseous ionic reactions. An intramolecular aromatic substitution resulting in the loss of a hydrogen or a substituent from an aromatic ring of the molecule ions by the attack of a nucleophilic heteroatom in the side-chain was first observed in the normal electron impact (EI) mass spectra and was studied by substituent effects on ion abundance, ionization energy and appearance energy. This led to the construction of a two-step mechanism of the intramolecular aromatic substitution with a rate-determining first addition step. Subsequently, this fragmentation reaction was studied for a series of systems by tandem mass spectrometry, confirming the two-step mechanism and yielding an excellent insight into the dynamics of the substitution process. The bimolecular variety of the nucleophilic aromatic substitution via radical cations was investigated recently by Fourier transform ion cyclotron resonance spectrometry. The results for a series of halogenated benzenes and NH_3, CH_3NH_2 and $(CH_3)_2NH$ as the nucleophile corroborate the conclusions drawn from the study of unimolecular reaction mechanisms. It is shown that in all cases the formation and further reaction of the addition intermediate play a crucial role. This can be perceived by the application of the configuration mixing reactivity model to the addition reaction, and by the concept of classical and distonic radical cations. This review on a specific reaction mechanism shows clearly the excellent techniques and methods which the developments in mass spectrometry have provided for a detailed study of the mechanisms of ionic reactions in the gas phase.

INTRODUCTION

Mass spectrometry is one of the most successful and powerful tools in analytical chemistry, in particular for the identification and structural analysis of organic compounds. In spite of the immense and dramatic developments in mass spectrometric ionization techniques which allow the mass spectrometric study of very large and very complex compounds,[1] the basis of the success of an analytical application of mass spectrometry is still the observation of the fragmentations of ionized and energized species in the gas phase. Even if the interpretation of the resulting peak pattern of the mass spectrum is performed by advanced computer techniques,[2] the essence of a mass spectrometric structure analysis is the requirement that the fragmentations obey the rules of the reaction mechanisms developed for other types of organic reactions. Thus, mass spectrometry not only has its position in analytical chemistry, but is also an important tool for mechanistic studies in physical organic and inorganic chemistry. From the very beginning of my own involvement with mass spectrometry, I was fascinated by this facet of organic mass spectrometry. Indeed, the famous paper by F. W. McLafferty[3] on the correlation between the structure of a compound and its mass spectrum was a strong stimulus for the idea of studying organic reactivity by mass spectrometry. The clarification of the mechanism of the McLafferty rearrangement[4] with its analogy to the Norrish type II photo-fragmentation showed clearly that mass spectrometry can be used not only to study bond-breaking processes of isolated ions in the gas phase, but also to obtain information about bond-making processes in ions. Electron impact (EI) ionization of organic molecules gives rise to organic radical cations. Radical cations are possible intermediates in radiolytic and electrochemical processes in the condensed phase,[5] but the chemistry of these reactive intermediates is not well known. One expects a high reactivity of organic radical cations because of their electron deficiency. This expectation is confirmed by the high reactivity of olefinic radical cations in cycloaddition reactions and related processes,[6] and a similar reactivity-enhancing effect of the 'electron–hole' can be expected for organic radical cations derived from alkenes and arenes in their reactions with electron-rich nucleophiles.

We became interested in the substitution reactivity of organic radical cations in 1967 during a study of the mass spectrometric fragmentations of aromatic thioamides.[7] Similarly to the mass spectra of *N*-

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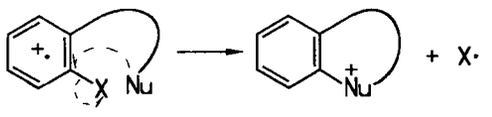


Scheme 1

phenylthiourea,[8] the mass spectra of thioformanilide and thioacetanilide exhibit a significant peak of $[M - H]^+$ ion. From a study of specifically deuterated derivatives and of derivatives carrying substituents at the *ortho* position of the phenyl group, it became obvious that this fragmentation corresponds to an *intramolecular substitution* at the aromatic ring by the functional group of the side-chain, as formulated generally by the cyclization process of Scheme 1. During the following years we have studied this intramolecular substitution for several systems using different mass spectrometric techniques, and eventually the analogous *intermolecular process* was investigated by Fourier transform ion cyclotron resonance (FT-ICR) spectrometry. Thus, surveying these studies gives an informative example for the development of techniques, concepts and theories of organic gas-phase ion chemistry over the last 25 years.

The fragmentation of the molecule ions of aromatic compounds by intramolecular aromatic substitution is special in several respects. First, the loss of a hydrogen atom or a substituent from the ionized aromatic ring by direct 'simple' bond cleavage is a high-energy process because of the large dissociation energy of bonds to sp^2 carbon atoms and is rarely observed with high intensity in the EI mass spectra of aromatic compounds. Typically, the loss of an 'aromatic' H or substituent X from the molecule ion of aromatic substances occurs after a preceding rearrangement of the toluene ion–cycloheptatriene ion class[9] by then breaking a bond to a sp^3 carbon atom. Thus, intramolecular aromatic substitution has to compete with this rearrangement. Second, for steric reasons the intramolecular substitution is expected to occur preferentially (or even exclusively for short side-chains) at the *ortho* position to the side-chain carrying the attacking nucleophile. Therefore, the fragmentation of the molecular ions by intramolecular substitution is related to the well known mass spectrometric '*ortho* effect' and may be used similarly in structure analysis. Finally, aromatic substitution is one of the cardinal reactions of organic chemistry, and in particular *the* mechanism of aromatic substitution involving radical ions is of current interest. Most everyday examples of aromatic substitution involve only even-electron species and correspond to electrophilic substitution by attack on the electron-rich aromatic ring by an electron-deficient species. Nucleophilic aromatic substitution requires a reverse electron distribution of the reagents and thus is known only for electron-poor arenes or occurs by a special elimination/addition mechanism. Recently, a careful kinetic study of the Kornblum reaction[10] and of related nucleophilic aromatic substitutions has shown[11] that these processes involve a single electron transfer (SET) step and correspond to radical chain reactions of substituted arene radical anions by an S_RN1 mechanism. Much less is known about aromatic substitution reactions involving radical cations. However, even in the case of the usual textbook example of electrophilic aromatic substitution, aromatic nitration, it is known that the crucial step of the substitution corresponds to the collapse of an aromatic radical cation–nitro radical pair.[12] In addition, arene radical cations are possible intermediates of the photo-stimulated substitution of electron-rich aromatic compounds. These circumstances have activated interest in a study of the reactivity of arene radical cations, in particular towards nucleophiles.

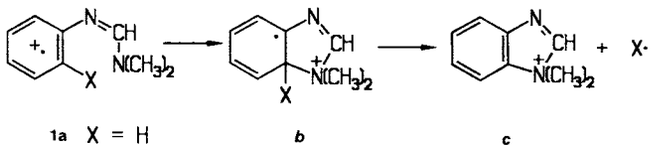
INTRAMOLECULAR AROMATIC SUBSTITUTION

The fragmentation of organic molecular ions by intramolecular substitutions is not restricted to aromatic compounds. In the case of certain amides and other nitrogen-containing compounds related to alkaloids, the so called S_Ni reaction was studied by M. Hesse and coworkers in great detail.[13] They demonstrated that this concept of S_Ni fragmentation is very helpful for structure elucidation of EI mass spectrometry, and in fact the generation of cyclic fragment ions by intramolecular substitution may be more common than usually assumed, in particular for the ions of modest internal energy investigated as metastable ions[14] and by tandem mass spectrometry.[15] The reason is that the energy of a costly bond-breaking process is at least partially compensated for by the bond formation during the substitution. However, intramolecular substitution requires a special orientation of the two reacting centres in the fragmenting ion, and hence is a good probe for the presence of this particular partial structure in the molecule.

The facile loss of a hydrogen or a substituent from the aromatic nucleus of the molecule ion of an aromatic compound is unexpected in view of the strong bond of the aromatic sp^2 carbon atom to this group. Nevertheless, numerous examples of this fragmentation process have been reported, and it is reasonable to assume that in all these cases there is (partial) compensation of the energy needed for bond cleavage by bond formation via intramolecular aromatic substitution.[16] The following discussion will be restricted to examples studied in our laboratory, however, and will be organized according to the different methods used for this studies, starting with the traditional mass spectrometric tools of isotopic labelling, of low-energy EI mass spectra and of substituent effects to study reaction mechanisms, and ending with the determination of reaction kinetics by the more sophisticated methods of FT-ICR spectrometry.

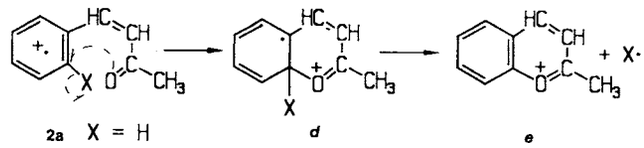
Electron impact mass spectra, *Z* values and substituent effects on ionization energies

The first compounds studied in detail were the *N*,*N*-dimethyl-*N'*-phenylformamidines **1** (Scheme 2).[17] The EI mass spectrum of the unsubstituted amidine **1a** (Fig. 1) is very simple, with the base peak due to the molecule ion. The most abundant fragment ion at 70 eV is the ion $[M–H]^+$, and the 15 eV mass spectrum contains only two peaks due to the fragment ions $[M - H]^+$ and $[M - CH_3]^+$. Hence the loss of the H atom is



1a X = H
1b X = F
1c X = Cl
1d X = Br
1e X = I

Scheme 2



2a X = H
2b X = F
2c X = CH_3
2d X = Cl
2e X = Br
2f X = I
2g X = NO_2

Scheme 3

clearly energetically favourable, and the mass spectra of a set of specifically deuterated derivatives of **1a** prove unequivocally that 85 ± 1% of the H atoms lost originate specifically from one of the *ortho* positions of the phenyl group, the remaining 15 ± 1% stemming from the *N,N*-dimethylformamidine group. The loss of an H atom from the phenyl ring is explained most easily by the formation of *N,N*-dimethylbenzimidazolium ions *c* by the mechanism depicted in Scheme 2.

The specific loss of H versus D from the phenyl ring of $[\mathbf{1a}]^{+\cdot}$ exhibits a kinetic isotope effect of $k_D/k_H = 0.7$ (at 70 eV), suggesting that the structure *b* in Scheme 2 presents either the transition state of a one-step intramolecular aromatic substitution or the intermediate of a two-step process with the last step (elimination of H and D) being rate determining. Before discussing this question more in detail, the fragmentations of the molecular ions of benzalacetones **2** (Scheme 3) are introduced as a further example of an intramolecular aromatic substitution of radical cations.

The molecule ion of the unsubstituted benzalacetone **2a** loses a hydrogen atom to form the ion $[M - H]^+$ in a relatively high yield (Fig. 2), and according to J. Ronayne, D. H. Williams and J. H. Bowie[18] this fragmentation is due to an intramolecular aromatic substitution resulting in thermodynamically stable 2-methylbenzpyrilium ions *e* (Scheme 3). The formation of ions *e* was proved subsequently by collisional activation (CA) mass spectrometry.[19] However, in contrast to the fragmentation the molecular ions of **1**, all six hydrogen atoms at the benzal moiety of **2** participate in the

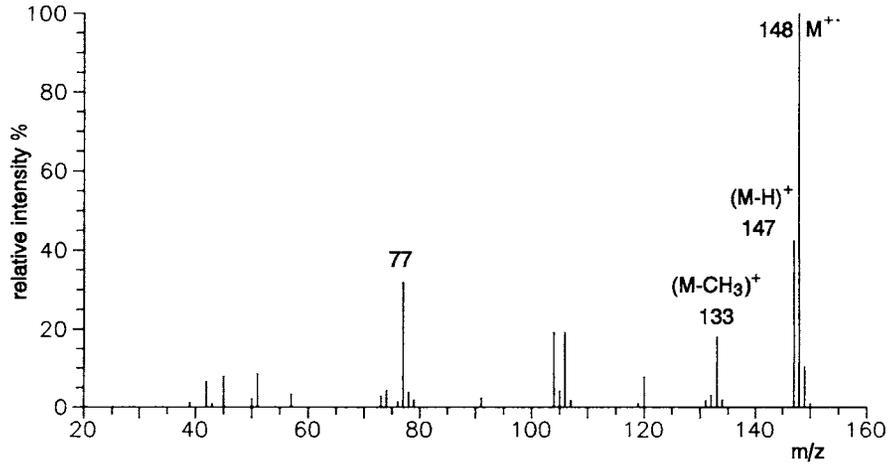


Figure 1. 70 eV mass spectrum of *N,N*-dimethyl-*N'*-phenylformamidine.

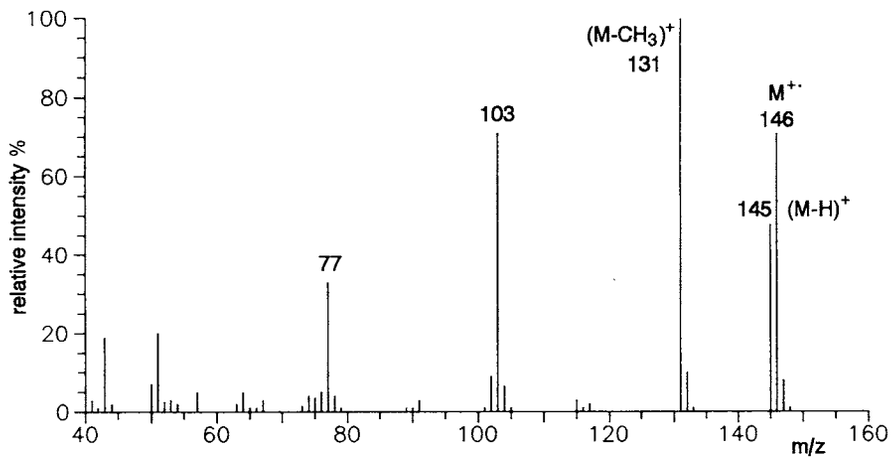
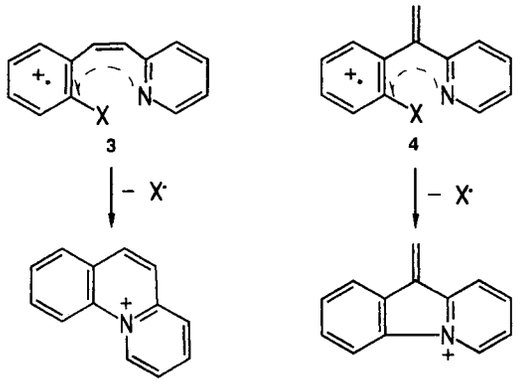


Figure 2. 70 eV mass spectrum of benzalacetone.



Scheme 4

loss of H from $[\mathbf{2}]^{+\cdot}$. This indicates that structure *d* in Scheme 3 now represents a distinct reaction intermediate with a sufficient lifetime for H and D atoms at the original benzal group to exchange their positions by fast hydrogen shifts.

One may speculate that the different fragmentation behaviour of deuterated derivatives of $[\mathbf{1a}]^{+\cdot}$ and $[\mathbf{2a}]^{+\cdot}$ with respect to the H–D scrambling during the H/D loss originates from the different size of the newly formed ring in *b* and *e*, respectively, but this is clearly not the case. For example, the molecule ions of 1-phenyl-1-(2-pyridyl)ethene (**3**)[20] and 1-phenyl-2-(2-pyridyl)ethene (2-stilbazole) (**4**)[21] lose an H atom specifically from the *ortho* position of the phenyl group irrespective of the formation of a five- or six-membered new ring (Scheme 4).

There are apparently two mechanisms for the intramolecular aromatic substitution of radical cations which are distinguished by an H–D exchange between the different positions of the phenyl group during the process, and which differ in the nature of the intermediate or transition state. These two types of mechanism may be exemplified by the intramolecular substitution of the molecular ions of **1** and **2**.

More information about the details of these mechanisms was obtained by a study of substituted derivatives. Substituent effects can be used in two different ways for the elucidation of fragmentation mechanisms. First, the hydrogen to be lost may be replaced with a suitable substituent X as in **1b–e** and **2b–g**. In this case it is detected easily whether the intramolecular substitution of the radical cation occurs 'directly' with the participation of only the H or X at the *ortho* position, or whether a rearrangement precedes the elimination step. Further, because of the different dissociation energies of the bonds to H and X, the relative intensities of the competing losses of H and X from the molecule ion gives some information about the energy requirements of the substitution process. Second, polar substituent effects on the rate constants are traditionally used to obtain information about the transition states or critical states of ionic reactions. Thus, the presence of an additional polar substituent at the *meta* or *para* position of the phenyl group of the parent radical cation **1a** and **2a** result in polar effects on the efficiency of the intramolecular substitution at the *ortho* position.

The polar substituent effects on the intramolecular aromatic substitution were measured by the so called *Z*

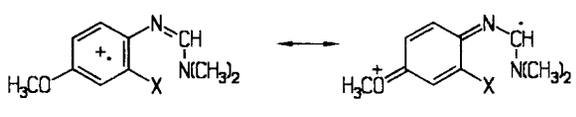
Table 1. Z/Z_0 values for substituted *N,N*-dimethyl-*N'*-phenylformamidines 1a and benzalacetones 2a

Substituent	Z/Z_0 1[a]	Z/Z_0 2[b]
H	1	1
p-OH	0.40	—
m-OH	1.00	—
p-OCH_3	0.30	0.67
m-OCH_3	0.95	1.88
p-CH_3	0.71	1.05
m-CH_3	0.93	
p-Cl	0.67	1.14
m-Cl	1.37	1.30
p-$COCH_3$	0.83	—
m-$COCH_3$	1.44	—
p-CF_3	1.14	—
m-CF_3	0.89	—
p-NO_2	0.92	0.41
m-NO_2	0.88	0.37

[a] Calculated for $[M - H]^+$.
[b] Calculated for $[M - H]^+ + [M - X]^+$.

values, which represent the intensity of the respective fragment ion peak relative to the intensity of the molecule ion peak, and which are correlated in favourable cases with the rate constant of the fragmentation.[22] Thus, the value of Z_X/Z_0 should indicate the effect of a substituent X on the fragmentation rate of the parent radical cation. The results obtained for *meta*- and *para*-substituted **1** and **2** are given in Table 1.

The *Z* values have to be discussed with some caution because the underlying kinetic scheme is only applicable if no further fragmentation of the fragment ions occurs. However, in the case of substituted $[\mathbf{1a}]^{+\cdot}$ and $[\mathbf{2a}]^{+\cdot}$ the *Z* values do not vary significantly in the 70 eV and 'low-energy' mass spectra, and the trend observed is typical of all other substitution reactions studied. Thus, a significant effect is only observed for an electron-donor substituent at a position *para* to the functionalized side-chain. Clearly, this is not a polar substituent effect on the critical state of the fragmentation but a 'ground-state effect' on the stability of the parent radical cations. The *para* substituents of **1a** and **2a** are in fact in a *meta* position with respect to the point of substitution and are not expected to influence particularly the transition state of the substitution. However, they interact by resonance with the functional group of the side-chain (Scheme 5). Hence a donor group at the *para* position should specifically lower the ionization energy by increasing the stability of the resulting radical cation. These results show clearly that *Z* values are of only limited advantage of detecting substituent effects because they do not distinguish between ground-state and transition-state effects. Hence, the concept of *Z* values has rightly been dismissed. P. Brown has



Scheme 5

Table 2. Ionization energies (*IE*) (in eV) of substituted *N,N*-dimethyl-*N'*-phenylformamidines 1a and *N,N*-dimethyl-*N'*-2-chlorophenylformamidines 1c, and appearance energies (*AE*) (in eV) of their ions $[M - H]^+$ and $[M - Cl]^+$, respectively

	Substituted 1a		Substituted 1c	
Substituent	*IE*(M)	*AE*($[M-H]^+$)	*IE*(M)	*AE*($[M-Cl]^+$)
H	7.3	9.0	7.3	8.6
4-$N(CH_3)_2$	6.1	9.0	6.4	9.1
5-$N(CH_3)_2$	6.3	8.8	6.4	8.9
4-OCH_3	6.9	9.3	7.0	8.9
5-OCH_3	7.2	9.2	7.1	8.7
4-CH_3	—	—	7.1	8.6
5-CH_3	—	—	7.1	8.5
4-NO_2	7.9	9.5	7.9	9.3
5-NO_2	7.8	9.5	7.7	9.1

suggested[23] comparing the *Z* values of *meta* and *para* derivatives to explore the different effects of polar substituents on ground states and transition states, and to measure the variation of these values with the energy of the ionizing electrons by the so-called 'wide-range kinetics.' However, in every case it is much safer to determine the ionization energy (*IE*) and the appearance energy (*AE*) of the relevant parent ions and product ions, even if they are measured only with a limited correctness of about 0.3 eV for *AE* and 0.1 for *IE* using a conventional mass spectrometer and the semi-logarithmic plot[24] method.

These errors are often systematic deviations and can be tolerated, because the information is drawn mainly from the variations in *IE* and *AE* between the parent compound and substituted derivatives. A good example of this is *IE*(**1**), *IE*(2-Cl-**1**) and *AE*(*c*) from substituted *N,N*-dimethyl-*N'*-phenylformamidines (**1a**) and *N,N*-dimethyl-*N'*-2-chlorophenylformamidines (**1c**)[25] presented in Table 2. Substituted **1c** eliminate the 2-Cl substituent by the intramolecular substitution to generate ion *c* abundantly and exhibit similar *Z* values to substituted **1a**. The *IE* values vary with the nature and position of the polar substituent as expected, but the *AE*(*c*) values are more or less constant and exhibit only a slight increase in the case of the electron-withdrawing substituents. Thus, the apparently slow substitution rates of the *para*-dimethylamino and *para*-methoxy derivatives $[\mathbf{1b}]^{+\cdot}$ and $[\mathbf{1c}]^{+\cdot}$ correlate with the formation of an increased number of unreactive states of the molecule ion at small internal energies, and no information about the stability of the intermediate state *c* is obtained from these substituent effects. Analogous substituent effects on the *IE* and *AE* of the product ions are observed for substituted benzalacetones **2**[26] and related compounds.[27]

The study of derivatives which may eliminate losely bound substituents X (good leaving group) instead of an H atom by intramolecular aromatic substitution is much more informative. From the observation of H–D isotope effects during the intramolecular aromatic substitution one expects a decisive effect of the dissociation energy of the bond to be broken on the reaction rate. Indeed, this is observed in all systems studied, indicated by a distinct increase in the intensity of the product ion peak in the mass spectra with a decrease in the dissociation energy of the bond to the substituent. The exception is the *ortho*-fluoro substituent, which is sometimes more abundantly lost than an H atom in spite of the stronger C—F bond. Table 3 gives the relative intensities of the substitution product ion peaks in the 70 eV mass spectra of differently *ortho*-substituted *N,N*-dimethyl-*N'*-2-X-phenylformamidines 2-X-**1** and 2-X-benzalacetones 2-X-**2**, the latter being compared also with the corresponding *meta*- and *para*-substituted derivatives. Besides the expected inverse correlation between the relative abundance of the product ions *c* and *e* and the dissociation energy of the substituent, the data reveal again a different behaviour of the two series of compounds, in line with the results of the study of specifically deuterated derivatives. The radical cations of **1a–e** eliminate specifically the *ortho* substituent and the loss of a substituent from the other positions of the phenyl group is absent or very sparse. In contrast, the mass spectra of **2a–g** exhibit a prominent peak of the substitution product ion *e* not only for the *ortho* compounds but also for the *meta* and *para* isomers. The relative abundance of *e* depends in this case on the dissociation energy of the C—X bond and the position of X.

The explanation is again a mechanism corresponding to a direct substitution in the case of **1** with *b* as a transition state (Scheme 2), and a two-step mechanism for the intramolecular substitution of **2** with *d* (Scheme 3) as a true intermediate.

However, the surprise came with the determination of the appearance energies of the product ions of these and

Table 3. Effect of the dissociation energy of the leaving group X on the relative abundance[a] of the ions $[M - X]^+$ in the EI mass spectra (70 eV) of substituted *N,N*-dimethyl-*N'*-phenylformamidines 2-X-1 and of substituted benzalacetones 2-X-2 and its positional isomers 3-X-2 and 4-X-2

	2-X-1		2-X-2		3-X-2		4-X-2	
X	$[M-X]^+$	$[M-H]^+$	$[M-X]^+$	$[M-H]^+$	$[M-X]^+$	$[M-H]^+$	$[M-X]^+$	$[M-H]^+$
F	37	23	34	14				
H	—	48	—	66	—	—	—	—
Cl	138	22	769	7	51	17	39	33
Br	142	22	1000	10				
I	105	14	—	—	—	—	—	—
NO_2	—	—	5000	20	12	12	17	17

[a] $[M-X]^+/M^{+\cdot}$ and $[M-H]^+/M^{+\cdot}$, respectively.

Table 4. Effect of the dissociation energy[a] of the leaving group X [D(C—X)] on the ionization energy[a] [IE(M)] and appearance energy[a] [AE(M—X)] of substituted *N,N*-dimethyl-*N'*-phenylformamidines 2-X-1 and benzalacetones 2-X-2

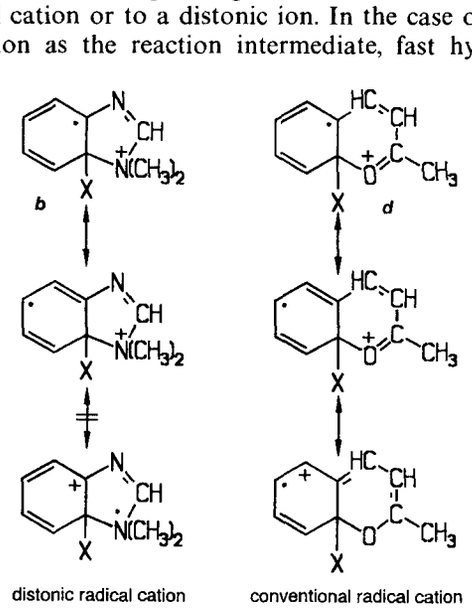
		2-X-1			2-X-2		
X	D(C—X)	IE(M)	AE([M—X]$^+$)	ΔE^b	IE(M)	AE([M—X]$^+$)	ΔE^b
F	4.97	7.6	9.0	1.4	8.9	9.5	0.6
H	4.42	7.3	9.0	1.7	8.8	9.4	0.6
CH_3	—	—	—	—	8.5	9.1	0.4
Cl	3.73	7.3	8.9	1.4	8.8	9.3	0.5
Br	3.03	7.2	8.7	1.5	8.7	9.2	0.5
I	2.38	7.3	8.7	1.4	8.3	8.8	0.5
NO_2	—	—	—		9.0	9.4	0.4

[a] In eV.
[b] $\Delta E = AE([M - X]^+) - IE(M)$.

other systems and its supposed correlation with the bond dissociation energy of X. The data are given in Table 4 for 2-X-**1** and 2-X-**2**. The one- and two-step models of the intramolecular substitution mechanism predict different possible effects of the dissociation energy of the C—X bond on the AE of the product ions. The one-step mechanism requires a direct influence of the dissociation energy on the critical energy of the substitution, which is approximated by the difference $AE - IE$, and the extent of this effect depends on the degree of bond cleavage in the critical complex, i.e. on an 'early' or 'late' transition state of the direct substitution. The two-step mechanism will show a bond strength effect on the AE of the product ion only if the second dissociation step is rate determining (or more correctly energy determining) for the total process. If the first addition or cyclization step is slow, the dissociation energy of the C—X bond will exert only a small effect. Surprisingly, however, in all cases studied the AE of the substitution product ions certainly shows no correlation with the dissociation energy of the C—X bond cleaved but remains more or less constant. The absence of any effect of the C—X dissociation energy is most clearly seen from the difference ΔE = AE(product ion) − IE(molecular ion), which approximates the critical energy of the substitution process. *N,N*-Dimethyl-*N'*-2-halophenylformamidines **1a–e** yield $\Delta E = 1.5 \pm 0.1$ eV, although the dissociation energy of the C—halogen bond in this series varies by more than 2.5 eV. For *ortho*-substituted benzalacetones **2a–g**, ΔE for loss of the *ortho* substituent remains essentially constant at 0.5 ± 0.1 eV, whereas ΔE for the loss of hydrogen and a *meta* and a *para* substituent usually varies between 0.4 and 0.9 eV. These nearly constant ΔE values for different *ortho* substituents in all substitution systems studied prove unequivocally that in every case the intramolecular aromatic substitution of a radical cation is a two-step process with a stable addition intermediate, and that the cyclization by the first addition step determines the critical energy of the total process. Thus, the D–H isotope effects observed for the substitution reaction were misleading.

Although this result of a study of the mechanism of the substitution reaction by the traditional methods of mass spectrometry was acceptable in view of the two-step mechanisms known for the other types of aromatic substitution, it left us with the need for an explanation for the unusual decoupling of product ion abundance (which depends on the C—X bond dissociation energy) and AE of the product ion (which does not depend on the C—X bond dissociation energy), for the distinct D–H isotope effect, and for the different behaviours of the addition intermediate with respect to a rearrangement by a ring walk of the hydrogen atoms at the phenyl group. This latter facet may be now explained by the modern concept of distonic ions. The term distonic ions was introduced into gas-phase ion chemistry by L. Radom and co-workers[28] to specify radical cations in which the positive charge and the unpaired radical electron reside each in a possibly delocalized but separate molecular orbital. An inspection of the intermediates *b* and *d* generated by the cyclization step from **1a** and **2a**, respectively, shows that *b* is a distonic ion with the positive charge localized at the quaternary ammonium moiety and only the unpaired electron is delocalized, but *d* is a conventional radical cation with the positive charge *and* the radical electron residing in the same delocalized orbital (Scheme 6).

It turned out that the two types of unimolecular aromatic substitution of radical cations can be classified generally by the electronic configuration of the cyclic intermediate corresponding either to a conventional radical cation or to a distonic ion. In the case of a distonic ion as the reaction intermediate, fast hydrogen



Scheme 6

migrations in the former phenyl group, resulting in H–D scrambling or in the loss of substituents from the *meta* and *para* positions, are not observed. In fact, this would correspond to 1,2-shifts of hydrogen in the radical part of the distonic ion, and radicals do not isomerize easily by these shifts.

Metastable ions, kinetic energy releases, reaction energy profiles and quantitative Hammond postulates

One most important breakthrough in the analysis and in the study of gas-phase ion chemistry by mass spectrometry was the development of the techniques of tandem mass spectrometry.[15] With regard to an investigation of the unimolecular reactions of gaseous ions, the direct observation of metastable ions, originally introduced as the direct analysis of daughter ions (DADI),[29] is of particular interest. These experiments are most conveniently performed by mass-analysed ion kinetic energy (MIKE) spectrometry in a double-focusing sector mass spectrometer with the magnetic sector preceding the electrostatic analyser (often called reversed Nier–Johnson geometry). The two main advantages in studying the fragmentations of metastable ions by this technique are the observation of the reactions of ions of a narrow range of internal energy, just sufficient to surmount the energy barrier of the fragmentation, and the measurement of the kinetic energy release (KER) associated with a fragmentation reaction.[14] The KER, determined from the peak shapes in the MIKE spectra due to the process studied gives especially valuable information about the potential energy surface of the reacting system and the minimum reaction energy path (MERP, reaction energy profile) in the neighbourhood of the transition state.

Tandem mass spectrometry permits also a direct determination of the structure of ions by their collision-induced decomposition (CID) in the field-free region of a mass spectrometer following the magnetic sector. For ion structure analysis, the collisional activation (CA) mass spectrum thus obtained from the ion being studied is compared with the CA mass spectra of reference ions of known structures ('fingerprinting'). A reliable method to establish the ion structure is particularly important in establishing a fragmentation mechanism in cases where it is not possible to determine the heat of formation of the product ion by *AE* measurement and make a choice between isomeric structures on the basis of these data. Such a case is fragmentation by intramolecular aromatic substitution. Thus, it was important to confirm the proposed formation of cyclic *product* ions during this process by CA mass spectrometry. These investigations showed in all cases that within a series of substituted derivatives the ions formed by loss of an H atom or a substituent X from the aromatic ring are indeed identical, and in those cases where the supposed product ion of the intramolecular substitution could be generated independently the structures of the product ions were verified unambiguously. Thus, the course of the substitution reaction was made perfectly clear by this new technique, but not the details of the mechanism.

The application of MIKE spectrometry to the study of intramolecular aromatic substitution of radical cations was of special interest because of the discrepancy between the dependence of the relative abundance of the product ions on the dissociation energy of the leaving group and the independence of the critical energy of this process, as discovered by the conventional methods of mass spectrometry. It is clear that this arises from a two-step mechanism of the fragmentation with the first addition step leading to the cyclic intermediate being energy determining. Obviously, this cyclic intermediate, i.e. *b* and *d* in the case of **1** and **2**, respectively, is produced as a chemically activated species, and the excess energy with respect to the dissociation into the products increases with decreasing bond energy to the leaving group X, resulting in an increase in the dissociation rate. Hence the reaction energy profiles of a series of **1** or **2** with different X should vary as shown schematically in Fig. 3. If this is the correct explanation for the increase in the relative abundance of the substitution product ions in the EI mass spectra of derivatives

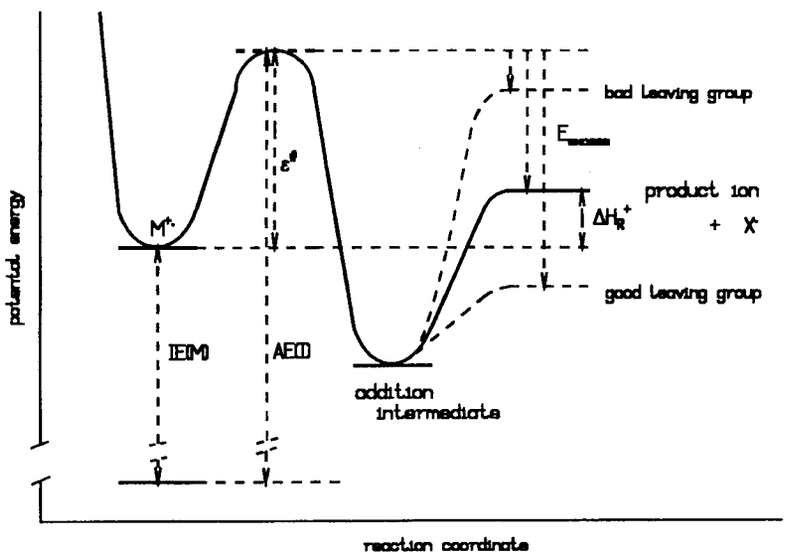


Figure 3. Reaction energy profile for the intramolecular aromatic substitution reaction.

with a good leaving group in spite of a constant critical energy, then the KER of metastable ions for this reaction should also depend explicitly on the dissociation energy of X.

The molecular ion of all compounds expected to lose an H atom or a substituent X by the intramolecular aromatic substitution mechanism exhibit an intense peak in their MIKE spectra due to this process, and in many cases this is the only signal observed. Clearly, the mass spectrometric fragmentation of these compounds by loss of a substituent from the aromatic ring is an energetically favourable process and certainly not a 'direct' bond cleavage. Further, the formation of two different types of intermediates, one without and the other with the possibility of rearranging by a hydrogen ring walk in the aromatic system, was corroborated conclusively. In particular, an abundant loss of substituents at the *meta* and *para* positions at the phenyl ring was observed in the MIKE spectra of the molecule ions of substituted benzalacetones **2** and related compounds,[26] and sometimes the MIKE spectra of the molecular ion of positional isomers are nearly identical. A more advanced rearrangement by hydrogen shifts is expected for metastable ions with a longer lifetime. However, even for these long-lived molecule ions a rearrangement is not observed in the MIKE spectra if the intermediate created by the first cyclization step corresponds to a distonic ion as in the case of **1**. Thus, tandem mass spectrometry was a very supportive tool to confirm unambiguously the conclusions derived by the more conventional mass spectrometric techniques.

As discussed before, the determination of the KER associated with the intramolecular aromatic substitution should be of particular help in understanding the mechanism of the intramolecular substitution. It is generally accepted that a rearrangement preceding a dissociation and constraining a 'reverse' activation barrier, $\varepsilon_r^{\ddagger}$, on the reaction path will lead to flat-topped or dish-topped peaks in the MIKE spectra because of a large KER with a non-statistical distribution of kinetic energy (T) values. In agreement with this rule, broad and dish-topped peaks are observed for the loss of hydrogen from the molecule ions of compounds being predisposed for intramolecular aromatic substitution. For the loss of H and a series of different substituents X from the molecular ions of benzalacetones **2**, 2-stilbazoles **3** and 1-phenyl-1-(2-pyridyl)ethenes **4**, the T_B values calculated from the peak width at the bottom of the peak are given in Table 5.

For all three series of compounds the KER associated with the loss of H is large, decreases for the elimination of the more strongly bonded F substituent and increases for the loss of a less strongly bonded CH_3 substituent. This agrees perfectly with the schematic reaction energy profile shown in Fig. 3. However, this profile predicts a further increase in the KER for halogen substituents because of the decreasing C—halogen bond energy in the set of halogens. To our surprise this was not observed, and on the contrary even a decrease compared with the loss of H occurred, which is striking for the loss of Cl from 2-Cl-**3** and 2-Cl-**4** (Table 5). Further, the peaks for the loss of Cl and the other halogen substituents are more or less Gaussian-shaped, indicating a statistical distribution of the energy available in the

Table 5. Energy data[a] (see text), position of the transition state (X_0*), kinetic energy release (T_B)[a] and energy partitioning quotient q for the formation of ions $[M - X]^+$ from molecule ions of substituted benzalacetones 2-X-2, 2-stilbazoles 2-X-3 and 1-phenyl-1-(2-pyridyl)ethenes 2-X-4

X	$\varepsilon^{\ddagger}$	ΔH_R^+	X_0*	E^{excess}	T_B	q
			2-X-2			
F	58	+50	0.86	13	10	0.80
H	58	+13	0.55	50	50	1.00
CH_3	58	−8	0.46	67	59	0.88
Cl	48	−54	0.31	105	33	0.32
Br	48	−113	0.23	164	38	0.23
I	48	−138	0.21	184	33	0.18
NO_2	39	−172	0.09	213	46	0.22
			2-X-3			
F	87	+21	0.88	18	17	0.95
H	96	+84	0.57	63	59	0.93
CH_3	106	−8	0.48	112	67	0.59
Cl	106	−33	0.43	142	29	0.21
Br	106	−105	0.33	213	33	0.16
I	96	−151	0.28	243	46	0.19
NO_2	48	−155	0.19	205	67	0.33
			2-X-4			
F	68	+59	0.85	13	13	1.00
H	77	+8	0.53	50	50	1.00
CH_3	58	−25	0.42	88	71	0.81
Cl	48	−54	0.32	105	17	0.16
Br	39	−125	0.19	167	29	0.18
I	48	−159	0.18	205	33	0.17

[a] In kJ mol^{-1}.

critical complex over all degrees of freedom. Nonetheless, the *AE* for the halogen loss had proved that the first addition step of the substitution still has the largest energy barrier of the whole process. Hence these observations apparently violate the rule that high energy rearrangements preceding the dissociation are detected by a large KER.[30] However, common wisdom is not always the truth. In fact, it is not noticed very often that there are *two* criteria for a fragmentation to produce a large KER. First, the dissociating ion must have a large amount of excess energy, which is often provided by a preceding rearrangement, but second, for the excess energy to appear as kinetic energy of the products, the dynamics of the process must channel a substantial amount of this excess energy into the dissociation coordinate. Obviously, the elimination of *ortho* substituents by an intramolecular aromatic substitution of radical cations exemplifies the interesting case that the dynamics of the process change *qualitatively* with the bonding energy of the substituent. If this bond is strong, the excess energy of the chemically activated intermediate formed in the first addition step is converted into kinetic energy of the products. However, if this bond is weak, the excess energy is distributed statistically over all degrees of freedom, leading to a small KER in spite of the large amount of excess energy.

Remarkably, such a behaviour for the partitioning of the excess energy, E_{excess}, of a reacting system was predicted by the fundamental studies of J. C. Polanyi[31] and

K. C. Kim and D. W. Setser[32] on the reaction dynamics of simple systems and can be associated with characteristic properties of the transition state and its movement on the reaction surface along the reaction coordinate.[33] These ideas have been combined with the Hammond postulate[34] of 'early' and 'late' transition states to the concept of a *quantitative Hammond postulate*,[35] which relates the position $0 < X_0^* < 1$ of the transition state to the potential-energy barrier, U^*, and the reaction energy, U_f, of a reaction. Then, the partitioning of E_{excess} released from the critical configuration between the excitation of internal modes of the product and the kinetic energy of the product depends on the position X_0^* of the transition state, early transition states favouring internal excitation and late transition states favouring the release of kinetic energy.

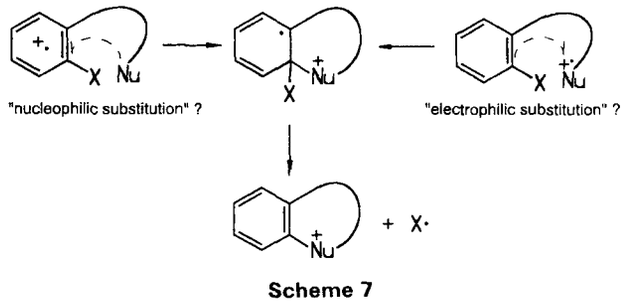
$$X_0^* = \frac{1}{2 - \frac{U_f}{U^*}} = \frac{1}{2 - \frac{\Delta H_R^+}{\Delta E}}$$

In the present context of the intramolecular aromatic substitution of gaseous radical cations in a mass spectrometer, the activation energy U^* can be approximated by $\varepsilon^\ddagger = \Delta E = AE(\text{production ion}) - IE(\text{educt})$, which is almost constant in the reactions studied. The reaction energy U_f corresponds to the heat of substitution, ΔH_R^+, and can be calculated from the heats of formation of the molecule ions and of the product ion and neutral fragment. This gives the values of X_0^* given in Table 5 for the three series of substitution reactions. Finally, E_{excess} available in the intermediate corresponds to the activation energy of the reverse reaction, $\varepsilon_r^\ddagger$, and can be estimated from the heats of formation of the critical complex and of the products, known for the AE and from calculations. These data can be combined to analyse the partitioning of E_{excess} between internal and external modes by the *energy partitioning quotient* $q = T_B/E_{excess}$. The results for the three series of intramolecular aromatic substitution of the molecular ions of *ortho*-substituted **2**, **3** and **4** are given in Table 5. Although the estimation of the relevant energy terms needed to calculate q is at most semi-quantitative, the trend of q throughout the three series of intramolecular aromatic substitutions is remarkably uniform. In every case the reaction system switches from a predominant release of E_{excess} as kinetic energy ($q > 0.6$) to a major internal excitation ($q < 0.3$) between the substitution of CH_3 and Cl, respectively, which conforms to a shift of the transition state on the reaction coordinate from a late (position ($X_0^* > 0.4$) to an early position ($X_0^* < 0.3$). Clearly, this result concurs with the general rules of reaction dynamics derived from fundamental theoretical considerations and much more elaborate experimental studies, and it is very satisfying that such interesting mechanistic details of a reaction mechanism are available experimentally by mass spectrometry.

At this point the details of the mechanism of the intramolecular aromatic substitution of radical cations as revealed by the miscellaneous mass spectrometric experiments can be summarized as follows. Analogous to other aromatic substitution reactions, the aromatic substitution within radical cations is a two-step process consisting of an addition (cyclization) of a suitable heteroatom of the side-chain to the ionized aromatic ring followed by the dissociation of an H atom or a substituent from the ring. In all cases studied the first addition step determines the activation energy of the total process, and generates the addition intermediate as a chemically activated species. The addition intermediate corresponds to the Wheland intermediate and Meisenheimer intermediate (positively and negatively charged σ-complex, respectively) of the electrophilic and nucleophilic aromatic substitution, but may adopt two different electronic configurations. One corresponds to a distonic ion with the positive charge localized at the group attached by the addition, and the other corresponds to a conventional radical cation with positive charge and unpaired electron delocalized in the same molecular orbital. Only in the latter case does the excess energy of the chemical activation induce fast hydrogen shifts around the aromatic ring parallel to the elimination of the substituent or the hydrogen atom at the *ortho* position attacked. However, in all systems studied the partitioning of E_{excess} of the intermediate during the dissociation step between kinetic energy and internal excitation of the products depends on the occurrence of late or early transition states. The clouded part of this detailed mechanistic model refers to the effect of additional polar *meta* or *para* substituents on the substitution at the *ortho* position. It appears that the substituent effect influences mainly the stability and electronic configuration of the parent radical cation, and it is by no means clear whether the substitution corresponds the attack of a nucleophilic heteroatom of the side-chain on an ionized aromatic ring, as expected for the 'electron–hole catalysis', or in fact is more precisely described by the attack of the heteroatom of the side-chain carrying the charge and an unpaired electron on the neutral aromatic ring (Scheme 7).

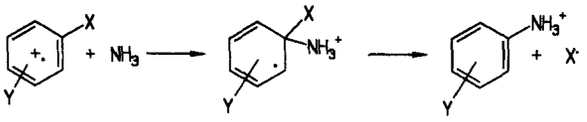
Fourier transform ion cyclotron resonance spectrometry, bimolecular rate constants and reactivity models

The two different charge distributions (Scheme 7) between the aromatic ring and the attacking group, which are feasible for an aromatic substitution reaction via radical cations, cannot be distinguished reliably by an intramolecular reaction of a radical cation. This poses no problems, however, for a study of bimolecular substitution reactions of either radical cations of halogenated arenes and suitable neutral nucleophiles or neutral haloarenes and radical cations of the nucleophiles. The initial charge distribution can be verifyed simply by a proper choice of reactants with suitable IE.



Scheme 7

In fact, gaseous substitution reactions corresponding to a replacement of the substituent of chlorobenzene and related arenes by an NH_3^+ group have been observed in a mass spectrometer under the conditions of chemical ionization with ammonia.[36] The study of reaction mechanisms requires a careful determination of the rate constant of the reaction and its dependence on the structure *of the* reactants. For gaseous ion–molecule reactions this is conveniently performed by FT-ICR spectrometry with an instrument equipped with an external ion source. This gives complete command over the composition of the neutral gas phase and the ions in the FT-ICR cell, which corresponds to the reaction vessel. Using chlorobenzene and the isomeric dichlorobenzenes and ammonia as reactants it became clear immediately that the formation of anilinium ions under these conditions occurs by the reaction of the haloarene radical cations with neutral NH_3 (Scheme 8), and that the reaction corresponds to a direct displacement (*ipso* substitution) of the substituent at the benzene ring.[37] The reaction of $NH_3^{+\cdot}$ with the neutral chlorobenzenes results only in an efficient charge transfer because of the large difference in the *IE* [$IE(NH_3) = 10.16$ eV,[38] $IE(C_6H_5Cl = 9.06$ eV,[38] $IE(C_6H_4Cl_2) = 8.99$–9.08[38]].



Scheme 8

The bimolecular rate constant, k_{bi}, of the reaction between the chlorobenzene radical cations and neutral ammonia is small and well below the collision rate constant k_{ADO},[39] corresponding to an reaction efficiency Eff. $= k_{bi}/k_{ADO} = 13\%$. This small efficiency shows clearly that there is a considerable activation energy barrier in the reaction path of the substitution. The efficiency does not depend on the dissociation energy of the leaving group X in a series of mono- and dihalobenzenes (Table 6),[40] hence the substitution must follow a mechanism containing at least two steps, and the rate-determining step has to be the addition of the nucleophilic NH_3 to the benzene radical cation. In fact, the reaction of the iodobenzene radical cations with NH_3 exhibits an especially low efficiency (Table 6), stressing the independence of k_{bi} from the dissociation energy of the substituent replaced. Thus, the MERP and the reaction energy profile (Fig. 4) of the bimolecular aromatic substitution via radical cations with this type of charge distribution between the reactant is completely analogous to that of the unimolecular intramolecular substitution of aromatic radical cations (Fig. 3) discussed in the previous sections with the difference that the (distonic) intermediate is now formed by a bimolecular addition process.

The discussion of a nucleophilic aromatic substitution via radical cations started with the assumption of a 'hole catalysis' of this process, and is it surprising that the experimental results for both the intramolecular substitution and the bimolecular reaction prove unequivocally that the addition of the electron-rich nucleophile to the electron-poor unsaturated radical

Table 6. Selected bimolecular rate constant (k_{bi}) and reaction efficiency (Eff.) for reactions of mono- and dihalobenzene radical cations with NH_3 and CH_3NH_2, respectively, and $CH_3NH_2^{+\cdot}$ with neutral mono- and dihalobenzenes

Neutral species	Radical cation	k_{bi}[a]	Eff.[b]
NH_3	Fluorobenzene	n.r.[c]	—
	Chlorobenzene	2.1	13
	Bromobenzene	2.2	13
	Iodobenzene	0.038	0.24
	1,2-Dichlorobenzene	2.4	15
	1,3-Dichlorobenzene	1.2	7
	1,4-Dichlorobenzene	0.07	0.4
	1-Bromo-4-chlorobenzene	0.24	1.5
	1-Chloro-4-iodobenzene	<0.001	<0.01
CH_3NH_2	Chlorobenzene	8.7	53
	Bromobenzene	9.2	58
	Iodobenzene	5.7	37
	1,2-Dichlorobenzene	8.6	54
	1,3-Dichlorobenzene	5.5	34
	1,4-Dichlorobenzene	5.4	34
	1-Chloro-4-iodobenzene	4.4	28
Chlorobenzene	CH_3NH_2	13	55
Bromobenzene		15	63
Iodobenzene		Only charge transfer	
1,2-Dichlorobenzene		15	50
1,3-Dichlorobenzene		13	54
1,4-Dichlorobenzene		10	57

[a] $\times 10^{-10}$ cm^3 molecules^{-1} s^{-1}.
[b] In % collision rate.
[c] n.r. = no reaction

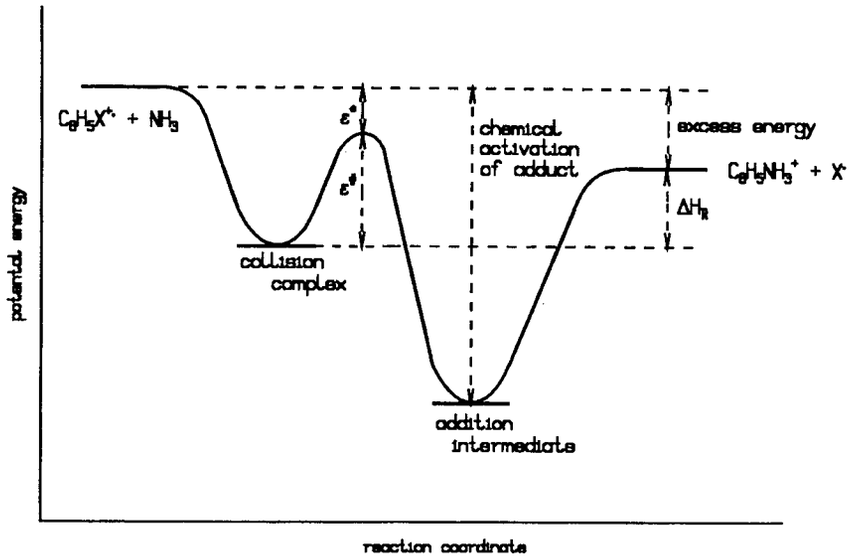
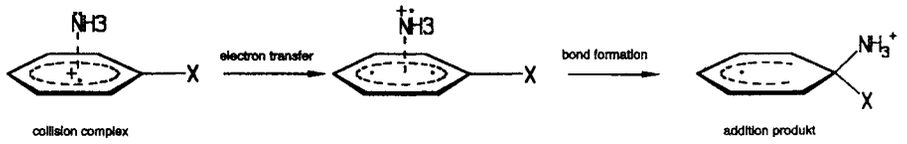


Figure 4. Reaction energy profile for the intermolecular aromatic substitution reaction $C_6H_5X^{+\cdot} + NH_3$.

cation is hampered kinetically by a substantial activation energy barrier. What is the source of this unexpected activation energy barrier? The answer comes from a more detailed analysis of the changes in the electronic configuration of the reactants during the addition step of the substitution reaction (Scheme 9). The main electronic difference arises from a charge migration during the addition, since the positive charge is at the arene radical cation at the beginning of the reaction, but localized at the quarternary ammonium substituent in the addition product. This corresponds to an electron transfer from the lone pair of NH_3 to the aromatic ring during the addition, and this can be described by dividing the addition step hypothetically into two steps: (i) electron transfer from NH_3 to the arene radical cation and (ii) bond formation between the now ionized NH_3 and an electronically excited but neutral arene.

This description is identical with the analysis of substitution reactions by the configuration mixing model of Shaik and co-workers,[41] which predicts a activation energy for the reaction between a radical cation and a nucleophile arising from an avoided crossing of the electronic configurations of the initial state and the final state of the reaction. According to this model, the activation energy barrier for the addition should increase with increasing difference in the *IE* of the nucleophile and the neutral precursor of the radical cation. This prediction gives an explanation for the observation discussed in the first section, that the intramolecular aromatic substitution of radical cations is inhibited by electron-donor substituents on the aromatic ring. This is paralleled in the series of bimolecular substitution reactions by the result that the radical cations of *p*- and *m*-chloroanisole do not react any more with NH_3 although the substitution of the chloro substituent would be still exothermic.[42] In this case the *IE* difference between NH_3 and the haloarene has increased from 1.09 for chlorobenzene to more than 2 eV for the chloroanisoles, implying a parallel increase in the activation energy for the addition of NH_3 to the chloroanisole radical cations.

A corollary of the configuration mixing reactivity model of Shaik and co-workers is the prediction that the addition of the radical cation of a nucleophile to the neutral arene should exhibit a distinctly lower activation energy barrier because with this charge distribution a charge migration during the addition is not necessary. Hence only other factors and not the *IE* difference will contribute to the energy barrier. In fact, electron-withdrawing substituents at the aromatic ring which should favour a charge localization at the heteroatom of the side-chain (see Scheme 7) do at least not hinder the intramolecular aromatic substitution, but it is difficult to realize this type of charge distribution among the reactant centres unambiguously in the unimolecular case. For bimolecular substitution reaction NH_3 has to be replaced with CH_3NH_2 ($IE = 8.97$ eV[38]) or $(CH_3)_2NH$ ($IE = 8.23$ eV[38]) with a lower *IE* than the halobenzenes to avoid competing fast charge-transfer reactions. The experiment shows for the reactions of $CH_3NH_2^{+\cdot}$ clearly increased efficiencies for the substitution and a different trend of the substituent effects on the reaction.[43] However, the reaction efficiencies for a substitution of the neutral halobenzenes by $(CH_3)_2NH^{+\cdot}$ are again small and indicate the presence of another bottleneck in the substitution reaction



Scheme 9

besides the addition step. This new bottleneck, not felt in the reactions of the halobenzene radical cations with neutral NH_3 because of the slow addition step, probably arises *from* a preferred addition of the amine radical cation in a *para* position to the substituent eventually replaced, and the necessity to rearrange the 'wrong' addition product into the reactive *ipso* addition product. Possibly this rearrangement is slow because all addition intermediates studied so far correspond to distonic ions. However, work is in progress to check this point and to elucidate this further mechanistic detail of nucleophilic aromatic substitution via radical cations.

CONCLUSION

It has been a long process to develop mass spectrometry over the last 25 years into a tool for fundamental studies in gas-phase ion chemistry. From the beginning this was driven by a successful interplay of experiment and theory and by contributions from many disciplines of science. Mechanistic organic chemistry was an essential part of this development, and the concepts of the elucidation of organic reaction mechanisms were applied early to the discussion of mass spectrometric fragmentation reactions.[22] Thus, it is typical that also the investigations of the aromatic substitution reactions via radical cations as presented in this account started with an analysis of the EI mass spectra of compounds specifically deuterated at different positions, by a search for analogous fragmentations in the mass spectra of related compounds and by a discussion of substituent effects. These methods still have their merits, and even today a well founded study of a mass spectrometric reaction mechanism is not possible without the careful preparation and measurement of derivatives labelled with stable isotopes. However, organic mass spectrometry (and, of course, also its inorganic twin) has gone beyond that. It is a pity that many studies reporting very interesting and surprising reactions of gaseous ions in a mass spectrometer are not continued to uncover the mechanisms by the proper use of additional mass spectrometric techniques, but substitute experiments by sometimes admittedly clever reasoning and the note that this is the gas-phase analogue of the 'so-and-so' reaction in solution. In my opinion, it is not exceptionally exciting to detect a more or less formal analogy to reactivity in solution, because chemistry in the gas and condensed phases is certainly not fundamentally different. However, a fascinating aspect of the study of ionic reactions in the gas phase by mass spectrometry is the possibility of observing the reactions of isolated species in a completely different situation from the ordinary laboratory environment. To see whether this will alter the reactivity of the species and will reveal new facets of the old theme of structure–reactivity relationships is important for a better understanding of chemistry. Hopefully, this discussion of an investigation of the intramolecular and intermolecular aromatic substitution reactions of radical cations has shown that the modern techniques of mass spectrometry can indeed be used to obtain a detailed picture of a reaction mechanism, and that it will encourage further the use of these methods for more studies in the exciting field of gas-phase ion chemistry.

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