Gas-Phase Reactions Between $O^{-\cdot}$ and C_6H_5F: On the Acidity of Fluorobenzene and 1,4-Difluorobenzene
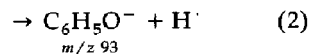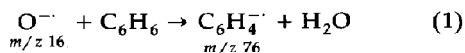
Henri E. K. Matimba, Steen Ingemann, and Nico M. M. Nibbering

Institute of Mass Spectrometry, University of Amsterdam, Amsterdam, The Netherlands

The gas-phase reactions of negative ions ($O^{-\cdot}$, NH_2^-, $C_2H_5NH^-$, $(CH_3)_2N^-$, $C_6H_5^-$, and $CH_3SCH_2^-$) with fluorobenzene and 1,4-difluorobenzene have been studied with Fourier transform ion cyclotron resonance mass spectrometry. The $O^{-\cdot}$ ion reacts predominantly by (1) proton abstraction, (2) formal $H_2^{+\cdot}$ abstraction, and (3) attack on an unsubstituted carbon atom. In addition to these processes, attack on a fluorine bearing carbon atom yielding F^- and $C_6H_4FO^-$ ions occurs with 1,4-difluorobenzene. Site-specific deuterium labeling reveals the occurrence of competing 1,2-, 1,3-, and 1,4-$H_2^{+\cdot}$ abstractions in the reaction of $O^{-\cdot}$ with fluorobenzene. Attack of the $O^{-\cdot}$ ion on the 3- and 4-positions in fluorobenzene with formation of the 3- and 4-fluorophenoxide ions, respectively, is preferred to reaction at the 2-position, as indicated by the relative extent of loss of a hydrogen and a deuterium atom in the reactions with labeled fluorobenzenes. The NH_2^-, $C_2H_5NH^-$, $(CH_3)_2N^-$, $C_6H_5^-$, and $CH_3SCH_2^-$ anions react with fluorobenzene and 1,4-difluorobenzene only by proton abstraction. The relative importance of H^+ and D^+ abstraction in the reaction of these anions with labeled fluorobenzenes indicates that the 2-position in fluorobenzene is more acidic than the 3- and 4-positions, suggesting that the literature value of the gas-phase acidity of this compound ($\Delta H^\circ_{\text{acid}} = 1620 \pm 8$ kJ mol^{-1}) refers to the former site. Based on the occurrence of reversible proton transfer between the CH_3O^- ion and 1,4-difluorobenzene, the $\Delta H^\circ_{\text{acid}}$ of this compound is redetermined to be 1592 ± 8 kJ mol^{-1}. (J Am Soc Mass Spectrom 1993, 4, 73–81)

Insight into the regioselectivity in the reactions of negative ions with molecules in the gas phase is of fundamental interest and importance for structure elucidations by negative chemical ionization [1] in combination with tandem mass spectrometric [2] methods, such as collision-induced dissociation or collision-induced charge inversion of the generated ions. The majority of the commonly used negative chemical ionization reagent gases yields ions that react predominantly by proton transfer or by adduct formation with the substrate, or both [1]. By contrast, the $O^{-\cdot}$ radical anion often undergoes a number of competing reactions with a typical organic molecule under chemical ionization conditions [1, 3]. The radical character of the $O^{-\cdot}$ ion is reflected, for example, in the often facile abstraction of a hydrogen atom with formation of HO^- ions and in the formal $H_2^{+\cdot}$ abstraction leading to a new radical anion and a water molecule. The latter process provides a unique method for the generation of radical anions in the gas phase, for example, the

radical anion of 1,2-dehydrobenzene [4–8] (eq 1) and carbene ions, such as $H_2C=C^{-\cdot}$ [9, 10], ^-CHCN [11–13], and ^-CHNC [13]. The $O^{-\cdot}$ ion is also known to react with carbonyl group [14, 15], leading to displacement of an alkyl radical [16], and even attack on one of the carbon atoms in benzene, with formation of a phenoxide ion and a hydrogen atom, occurs readily (eq 2) [4, 8]:

$$O^{-\cdot} + C_6H_6 \rightarrow C_6H_4^{-\cdot} + H_2O \quad (1)$$
$$\underset{m/z\ 16}{} \qquad \underset{m/z\ 76}{}$$

$$\rightarrow C_6H_5O^- + H^\cdot \quad (2)$$
$$\underset{m/z\ 93}{}$$

The formation of the ^-CHCN ion in the reaction of $O^{-\cdot}$ with acetonitrile [11–13] is clearly a result of a 1,1-$H_2^{+\cdot}$ abstraction. Competing 1,1- and 1,3-$H_2^{+\cdot}$ abstractions have been shown to occur in the reactions with acetone [17] and larger ketones of [16], whereas deuterium labeling has shown that the reaction with benzene involves almost exclusively a 1,2-$H_2^{+\cdot}$ abstraction [4, 6, 7]. As part of a study concerned with the gas-phase acidity of $C_6H_4X^\cdot$ radicals, we reacted the $O^{-\cdot}$ ion with 4-deutero-fluorobenzene and observed

the occurrence of competing $HD^{+ \cdot}$ and $H_2^{+ \cdot}$ abstractions (eq 3) [6]. The occurrence of both these processes in combination with the results for benzene prompted us to perform a more systematic study of the reaction between the $O^{- \cdot}$ ion and site-specifically deuterium-labeled fluorobenzenes to determine the positional origin of the hydrogen/deuterium atoms incorporated in the water molecule expelled from the collision complex:

$$
\begin{array}{c}
O^{- \cdot} \quad + \\
m/z\ 16
\end{array}
\longrightarrow
\begin{cases}
\longrightarrow C_6H_3F^{- \cdot} + HDO \quad (3a) \\
\quad\quad m/z\ 94 \\
\longrightarrow C_6H_2DF^{- \cdot} + H_2O \quad (3b) \\
\quad\quad m/z\ 95
\end{cases}
$$

In a recent report, Meot-Ner and Kafafi [18] applied AM1 calculations to probe the gas-phase acidities of the different positions within monosubstituted aromatic compounds. For fluorobenzene, the calculations indicated that the 2-position should have the same acidity as the 3-position, whereas the 4-position should be approximately 6 kJ mol^{-1} less acidic than the other sites [18]. For chlorobenzene, experiments have shown that the 2-position is approximately 8 kJ mol^{-1} more acidic than the 3- and 4-positions, both being essentially equal with respect to acidity [19]. The results for chlorobenzene and the calculations of the acidity of fluorobenzene suggest that only minor differences are to be expected among the acidities of the various positions in a monosubstituted aromatic compound. Except for the study of chlorobenzene, no attempts have been made to experimentally determine the relative gas-phase acidities of the different positions in a halogen-substituted aromatic compound or to examine whether specificity in the deprotonation of such a species can be obtained. In this study we have reacted a series of negative ions with different isotopomers of fluorobenzene, thus allowing experimental insight to be obtained into the site(s) of deprotonation of this compound as a function of the exothermicity of the process and the nature of the reactant ion.

Experimental

The experiments were performed with Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry [20]. The FT-ICR mass spectrometer used in the present study was designed and constructed at the University of Amsterdam, and the general operating procedure of the instrument has been described elsewhere [21, 22]. The primary negative ions, $O^{- \cdot}$, HO^-/DO^-, and NH_2^-, were generated by dissociative electron capture to N_2O (electron energy 1.2–1.5 eV) [23], H_2O/D_2O (6 eV), and NH_3 (5 eV), respectively. The $C_2H_5NH^-$, $(CH_3)_2N^-$, $C_6H_5^-$, and $CH_3SCH_2^-$ anions were all formed by proton abstraction from the appropriate conjugate acids by the NH_2^- ion. Unwanted ions

were ejected from the FT-ICR cell by applying suitable radiofrequency pulses to the excitation plates of the cell. The total pressure in the instrument was approximately 8×10^{-5} Pa in most of the experiments, as measured with an uncalibrated ionization gauge placed in a side arm of the main vacuum system. The ratio among the partial pressures of the precursor of the primary negative ions, the fluorobenzene, and the conjugate acid of the anion of interest was normally 1.5:1:1. The temperature of the trapping plate situated opposite to the filament side was measured to be about 330 K. The inlet systems, the leak valves, and the vacuum vessel of the instrument were at room temperature.

Most of the chemicals used in the present study were commercially available and were used without further purification. The 4-deutero-fluorobenzene (96% d_1) compound was prepared by reacting 1-fluoro-4-iodobenzene with zinc in a mixture of D_2O and acetic acid anhydride [24]. The 2,5-dideutero-fluorobenzene (96% d_2) compound was likewise synthesized from 1-fluoro-2,5-diiodobenzene. The 2,4,6-trideutero-fluorobenzene compound (99% d_3) was prepared by hydrogen–deuterium exchange between aniline and D_2O/DCl, followed by diazotation and thermal decomposition of the tetrafluoroborate salt of the diazonium species [25]. The 2,6-dideutero-fluorobenzene compound (97% d_2) was prepared by hydrogen–deuterium exchange between 4-bromoaniline and D_2O/DCl, followed by diazotation and thermal decomposition of the tetrafluoroborate salt, yielding 3,5-dideuterio-1-bromo-4-fluorobenzene, which was converted subsequently into the desired fluorobenzene by quenching the Grignard reagent with NH_4Cl dissolved in water [25]. The 3,5-dideutero-fluorobenzene compound (96% d_2) was synthesized by first forming 2,6-dideutero-1-bromo-4-fluorobenzene by hydrogen–deuterium exchange between 4-fluoro-aniline and D_2O/DCl, followed by a Sandmeyer reaction [25]. Quenching of the Grignard reagent of the bromo compound with a NH_4Cl dissolved in water then yielded the 3,5-dideutero-fluorobenzene. The 2,6-dideutero-1,4-difluorobenzene (96% d_2) compound was prepared by hydrogen–deuterium exchange between 4-fluoro-aniline and D_2O/DCl, followed by diazotation and thermal decomposition of the tetrafluoroborate salt of the diazonium species. All labeled fluorobenzenes were purified by preparative gas chromatography (column reoplex 400, temperature 110 °C). The label contents given were determined by electron impact mass spectrometry.

Results

Reactions of Negative Ions with Fluorobenzene

The $O^{- \cdot}$ radical anion reacts with fluorobenzene to form the product ions shown in eqs 4–7, where the percentages represent the relative abundances of the

product ions after a reaction time of 200 ms:

$$O^{-\cdot} + C_6H_5F \xrightarrow{\approx 5\%} \underset{m/z\ 17}{HO^-} + C_6H_4F^{\cdot}$$

$$\Delta H_r^{\circ} \approx -3\ kJ\ mol^{-1} \quad (4)$$

$$\xrightarrow{\approx 45\%} \underset{m/z\ 94}{C_6H_3F^-} + H_2O \quad (5)$$

$$\xrightarrow{\approx 15\%} \underset{m/z\ 95}{C_6H_4F^-} + HO^{\cdot}$$

$$\Delta H_r^{\circ} \approx +20\ kJ\ mol^{-1} \quad (6)$$

$$\xrightarrow{\approx 35\%} \underset{m/z\ 111}{C_6H_4FO^-} + H^{\cdot} \quad (7)$$

The predominant reactions are formal $H_2^{+\cdot}$ abstraction (eq 5) and attack on a carbon atom, leading to expulsion of a hydrogen atom from the collision complex (eq 7). Hydrogen atom abstraction with formation of HO^- is estimated to be near thermoneutral (thermochemical data have been taken from Lias et al. [26]) and occurs only to a minor extent (eq 4). The HO^- ions react subsequently with fluorobenzene by proton transfer, with formation of $C_6H_4F^-$ ions, and generate very minor amounts of $C_6H_5O^-$ ions by nucleophilic attack on the fluorine-bearing carbon atom [27–29]. The $C_6H_4F^-$ ions are also generated by proton transfer to the $O^{-\cdot}$ ion (eq 6), even though this process is endothermic by approximately 20 kJ mol⁻¹ ($\Delta H_{acid}^{\circ}(HO^{\cdot})$ = 1599 ± 2 kJ mol⁻¹) [26]. Dissociative electron capture by N_2O is known to result in $O^{-\cdot}$ ions with an average kinetic energy of 0.38 eV when the energy of the ionizing electrons is 1.5 eV (see Experimental) [23]. In the present experiments, the $O^{-\cdot}$ ions were isolated 100–200 ms after their formation, implying that the percentages given in eqs 4–7 represent the product ion distribution for reactant ions with a kinetic energy above thermal.

The relative abundances of the ions formed by proton or deuteron abstraction and by competing $H_2^{+\cdot}$, $HD^{+\cdot}$, and $D_2^{+\cdot}$ abstractions in the reactions of the $O^{-\cdot}$ ion with the deuterium-labeled fluorobenzenes are shown in Table 1. The relative abundances of the ions formed by loss of a hydrogen or a deuterium atom from the collision complex are shown in Table 2.

The NH_2^-, $C_2H_5NH^-$, $(CH_3)_2N^-$, $C_6H_5^-$ and $CH_3SCH_2^-$ anions react with fluorobenzene exclusively by proton transfer. The reaction of the three nitrogen-containing anions occurred readily, with conversion into products being complete after a reaction time of 400 ms for the NH_2^- ion at a pressure of approximately 3×10^{-5} Pa of C_6H_5F (see Experimental). Conversion into products was 80% to 90% after 400 ms for the $C_2H_5NH^-$ and $(CH_3)_2N^-$ ions at the same pressure of fluorobenzene. The $C_6H_5^-$ and $CH_3SCH_2^-$ ions reacted much more slowly with fluorobenzene than the nitrogen-containing anions, as indicated by conversion into products, which was 25% for

Table 1. Relative extent of H^+, $H_2^{+\cdot}/D^+$, $HD^{+\cdot}$, and $D_2^{+\cdot}$ abstraction in the reactions of the $O^{-\cdot}$ radical anion with deuterium-labeled fluorobenzenes[a]

Compound	Abstraction[b] of			
	H^+	$H_2^{+\cdot}/D^+$	$HD^{+\cdot}$	$D_2^{+\cdot}$
$4\text{-}D\text{-}C_6H_4\text{-}F$	10	50	40	—
$2,6\text{-}D_2\text{-}C_6H_3\text{-}F$	3	40	50	7
$3,5\text{-}D_2\text{-}C_6H_3\text{-}F$	13	25	55	7
$2,5\text{-}D_2\text{-}C_6H_3\text{-}F$	12	32	50	6
$2,4,6\text{-}D_3\text{-}C_6H_2\text{-}F$	2	15	68	15

[a] Reaction time 200–300 ms (see text); values have been corrected for incomplete labeling and ^{13}C-isotope contributions.
[b] Expressed as percent of the total yield of product ions from these processes.

$C_6H_5^-$ and 5% for $CH_3SCH_2^-$ after 400 ms.

The relative amounts of the $[M - H]^-$ and $[M - D]^-$ ions formed in the reactions of the anions with a series of site-specific deuterium-labeled fluorobenzenes are shown in Table 3. The values shown for the NH_2^-, $C_2H_5NH^-$, and $(CH_3)_2N^-$ ions represent the relative amounts of $[M - H]^-$ and $[M - D]^-$ ions generated within a reaction time of 200–400 ms, whereas the results for the $C_6H_5^-$ and $CH_3SCH_2^-$ ions are relative amounts of $[M - H]^-$ and $[M - D]^-$ ions formed within 0.5–1 s.

The ratio between the abundances of the $[M - H]^-$ and $[M - D]^-$ ions remained nearly constant with reaction time in most of the experiments. A slight increase in the abundance of the $[M - D]^-$ ions relative to that of the $[M - H]^-$ ions at reaction times longer than 1 s was observed in some of the experiments with the $C_6H_5^-$ and $CH_3SCH_2^-$ ions, which react slowly with fluorobenzene. The change in the relative abundances varied from experiment to experiment, implying that the slight increase in the relative amount of the $[M - D]^-$ ions with reaction time was caused by hydrogen–deuterium exchange between the $[M - H]^-$ ions from the labeled fluorobenzenes and traces of water inevitably present in the FT-ICR cell.
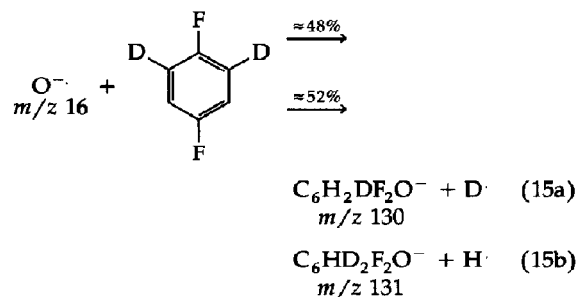
Table 2. Relative extent of loss of a hydrogen and a deuterium atom from the collision complex formed in the reactions of the $O^{-\cdot}$ ion with the labeled fluorobenzenes

Compound	Percent loss of H and D atoms			
	Experimental results[a]		Statistical results[b]	
	H	D	H	D
$4\text{-}D\text{-}C_6H_4\text{-}F$	70	30	80	20
$2,6\text{-}D_2\text{-}C_6H_3\text{-}F$	75	25	60	40
$3,5\text{-}D_2\text{-}C_6H_3\text{-}F$	40	60	60	40
$2,4,6\text{-}D_3\text{-}C_6H_2\text{-}F$	65	35	40	60

[a] The relative abundances of the ions formed by loss of H and D atoms from the collision complex were independent of reaction time; values have been corrected for incomplete labeling and contributions from the ^{13}C-isotope of the ions generated by elimination of a D atom.
[b] Calculated on the assumption that the $O^{-\cdot}$ ion attacks the unsubstituted carbon atoms with an equal probability.

Table 3. Relative extent of proton and deuteron abstraction[a] in the reactions of anions with labeled fluorobenzenes[b]

Anion (A⁻)	ΔH°_{acid} (HA)[c] (kJ mol⁻¹)	4-D–C₆H₄–F		2,6-D₂–C₆H₃–F		3,5-D₂–C₆H₃–F		2,4,6-D₃–C₆H₂–F	
		[M − H]⁻	[M − D]⁻	[M − H]⁻	[M − D]⁻	[M − H]⁻	[M − D]⁻	[M − H]⁻	[M − D]⁻
NH₂⁻	1689	80	20	45	55	85	15	45	55
C₆H₅⁻	1677	85	15	35	65	90	10	25	75
C₂H₅NH⁻	1671	80	20	20	80	85	15	30	70
(CH₃)₂N⁻	1658	80	20	30	70	85	15	15	85
CH₃SCH₂⁻	1645	95	5	20	80	95	5	10	90

[a] Expressed as a percent of the total yield of the [M − H]⁻ and [M − D]⁻ ions.
[b] See text.
[c] Values from ref 26.

This is in agreement with the result that the conjugate base of fluorobenzene undergoes facile consecutive exchange of all four hydrogen atoms for deuterium atoms in the presence of D_2O, as shown in eq 8 and Figure 1 (see refs 3 and 30 for a discussion of hydrogen–deuterium exchange reactions of anions in the gas phase):

$$C_6H_4F^- \xrightarrow{D_2O} \to \to \to C_6D_4F^- \quad (8)$$
$$\underset{m/z\ 95}{} \qquad\qquad \underset{m/z\ 99}{}$$

Reactions of Negative Ions with 1,4-Difluorobenzene

The reactions of the O^- ion with 1,4-difluorobenzene are shown in eqs 9–13, together with the product ion distribution obtained after a reaction time of 200 ms. Nucleophilic attack on a fluorine-bearing carbon atom [27–29] (eqs 9 and 10) occurs in addition to H_2^+ abstraction (eq 11) and elimination of a hydrogen atom from the collision complex (eq 13). Attack on a fluo-

rine-substituted carbon atom leads to fewer F^- ions than $C_6H_4FO^-$ ions, even though the former process is more exothermic than the latter reaction [26]. Proton abstraction (eq 12) is exothermic by 8 kJ mol⁻¹ (vide infra) and, as expected, more significant than in the reactions with fluorobenzene (see eq 6):

$$O^{-\cdot} + 1,4\text{-}F_2C_6H_4 \overset{\approx 5\%}{\to} F^- + C_6H_4FO^{\cdot}$$
$$\underset{m/z\ 16}{} \qquad\qquad\qquad \underset{m/z\ 19}{}$$
$$\Delta H^\circ_r \approx -191\ \text{kJ mol}^{-1} \quad (9)$$

$$\overset{\approx 10\%}{\to} C_6H_4FO^- + F^{\cdot}$$
$$\underset{m/z\ 111}{}$$
$$\Delta H^\circ_r \approx -92\ \text{kJ mol}^{-1} \quad (10)$$

$$\overset{\approx 30\%}{\to} C_6H_2F_2^{-\cdot} + H_2O \quad (11)$$
$$\underset{m/z\ 112}{}$$

$$\overset{\approx 35\%}{\to} C_6H_3F_2^- + HO^{\cdot}$$
$$\underset{m/z\ 113}{}$$
$$\Delta H^\circ_r \approx -8\ \text{kJ mol}^{-1} \quad (12)$$

$$\overset{\approx 20\%}{\to} C_6H_3F_2O^- + H^{\cdot} \quad (13)$$
$$\underset{m/z\ 129}{}$$

With 2,6-dideutero-1,4-difluorobenzene, abstraction of D_2^+ is observed to some extent (eq 14):

$$O^- + \qquad\qquad \longrightarrow C_6H_2F_2^{-\cdot} + D_2O \quad (14)$$
$$\underset{m/z\ 16}{} \qquad\qquad\qquad\qquad \underset{m/z\ 112}{}$$

Competing abstractions of $HD^{+\cdot}$ and $H_2^{+\cdot}$ may occur also in the reactions of the O^- ion with this compound, but the determination of the relative importance of these processes is hampered by the occurrence of other reactions. For example, attack on a fluorine-bearing carbon atom yields a $C_6H_2D_2FO^-$ (m/z 113) ion that is isobaric with the $C_6HDF_2^-$ ion generated by $HD^{+\cdot}$ abstraction. Elimination of a deuterium atom occurs nearly to the same extent as loss of a hydrogen atom (eq 15) from the collision complex, indicating

Figure 1. The hydrogen–deuterium exchange between the conjugate base of fluorobenzene and D_2O followed as a function of reaction time. The lines represent a graphical interpolation between the individual data points; d_0–d_4 indicate the $C_6H_4F^-$ to $C_6D_4F^-$ ions.

that this process is not associated with a significant isotope effect:

$$C_6H_2DF_2O^- + D \cdot \quad (15a)$$
$$m/z \ 130$$

$$C_6HD_2F_2O^- + H \cdot \quad (15b)$$
$$m/z \ 131$$

The NH_2^-, $C_2H_5NH^-$, $(CH_3)_2N^-$, $C_6H_5^-$, and $CH_3SCH_2^-$ anions react with 2,6-dideutero-1,4-di-fluorobenzene only by proton or deuteron abstraction. The relative amounts of the $[M - H]^-$ and $[M - D]^-$ ions generated provide a measure of the intramolecular kinetic isotope effect associated with the acid/base reaction between the anions and the 1,4-difluoro-benzene compound. The isotope effect appears small for the three nitrogen-containing ions, whereas pronounced effects are observed for the two carbanions (Table 4).

The estimated exothermicity of the proton transfer reaction is also shown in Table 4 and is based on redetermination of the gas-phase acidity of 1,4-di-fluorobenzene. The previous value was placed roughly between the acidities of CH_3OH ($\Delta H_{acid}^\circ = 1592 \pm 8$ kJ mol^{-1}) and C_2H_5OH ($\Delta H_{acid}^\circ = 1579 \pm 8$ kJ mol^{-1}) [27]. During the present study, the reaction between the CH_3O^- ion and 1,4-difluorobenzene was observed to be reversible (eq 16 and Figure 2), thus allowing more accurate determination of the gas-phase acidity of this compound:

$$CH_3O^- + \quad \rightleftharpoons [M - H]^- + CH_3OH \quad (16)$$
$$m/z \ 31 \qquad\qquad\qquad m/z \ 113$$
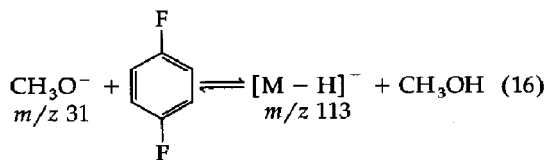
Table 4. Intramolecular kinetic isotope effect associated with the proton/deuteron abstraction reactions between anions and 2,6-dideutero-1,4-difluorobenzene[a]

Anion	$-\Delta H_f^\circ$[b] (kJ mol^{-1})	k_H/k_D[c]
NH_2^-	97	1.3 ± 0.1
$C_6H_5^-$	85	1.5 ± 0.1
$C_2H_5NH^-$	79	1.3 ± 0.2
$(CH_3)_2N^-$	66	1.0 ± 0.1
$CH_3SCH_2^-$	53	2.1 ± 0.1

[a] See text; values have been corrected for incomplete labeling and ^{13}C-isotope contributions.
[b] Estimated from data given in ref 26 and ΔH_{acid}°(1,4-difluoro-benzene) = 1592 ± 8 kJ mol^{-1} (see text).
[c] Average of three to six experiments.
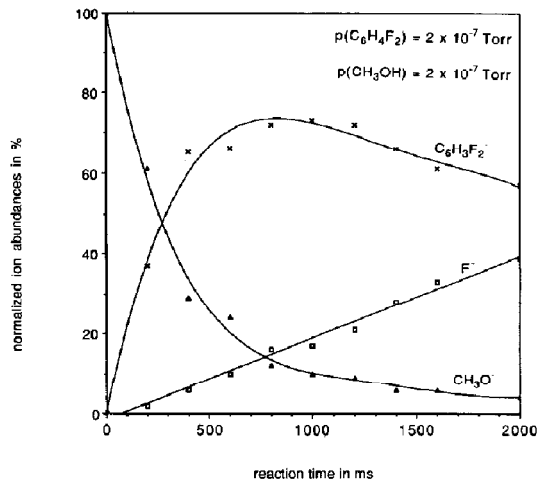
Figure 2. Normalized ion abundances as a function of time for the reaction between the CH_3O^- ions and 1,4-difluorobenzene (see text).

In addition to proton transfer, the reaction between the methoxide ion and 1,4-difluorobenzene is known to yield F^- ions by nucleophilic aromatic substitution and minor amounts of $C_6H_4FO^-$ ions by a subsequent S_N2 reaction in the collision complex [27–29]. The results in Figure 2 indicate that the ratio between the abundances of the CH_3O^- ion and the conjugate base of 1,4-difluorobenzene is approximately constant at reaction times longer than 1 s despite the nucleophilic aromatic substitution reaction. Based on the results in Figure 2, the equilibrium constant for eq 16 is determined to be 13.6, which results in ΔG_{acid}°(1,4-difluorobenzene) = 1558 ± 8 kJ mol^{-1} if the temperature of the system is assumed to be 300 K (see Experimental). The entropy change associated with removal of a proton from 1,4-difluorobenzene (ΔS_{acid}°) is estimated to be 114 J K^{-1} mol^{-1} [31, 32], thus leading to ΔH_{acid}°(1,4-difluorobenzene) = 1592 ± 8 kJ mol^{-1}, with $T = 300$ K.

Discussion

Abstraction of $H_2^{+\cdot}$ from Fluorobenzene

The mechanism advanced for $H_2^{+\cdot}$ abstraction from benzene involves initial hydrogen atom abstraction, yielding a $[HO^- + C_6H_5^\cdot]^*$ ion/molecule complex [3, 7]. Subsequently, proton abstraction occurs from the 2-position in the newly generated phenyl radical, with formation of the radical anion of 1,2-dehydrobenzene. The $H_2^{+\cdot}$ abstraction from fluorobenzene can also be formulated as hydrogen atom abstraction followed by proton abstraction. Hydrogen atom abstraction may occur at the different sites in fluorobenzene and thus lead to any of the three isomeric $C_6H_4F^\cdot$ radicals shown in Scheme I.
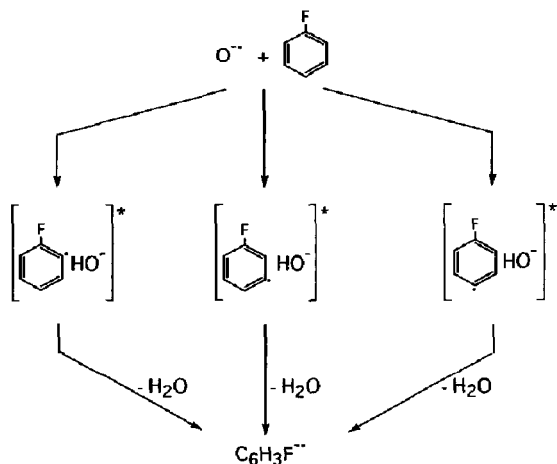
Scheme I. Proposed mechanism for H_2^+ abstraction from fluorobenzene.

Scheme II. Proposed pathway for the formation of the radical anion of 1-fluoro-2,6-dehydrobenzene in the reaction of the O^- radical anion with 2,6-dideutero-fluorobenzene.

The gas-phase acidity of the 2-position in the phenyl radical has been placed recently at 1592 ± 8 kJ mol^{-1} [6, 7]. The phenyl radical is thus substantially more acidic in the gas phase than water ($\Delta H_{acid}^\circ = 1635 \pm 2$ kJ mol^{-1}) and also more acidic than fluorobenzene ($\Delta H_{acid}^\circ = 1620 \pm 8$ kJ mol^{-1}) (see above). The different positions within any of the three isomeric $C_6H_4F^{\cdot}$ radicals are therefore likely to be more acidic than water in the gas phase, and as a result, the hydroxide ion in the $[HO^- + C_6H_4F^{\cdot}]^*$ complexes may abstract a proton from any of the sites in a given radical (Scheme I).

An accurate determination of the relative extent of H_2^+ abstraction from the labeled fluorobenzenes is hindered owing to the occurrence of endothermic D^+ transfer driven by the excess kinetic energy of the reactant O^- ions (see eq 6 and Results). In the reactions with the 2,6-dideutero- and 2,4,6-trideutero-labeled compounds, scarcely any H^+ transfer occurs, indicating that the O^- ion mainly abstracts a proton from the 2-position in fluorobenzene (vide infra). Based on this result, it can be anticipated that D^+ abstraction from the 3,5-dideutero-compound is negligible, suggesting that the results for this compound are close to representing the relative importance of the H_2^+, HD^+, and D_2^+ abstractions. The experimental result (29:63:8) (see also Table 1) is very close to the ratio estimated for nonselective abstraction of H_2^+, HD^+, and D_2^+ (30:60:10), providing some support for the suggestion that the initial hydrogen atom abstraction leads to the isomeric $C_6H_4F^{\cdot}$ radicals and that proton abstraction can occur from any of the positions in a given radical (Scheme I).

The competing H_2^+, HD^+, and D_2^+ abstractions can lead, in principle, to the radical anions of isomeric fluorine-substituted 1,2-, 1,3- and 1,4-dehydrobenzenes. For example, D_2^+ abstraction from 2,6-dideutero-fluorobenzene may yield the radical anion of
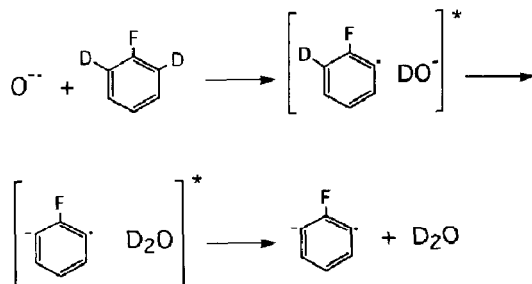
1-fluoro-2,6-dehydrobenzene, provided that the discrete steps leading to loss of D_2O from the collision complex are essentially irreversible (Scheme II). This is an essential requirement, because reversibility in the proton transfer step may cause the positional specificity of the label to be lost and lead to the generation of, for example, the radical anion of 1-fluoro-2,5-dehydrobenzene, as indicated in Scheme III. It should be mentioned, however, that the generation of isomeric radical anions in the reaction of O^- with fluorobenzene is indicated by our previously reported finding that the ions formed by H_2^+ abstraction from 4-deutero-fluorobenzene (eq 3a) do not undergo hydrogen–deuterium exchange with D_2O, whereas the ions generated by HD^+ abstraction (eq 3b) react slowly with D_2O by exchange accompanied by isomerization to less basic radical anions [6]. Based on the present results, it is not possible to reach a conclusion as to the structures of the ions generated by H_2^+, HD^+, and D_2^+ abstraction from the different labeled fluorobenzenes. Nevertheless, the results in Table 1 reveal that in a formal sense 1,3- and 1,4-H_2^+ abstractions from fluorobenzene may be as favorable as the 1,2-H_2^+ abstrac-
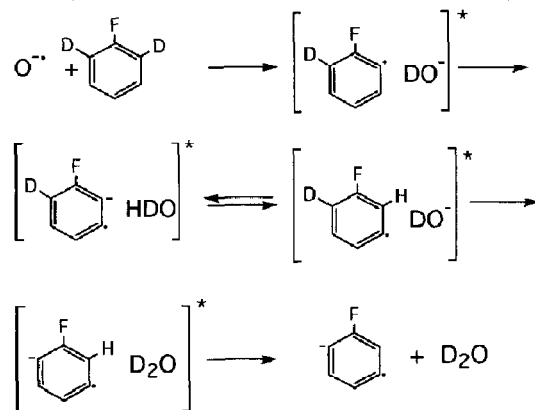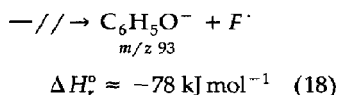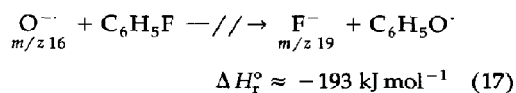

Scheme III. Proposed pathway for the formation of the radical anion of 1-fluoro-2,5-dehydrobenzene in the reaction of the O^- radical anion with 2,6-dideutero-fluorobenzene.

tion, in contrast to the result for the reaction of the $O^{-\cdot}$ radical anion with benzene.

Attack of the $O^{-\cdot}$ Ion on a Carbon Atom in Fluorobenzene

The mechanistic aspects of nucleophilic aromatic substitution in gas-phase reactions of anions with fluorine-containing compounds have been discussed in detail elsewhere [27–29]. With fluorobenzene, the CH_3O^- and $C_2H_5O^-$ ions react slowly to form F^- and $C_6H_5O^-$ ions, whereas the attack on a fluorine-substituted carbon atom is more facile when a difluorobenzene is the substrate [27]. In line herewith, attack of the $O^{-\cdot}$ ion on a substituted carbon atom occurs in the reaction with the 1,4-difluorobenzene compound but not in the reaction with C_6H_5F, even though the formation of F^- or $C_6H_5O^-$ ions is exothermic [26] (eqs 17 and 18):

$$\underset{m/z\ 16}{O^{-\cdot}} + C_6H_5F \longrightarrow // \longrightarrow \underset{m/z\ 19}{F^-} + C_6H_5O^\cdot$$

$$\Delta H_r^o \approx -193\ \mathrm{kJ\ mol^{-1}} \quad (17)$$

$$\longrightarrow // \longrightarrow \underset{m/z\ 93}{C_6H_5O^-} + F^\cdot$$

$$\Delta H_r^o \approx -78\ \mathrm{kJ\ mol^{-1}} \quad (18)$$

In the reaction with fluorobenzene, three isomeric $C_6H_4FO^-$ ions can be formed, as shown in Scheme IV. The estimated reaction enthalpies [26] also given in Scheme IV show that the formation of the 3-fluorophenoxide ion is approximately 20 kJ mol^{-1} more exothermic than generation of the 2- and 4-fluorophenoxide ions.

The results for an attack on an unsubstituted carbon atom in 4-deutero-fluorobenzene reveal a more pronounced loss of a deuterium atom from the collision complex than expected for a nonselective attack of the $O^{-\cdot}$ ion (see Table 2). A more significant loss of a deuterium than of a hydrogen atom than predicted from a statistical process is also observed in the reaction with 3,5-dideutero-fluorobenzene. A complementary result is obtained for the 2,4,6-trideutero-

Scheme IV. Proposed mechanism for attack of the $O^{-\cdot}$ radical anion on an unsubstituted carbon atom in fluorobenzene.

compound, whereas loss of a deuterium atom in the reaction with 2,6-dideutero-fluorobenzene occurs to a lesser extent than estimated for a nonselective process. The labeling experiments thus reveal that attack of the $O^{-\cdot}$ ion on the 2-position is less favored than reaction at the 3- and 4-positions.

The absence of a significant isotope effect on the loss of a hydrogen or deuterium atom in the reaction of $O^{-\cdot}$ with 2,6-dideutero-1,4-difluorobenzene (eq 15) indicates that bond formation between the reactant ion and a carbon atom is the rate-determining step in the process. In the reaction with fluorobenzene, attack on the 2-position may result in the species a shown in Scheme IV. Although the charge and radical distributions within a–c in Scheme IV are unknown, it may be anticipated that the electronic repulsion between the oxygen and fluorine atom in a can cause the energy barrier toward attack at the 2-position to be slightly higher than the barriers for attack on the 3- and 4-positions, thus leading to the observed preference for reaction at these sites.

Proton Abstraction from Fluorobenzene

According to the AM1 calculations by Meot-Ner and Kafafi [18], only minor differences in the gas-phase acidities of the various positions within a monosubstituted benzene compound are to be expected. The relative acidities of the different positions within a molecule have been probed in several instances by performing hydrogen–deuterium exchange reactions between the deprotonated species and a suitable exchange reagent [3, 29, 30]. For example, all hydrogen atoms in the anion generated by proton abstraction from one of the ring positions in 4-F–C_6H_4–OCH_3 are exchanged for deuterium atoms in the presence of D_2O [29]. The exchange of the hydrogen atoms from the aromatic part of the molecule, however, proceed faster than the exchange of the hydrogen atoms from the methyl group, implying a lower acidity of this part of the molecule than of the aromatic ring positions. In view of such findings, the facile exchange of all hydrogen atoms of the conjugate base of fluorobenzene with D_2O (see Figure 1) could be taken as support for the prediction that the different positions within fluorobenzene should be almost equal in acidity. An equally thermochemical acidity of the various positions in fluorobenzene could mean that the relative extent of the $[M - H]^-$ and $[M - D]^-$ ions is determined solely by the isotope effect on the acid/base reaction. An isotope effect is to be expected, as indicated by the results for the reactions of the anions with 2,6-dideutero-1,4-difluorobenzene. For this compound, the isotope effect is small for the NH_2^-, $C_2H_5NH^-$, and $(CH_3)_2N^-$ ions, whereas a pronounced effect is observed for the $C_6H_5^-$ and $CH_3SCH_2^-$ ions (Table 4).

The $[M - H]^-$ and $[M - D]^-$ ions are formed in the reactions of the NH_2^-, $C_2H_5NH^-$, and $(CH_3)_2N^-$ ions with 4-D–C_6H_4–F (Table 3) in an abundance ratio
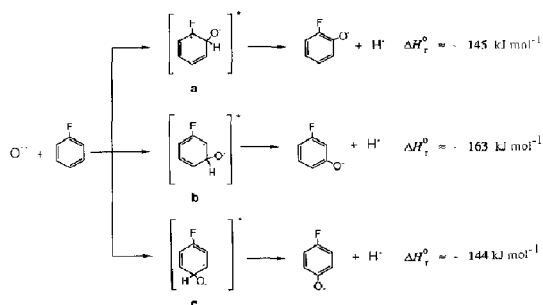
equal to that expected for a nonselective proton and deuteron abstraction (80% $[M - H]^-$ and 20% $[M - D]^-$). In the reaction with the $C_6H_5^-$ and $CH_3SCH_2^-$ ions, deuteron abstraction occurs to a lower extent (15% and 5%, respectively) than expected for a nonselective process. These results could be in keeping with a negligible isotope effect for the three nitrogen-containing anions and a significant isotope effect in the reaction with the two carbanions. Such behavior, however, would result in similar abundance ratios for the $[M - H]^-$ and $[M - D]^-$ ions generated from the 2,6-dideutero-fluorobenzene and the 3,5-dideutero-compound, in contrast to observation (Table 3). In the reactions with the former compound, a larger relative amount of the $[M - D]^-$ ions are generated than expected from statistical abstraction of a proton and a deuteron, which would result in 60% $[M - H]^-$ and 40% $[M - D]^-$ ions. Furthermore, the preference for abstracting a deuteron from the 2-position increases roughly as the basicity of the anion decreases (Table 3). Complementary results are obtained for the 3,5-dideutero-labeled compound in the sense that deuteron abstraction occurs to a minor extent compared with proton abstraction, and with the weakest base, $CH_3SCH_2^-$, only approximately 5% $[M - D]^-$ ions are generated. In addition, in the reactions of the anions with the 2,4,6-trideutero-compound, deuteron transfer becomes more important as the basicity of the anion decreases. In conclusion, the present results indicate that abstraction of a proton from the 2-position is preferred to abstraction of a proton from the 3- and 4-positions within fluorobenzene.

The abundances of the $[M - H]^-$ and $[M - D]^-$ ions reflect, of course, the relative rates of the processes leading to these ions. In view of the occurrence of an isotope effect on the reaction with 2,6-dideutero-1,4-difluorobenzene, it is to be expected that a kinetic barrier exists for the deprotonation of fluorobenzene. Whether the trend in the ratios of the abundances of the $[M - H]^-$ and $[M - D]^-$ ions can be correlated with the thermochemical acidity of the different sites within fluorobenzene will then depend on the relative heights of the barriers toward proton abstraction from the 2-, 3-, and 4-positions. The heights of these energy barriers will in general terms be determined by the stability of the generated anions and the intrinsic energy barrier (i.e., the barrier for the hypothetical situation where the change in the free energy for the process is equal to zero) [33, 34] toward abstracting a proton from a given position. In the absence of arguments for postulating a larger intrinsic barrier toward proton abstraction from the 3- and 4-positions than for the 2-position in fluorobenzene, it can be concluded that the trend in the ratios of abundances of the $[M - H]^-$ and $[M - D]^-$ ions from the labeled fluorobenzenes is a result of a more favorable thermochemistry for proton/deuteron abstraction from the 2-position than from the other positions. In other words, the results in Table 1 indicate that the 2-position is the most acidic site within fluorobenzene and that the literature value of 1620 ± 8 kJ mol^{-1} for $\Delta H^\circ_{acid}(C_6H_5F)$ refers to this position. Whether the 3- and 4-positions in fluorobenzene are similar or different with respect to acidity remains, however, to be clarified.

Acknowledgment

References

1. Harrison, A. G. *Chemical Ionization Mass Spectrometry*; CRC: Boca Raton, FL, 1983.
2. Busch, K. L.; Glish, G. L.; McLuckey, S. A. *Mass Spectrometry/Mass Spectrometery*; Verlag Chemie: Weinheim, 1988.
3. Nibbering, N. M. M. *Adv. Phys. Org. Chem.* **1988**, *24*, 1–53.
4. Bruins, A. P.; Ferrer-Correia, A. J. V.; Harrison, A. G.; Jennings, K. R.; Mitchum, R. K. *Adv. Mass Spectrom.* **1978**, *7A*, 355–358.
5. Leopold, D. G.; Miller, A. E. S.; Lineberger, W. C. *J. Am. Chem. Soc.* **1986**, *108*, 1379–1384.
6. Matimba, H. E. K.; Crabbendam, A. M.; Ingemann, S.; Nibbering, N. M. M. *J. Chem. Soc. Chem, Commun.* **1991**, 644–645.
7. Guo, Y.; Grabowski, J. J. *J. Am. Chem. Soc.* **1991**, *113*, 5923–5931.
8. VanOrden, S. L.; Malcomson, M. E.; Buckner, S. W. *Anal. Chim. Acta* **1991**, *246*, 199–210.
9. Dawson, J. H. J.; Nibbering, N. M. M. *J. Am. Chem. Soc.* **1978**, *100*, 1928–1929.
10. Guo, Y.; Grabowski, J. J. *Int. J. Mass Spectrom. Ion Processes* **1990**, *97*, 253–264.
11. Dawson, J. H. J.; Nibbering, N. M. M. *Int. J. Mass Spectrom. Ion Processes* **1980**, *33*, 3–19.
12. Grabowski, J. J.; Melly, S. J. *Int. J. Mass Spectrom. Ion Processes* **1987**, *81*, 147–164.
13. Matimba, H. E. K.; Crabbendam, A. M.; Ingemann, S.; Nibbering, N. M. M. *Int. J. Mass Spectrom. Ion Processes* **1992**, *114*, 85–97.
14. van der Wel, H.; Nibbering, N. M. M. *Int. J. Mass Spectrom. Ion Processes* **1986**, *72*, 145–153.
15. van der Wel, H.; Nibbering, N. M. M. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 479–490.
16. Marshall, A.; Tkaczyk, H.; Harrison, A. G. *J. Am. Soc. Mass Spectrom.* **1991**, *2*, 292–298.
17. Dawson, J. H. J.; Noest, A. J.; Nibbering, N. M. M. *Int. J. Mass Spectrom. Ion Processes* **1979**, *30*, 189–191.
18. Meot-Ner (Mautner), M.; Kafafi, S. A. *J. Am. Chem. Soc.,* **1988**, *110*, 6297–6303.
19. Wenthold, P. G.; Paulino, J. A.; Squires, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 7414–7415.
20. Marshall, A. G.; Verdun, F. R. *Fourier Transforms in NMR, Optical and Mass-Spectrometry*; Elsevier: Amsterdam, 1990.
21. Koning, L. J. de; Kort, C. W. F.; Pinkse, F. A.; Nibbering, N. M. M. *Int. J. Mass Spectrom. Ion Processes* **1989**, *95*, 71–92, and references cited therein.
22. Peerboom, R. A. L.; Ingemann, S.; Nibbering, N. M. M.; Liebman, J. F. *J. Chem. Soc. Perkin Trans. 2* **1990**, 1825–1828, and references cited therein.
23. Chantry, P. J. *J. Phys. Chem.* **1969**, *51*, 3369–3379.
24. Bak, B. *J. Org. Chem.* **1956**, *21*, 797–798.

25. Vogel, A. I., *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: New York, 1989.

26. Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl. 1.

27. Briscese, S. M. J.; Riveros, J. M. *J. Am. Chem. Soc.* **1975**, *97*, 230–231.

28. Ingemann, S.; Nibbering, N. M. M.; Sullivan, S. A.; DePuy, C. H. *J. Am. Chem. Soc.* **1982**, *104*, 6520–6527.

29. Ingemann, S.; Nibbering, N. M. M. *J. Org. Chem.* **1983**, *48*, 183–191.

30. Grabowski, J. J.; DePuy, C. H.; Doren, J. M. van; Bierbaum, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 7384–7389.

31. Bartmess, J. E.; McIver, Jr., R. T. In *Gas Phase Ion Chemistry*, Vol. 2; Bowers, M. T., Ed.; Academic Press: New York, 1979; p 87.

32. Cumming, J. B.; Kebarle, P. *Can. J. Chem.* **1978**, *56*, 1–9.

33. Marcus, R. A.; Sutin, N. *Biochim. Biophys. Acta* **1985**, *811*, 265–322.

34. Han, C. C.; Brauman, J. I. *J. Am. Chem. Soc.* **1989**, *111*, 6491–6496.