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Regioselective Activation of Ipso and Ortho Positions in Chlorobenzene by FeO^+

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Abstract: The gas-phase reactions of phenyl halides C_6H_5X (X = F−I) with FeO^+ are examined using tandem mass spectrometry. The predominant dissociations involve losses of CO (X = F−I), HX (X = F, Cl), and X (X = I). For chlorobenzene **1**, mechanistic insight is obtained from detailed labeling experiments, MS/MS studies, and comparison with structural isomers generated via independent routes. The experiments demonstrate that ring hydroxylation to a phenol, a reaction typical for FeO^+ and unsubstituted benzene, does not occur for **1**/FeO^+. Instead, initial coordination of FeO^+ at the functional group ("docking") predominates, thereby enforcing activation of the adjacent ipso and ortho positions, while meta and para positions do not participate.

Introduction

Aromatic halides stemming from anthropogenic as well as from natural sources are ubiquitous in natural ecosystems. Therefore, the determination of their biodegradation routes, including in particular cleavage of carbon−halogen bonds, is of profound interest.[1] Important metabolic pathways involve oxidations catalyzed by transition metals incorporated in intra- and extracellular enzymes such as cytochrome P-450 and other powerful oxidation catalysts.[2,3] Presently, it is the accepted view that cytochrome P-450 mediated metabolism of chlorobenzene,[4] fluorobenzene,[5] and bromobenzene[6] occurs via preferential hydroxylation in ortho and para positions in the first step. In very few cases, an ipso substitution of the halide by a hydroxy group has been reported.[7] However, many metabolic studies lack mass balances and often only address the monohydroxylated products. Hence, C−X bond cleavage in the ipso position might have escaped detection.

A complementary way to elucidate mechanistic details of metal-mediated reactions is provided by conducting experiments in the diluted gas phase of a mass spectrometer. In these studies, the complexity of the active enzyme that mediates the decomposition of arenes is reduced to a single FeO^+ unit serving as the simplest conceivable model system.[8,9] This approach allows the uncovering of the intrinsic chemical behavior of the reactive metal−oxo species and to probing of the electronic structure role under rigorous exclusion of many complicating parameters such as solvent effects, counterions, ligands, or enzyme backbones. For this reason, the reactions of FeO^+ with benzene,[10,11] alkylbenzenes,[10b,12] donor-substituted benzenes,[13,14] and some aromatic heterocycles[15] have been studied recently. The present paper investigates the FeO^+-mediated activation and degradation of chlorobenzene **1** in detail. Trends within the series of monosubstituted phenyl halides are uncovered by a comparison of **1** with its congeners fluorobenzene (**2**), bromobenzene (**3**), and iodobenzene (**4**).

Experimental Section

Substrates. Most unlabeled compounds are commercially available and were used without further purification. [2-D_1]-Chlorobenzene (**1a)** and [4-D_1]-chlorobenzene (**1b**) were synthesized by preparation of Grignard reagents from 2-bromochlorobenzene and 4-bromochlorobenzene, respectively, followed by deuteriolysis with CH_3OD. [3,5-D_2]-Chlorobenzene (**1c**), [2,4,6-D_3]-chlorobenzene (**1d**), and [1-$^{13}C_1$]-chlorobenzene (**1f**) were prepared by Sandmeyer reactions of the corresponding anilines with $HCl/NaNO_2/CuCl$ (35% yield on a 1 mmol scale).[16] [2,4,6-D_3]-Aniline was synthesized by repeated H/D exchange of aniline with D_2O catalyzed by D_2SO_4.[17] Likewise, [3,5-D_2]-aniline was made by 3-fold D/H exchange of [2,3,4,5,6-D_5]-aniline in an excess

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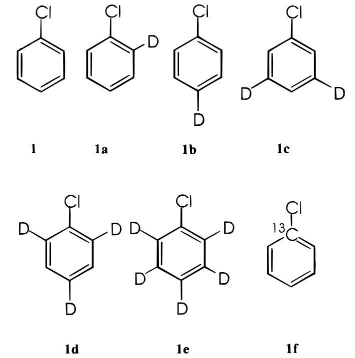
of water catalyzed by H_2SO_4.[17] [2,3,4,5,6-D_5]-Aniline was obtained in two steps via nitration of [D_6]-benzene with HNO_3/H_2SO_4 and subsequent reduction of [2,3,4,5,6-D_5]-nitrobenzene with $NaBH_4$ on Pd/C.[18] [1-$^{13}C_1$]-Aniline was obtained from [1-$^{13}C_1$]-phenyl triflate via a palladium-catalyzed amination using benzophenone imine, $Pd(OAc)_2$, Cs_2CO_3, and 1′-(*N*,*N*-dimethylamino)-1-(dicyclohexylphosphino)biphenyl, followed by acidic hydrolysis (61% yield).[19,20] The purity of the reagents, especially of benzophenone imine, turned out to be crucial for obtaining satisfactory yields in this step. [1-$^{13}C_1$]-Phenyl triflate was obtained from [1-$^{13}C_1$]-phenol by esterification with trifluorosulfonic acid anhydride[22] in pyridine (90% yield). [1-$^{13}C_1$]-Phenol was synthesized by first preparing [1-$^{13}C_1$]-4-nitrophenol from [2-$^{13}C_1$]-acetone and 2-nitromalonaldehyde monohydrate (50% yield) and subsequently removing the nitro group by reduction with $NaBH_4$ on Pd/C, diazotization, and reaction with hypophosphorous acid (65% yield).[17] [2-$^{13}C_1$]-Acetone was obtained by pyrolysis of [1-$^{13}C_1$]-barium acetate at 450 °C in 90% yield.[17] *o*-, *m*-, and *p*-chloroethoxybenzene were prepared by heating mixtures of the corresponding sodium chlorophenolates and ethyl tosylate in ethanol under reflux for 5 h. Phenylchloroformate was obtained by stirring a mixture of phenol, dimethylaniline (1 equiv), and phosgene (1.25 equiv) in toluene for 12 h at room temperature.[23] All compounds were characterized via GC/MS and NMR spectrometry.

Sector-Field MS. Mass spectrometric experiments were performed with a modified VG/ZAB/HF/AMD four-sector mass spectrometer of BEBE configuration (B stands for magnetic and E for electric sector), which has been described in detail elsewhere.[24] Briefly, N_2O, $Fe(CO)_5$, and the liquid arenes were admitted to the ion source via the heated septum inlet system in a ca. 10:1:1 ratio. The mixture was ionized by a beam of electrons (100 eV) in a chemical ionization source at a source housing pressure of about 10^{-4} mbar (repeller voltage ca. 0 V). Note that chemical ionization of a three-component mixture neither generates ions with well-defined internal energies nor provides control of the sequence of steps for the generation of the desired complexes. A plausible sequence for the generation of (arene)FeO^+ complexes starts with the generation of Fe^+ by chemical ionization of $Fe(CO)_5$. Subsequent reaction of Fe^+ with N_2O yields FeO^+,[25] which affords the (arene)FeO^+ complex by association.[10b] Alternatively, the sequence of oxygen atom transfer and ligation might be inverted, i.e., Fe(arene)$^+$ is oxidized by N_2O to (arene)FeO^+.[10d] The ions of interest were accelerated to 8 keV kinetic energy and mass-selected by means of B(1)/E(1). The following precautions were taken to make sure that the mass-selected ions actually had the desired elemental composition. (i) The mass resolution was kept at $m/\Delta m \geq 3000$. For example, it was possible to resolve $(C_6H_5{}^{35}Cl)FeO^+$ from the interferent $Fe(CO)_3(N_2O)^+$ (both 184 amu). (ii) For all complexes bearing chlorine, spectra were recorded for the ^{35}Cl as well as for the ^{37}Cl isotope and found to be consistent with each other. (iii) The spectra of deuterium-containing substrates are also fully consistent with the fragmentation pattern of unlabeled substrates. (iv) In addition, the bimolecular reaction of **1f** with mass-selected FeO^+ was examined using FT-ICR mass spectrometry,[30] and the observed product ratio is in agreement with the results using sector-field mass spectrometry. For these reasons, we can by and large rule out isobaric interferences in the spectra. Unimolecular fragmentations occurring in the field-free region preceding the second magnet were recorded by scanning B(2); the mass spectra obtained in this manner will be referred to as metastable ion (MI) spectra. For collisional activation (CA) studies, the precursors were selected by means of B(1)/E(1) and collided with helium between E(1) and B(2) at 80% transmission of the incident ion beam; this corresponds to an average of 1.1−1.2 collisions.[26] For CA/CA experiments, the B(1)/E(1) mass-selected precursor ions were collided with helium in the field-free region preceding B(2), the fragments of interest were selected using B(2), collided with helium in the field-free region between B(2) and E(2), and the resulting product ions were recorded by scanning E(2). Collisional activation of ions having high kinetic energies might give rise to products that differ from those formed upon dissociation close to the potential energy threshold. The CA mass spectra show a superposition of three contributions: (i) direct bond cleavages that are characteristic for the structure of the ionic precursor; (ii) delayed, collision-induced dissociations that might be preceded by rearrangements; and (iii) unimolecular ion dissociations of metastables arising from those particles that have not been hit by the target gas. Therefore, structural assignments by collisional activation mass spectrometry rely on comparisons of structural isomers. Only if the spectra of several, well-defined precursors exhibit characteristic differences can conclusions on structural features be drawn. All spectra were accumulated and on-line processed with the AMD-Intectra data system; 5−20 scans were accumulated to improve the signal-to-noise ratio.

Chart 1

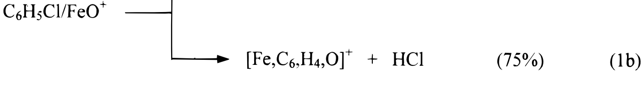


1 **1a** **1b** **1c**

1d **1e** **1f**

Results and Discussion

Chlorobenzene. The unimolecular dissociation of metastable **1**/FeO^+ complexes yields losses of CO and HCl according to reaction 1.



$$C_6H_5Cl/FeO^+ \longrightarrow [Fe,C_5,H_5,Cl]^+ + CO \quad (100\%) \quad (1a)$$

$$C_6H_5Cl/FeO^+ \longrightarrow [Fe,C_6,H_4,O]^+ + HCl \quad (75\%) \quad (1b)$$

The regioselectivity of both processes has been elucidated by labeling experiments (Chart 1, Table 1). Reaction 1b involves primarily hydrogens from the ortho positions, as HCl and DCl are lost in 99:1, 94:6, and 19:81 ratios from **1b**/FeO^+, **1c**/FeO^+, and **1d**/FeO^+, respectively. The experimental data indicate that the para position hardly participates in expulsion of HCl, and its contribution may therefore be neglected in the following analysis. Thus, assuming equal kinetic isotope effects for the

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Table 1. Neutral Fragments Lost in the Metastable Ion Spectra of **1**/FeO^+ and Its Labeled Analogues Obtained by Chemical Ionization with $Fe(CO)_5$ and N_2O

substrate	CO	^{13}CO	HCl	DCl
1	100		75	
1a	100		45	14
1b	100		91	1
1c	100		78	4
1d	100		8	33
1e	100			34
1f	90	45	100	

activations of the ortho and meta positions, we obtain an ortho:meta selectivity of 88:12 and a kinetic isotope effect of $k_H/k_D = 2.5 \pm 0.3$ for reaction 1b.[27] The shift in the CO:HCl product ratio from 100:75 for **1**/FeO^+ to CO:DCl = 100:34 for the fully deuterated ion **1e**/FeO^+ illustrates that dehydrochlorination is subject to a larger kinetic isotope effect than loss of carbon monoxide.

The structure of the ionic product of reaction 1b with the elemental composition $[Fe,C_6,H_4,O]^+$ can be probed in a CA/CA experiment, which gives, among uncharacteristic signals, rise to neutral losses of CO (100%) and $[C_6,H_4,O]$ (13%), but not of water (Table 2). Interestingly, $[Fe,C_5,{}^{13}C,H_4,O]^+$ ions generated by HCl loss from **1f**/FeO^+ lose ^{12}CO and ^{13}CO in an approximate 1:1 ratio. Thus, expulsion of carbon monoxide does not occur exclusively from a single position nor is the ^{13}C-label distributed statistically over the ring. Instead, the 1:1 ratio suggests that exchange of the ipso position with one of the ortho positions of the ring occurs in the course of HCl-loss from **1**/FeO^+. What is the structure of the $[Fe,C_6,H_4,O]^+$ ions generated in reaction 1b? The iron-bound hydroxyarynes **5** and/or **5′** (Scheme 1) can be excluded, as these are known to lose water upon collisional activation,[14] while this process is not observed for [**1**/FeO^+-HCl]. Loss of water as a characteristic feature of **5** and/or **5′** is also indicated by the data for the *m*- and *p*-chlorophenol/Fe^+ complexes (Table 2). Due to its symmetry, an iron-bound benzooxirene[28] **6** would rationalize the ^{13}C-labeling distribution observed for the decarbonylation of [**1f**/FeO^+-HCl]. However, theoretical calculations predict facile interconversion of bare benzooxirene to the more stable α-ketocarbene isomer;[28] thus we expect **6** to collapse readily into the benzoferraoxetane **7**. Likewise, while the (aryne)FeO^+ structure **8** can account for the loss of $^{12}CO/^{13}CO$ from [**1f**/FeO^+-HCl], also **8** is anticipated to isomerize to **7**.[29] These conjectures are supported by the fact that the CA/CA fragmentation pattern of [**1**/FeO^+-HCl] equals that of several other precursors which all have been proposed to yield the metallacycle **7**.[14] Further, it has been demonstrated previously that **7a** loses exclusively ^{13}CO, but not ^{12}CO, upon collisional activation.[14] Thus, the carbon atoms in the metallacycle remain distinguishable under CA/CA conditions, and a facile interconversion of **7a** and **7b** can be ruled out. Therefore, the observed participation of ipso and ortho positions in reaction 1b has to *precede* the formation of **7a** and **7b**. A possible rationalization of the $^{12}C/^{13}C$ labeling data obtained for **1f** is provided by invoking **6a** and/or **8a** as intermediates, which are C_s-symmetric with respect to the ring skeleton. In summary, we presume that $[Fe,C_6,H_4,O]^+$ ions have the metallacyclic structure **7** formed via intermediates in which the positional integrity of the original ipso and one ortho position is lost.

The expulsion of neutral CO from **1** and FeO^+ (reaction 1a) is by necessity preceded by carbon−oxygen bond formation. Does this process exhibit any regioselectivity with respect to ipso, ortho, meta, or para attack of FeO^+ at **1**? We have addressed this question by a ^{13}C-labeling experiment in combination with the independent generation of structural $[Fe,C_6,H_5,Cl,O]^+$ isomers. The complex of FeO^+ with ipso-labeled $[1\text{-}^{13}C_1]$-chlorobenzene **1f** lose ^{12}CO and ^{13}CO in a 67:33 ratio. This finding unambiguously demonstrates a nonstatistical participation of the ipso position in the decarbonylation of **1**.[30] CA/CA experiments have been performed to gain structural information about the ionic product of reaction 1a, and the experimentally observed neutral fragments (Table 2) of $Cl^\bullet$ (20%) and $C_5H_5^\bullet$ (100%) are in line with the formation of a half-sandwich complex $(c\text{-}C_5H_5)FeCl^+$ for the product ions. However, this assumption must remain unproven, because we were not able to generate a reference complex with $(c\text{-}C_5H_5)FeCl^+$ structure for comparison using different precursors.

The loss of ^{12}CO from **1f**/FeO^+ demonstrates that decarbonylation of **1** by FeO^+ does not only involve the ipso position of the ring. To assess the contributions from ortho, meta, and para positions, we have attempted to generate the ortho, meta, and para isomers of three possible ring-oxidation intermediates having the elemental composition $[Fe,C_6,H_5,Cl,O]^+$ by independent routes (Scheme 2). In addition, also a putative intermediate for ipso substitution is considered. First, the chlorophenol/Fe^+ complexes *o*-, *m*-, and *p*-**9** are generated from $Fe(CO)_5$ and the respective chlorophenols. Next, we assume that ionization of a mixture of $Fe(CO)_5$ and the respective chloroethoxybenzenes yields *o*-, *m*-, and *pa*-**10** upon loss of C_2H_4;[32,33] the structures represent the keto forms of the chlorophenol/Fe^+ congeners. This conjecture is strongly supported by a previous study on $[Fe,C_6,H_6,O]^+$ ions,[10b] which demonstrated that elimination of C_2H_4 from ethoxybenzene/Fe^+ actually yields 2,4-cyclohexadienone/Fe^+, and not phenol/Fe^+. Third, the intermediate structures *o*-, *m*-, and *p*-**11** have been accessed by ionizing mixtures of the respective chlorobenzoic acids with $Fe(CO)_5$, taking into account that chlorobenzoic acid/Fe^+ complexes undergo unimolecular losses of CO.[10b,34] *o*-, *m*-, and *p*-**11** correspond to intermediates formed by insertion of FeO^+ into a C−H bond of **1**. Finally, $[Fe,C_6,H_5,Cl,O]^+$ was approached from $Fe(CO)_5$ and phenylchloroformate $C_6H_5OC(O)$-

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[27] $(I_{HCl}/I_{DCl})(\textbf{1c}/FeO^+) = 78/4 = KIE(k_o/k_m)$, $(I_{HCl}/I_{DCl})(\textbf{1d}/FeO^+) = 8/33 = KIE(k_m/k_o)$, and $(I_{HCl}/I_{DCl})(\textbf{1a}/FeO^+) = 45/14 = (k_o + 2k_m)/(k_o/KIE)$ give averaged values of $k_o/k_m = 88:12$ and KIE = 2.5.

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[30] We note in passing that the $^{12}CO:^{13}CO$ ratio is subject to internal energy effects, as the bimolecular reaction of mass-selected FeO^+ with **1f** in a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer yields losses of ^{12}CO and ^{13}CO in a 42:58 ratio. In addition to the elimination of ^{12}CO (19%) and ^{13}CO (25%), the bimolecular reaction of FeO^+ and **1f** yields losses of HCl (39%), $C_5{}^{13}CH_5O$ (6%), FeOCl (3%), $C_5{}^{13}CH_4Cl$ (2%), and $C_5{}^{13}CH_5ClO$ (6%) under FT-ICR conditions. The product distribution is broader compared to sector-MS, because a higher average internal energy is sampled by the FT-ICR experiment. For experimental details and a comparison of the two techniques, see refs 13, 14, and 31.

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[32] The following neutral fragments are formed upon metastable ion dissociation of the precursor complexes: *o*-chloroethoxybenzene/Fe^+: $-CH_3$ (6%); $-C_2H_4$ (100%); −HCl (1%); $-CH_3CO$ (5%). *m*-Chloroethoxybenzene/Fe^+: $-CH_3$ (1%); $-C_2H_4$ (100%); −HCl (10%); −[C,H,Cl,O] (3%). *p*-Chloroethoxybenzene/Fe^+: $-C_2H_4$ (100%); −HCl (4%).

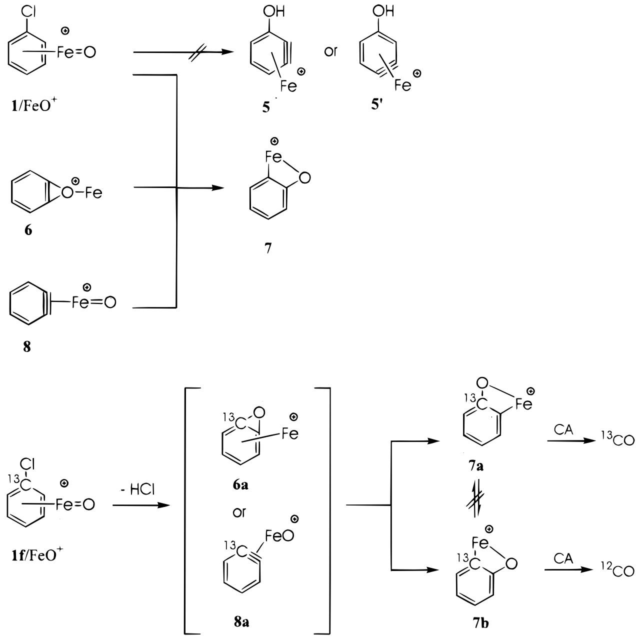
[33] High-resolution experiments by FT-ICR-mass spectrometry assured unequivocally that the neutral fragment lost from Fe^+ + chloroethoxybenzene with the nominal mass 28 is actually C_2H_4 and not CO.

[34] The following neutral fragments are formed upon metastable dissociation of the precursor complexes: *o*-Chlorobenzoic acid/Fe^+: −CO (4%); $-CO_2$ (100%); −[Fe,Cl,O] (12%). *m*-Chlorobenzoic acid/Fe^+: $-H_2O$ (3%); −CO (100%); −[Fe,Cl,H,O] (20%). *p*-Chlorobenzoic acid/Fe^+: −CO (100%); −[Fe,Cl,H,O] (11%).

Table 2. Relevant Neutral Losses in the CA/CA Spectra of $[Fe,C_6,H_4,O]^+$ and $[Fe,C_5,H_5,Cl]^+$ Fragments Obtained from Different Precursors upon Chemical Ionization with $Fe(CO)_5$

substrate	neutral fragment lost between E(1) and B(2)	H_2O	CO	^{13}CO	Cl	HCl	C_5H_5	$[C_6,H_4,O]$	$[C_5,H_5,Cl]$
1/N_2O	HCl		100					13	
1f/N_2O	HCl		100	100				15	
o-chlorophenol	HCl		100					13	
m-chlorophenol	HCl	27	100					34	
p-chlorophenol	HCl	73	100					40	
o-chloroethoxybenzene	HCl		100					10	
m-chloroethoxybenzene	HCl	30	100					15	
p-chloroethoxybenzene	HCl	65	100					90	
1/N_2O	CO				20	20	100		17
o-chlorophenol	CO				15	16	100		16
o-chloroethoxybenzene	CO				13	12	100		10

Scheme 1



Cl.[35] The so-formed ions are assumed to possess a C_6H_5O-Fe^+-Cl structure **12**, which may be regarded as a central intermediate in the ipso substitution occurring in **1**/FeO^+. Collisional activation experiments have been applied for each of these isomers to ascertain whether the assumed connectivity was actually realized from each precursor mixture. The fragmentation patterns are in line with the proposals outlined above for most isomers, with one exception. *o*-Chlorobenzoic acid/Fe^+ complexes hardly lose CO, and the $[Fe,C_6,H_5,Cl,O]^+$ ions formed from *o*-chlorobenzoic acid/$Fe(CO)_5$ do not show a characteristic loss of OH upon collisional activation; hence the ions might *not* possess the assumed (*o*-Cl(C_6H_4)-Fe^+-OH structure, and we refrain from drawing mechanistic conclusions from this isomer.

The metastable ion fragmentations of all $[Fe,C_6,H_5,Cl,O]^+$ complexes are listed in Table 3. The fragmentation patterns of the meta and para isomers are quite similar, no matter whether **9**, **10**, or **11** is approached. The spectra are featured by the dominant formation of HCl in conjunction with approximately equal intensities for the losses of CO and H_2O. In contrast, the ortho isomers show two distinct differences compared to their meta and para analogues. Formation of water is absent in all cases, and the ratio of CO vs HCl loss is significantly higher for the ortho isomers of **9**, **10**, and **11**. Note that for *o*-**10**, expulsion of CO is by far more intense than that of HCl. For the formal ipso-substitution intermediate **12**, elimination of CO constitutes the main dissociation process accompanied by a small amount of HCl loss.

Scheme 2

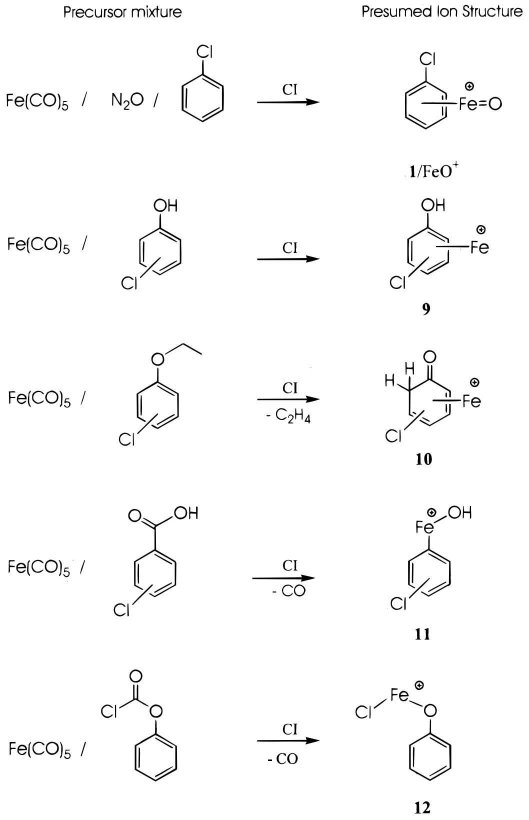


Table 3. Neutral Fragments in the Metastable Ion Spectra of $[Fe,C_6,H_5,Cl,O]^+$ Complexes Obtained from Different Precursors by Chemical Ionization with $Fe(CO)_5$

substrate	H_2O	CO	Cl	HCl
chlorobenzene/N_2O		100		75
o-chlorophenol		32		100
m-chlorophenol	7	8		100
p-chlorophenol	7	12		100
o-chloroethoxybenzene	<1	100		22
m-chloroethoxybenzene	14	24	1	100
p-chloroethoxybenzene	11	14	2	100
o-chlorobenzoic acid		57		100
m-chlorobenzoic acid	11	14		100
p-chlorobenzoic acid	13	13		100
phenylchloroformate		100		10

On the basis of the experimental data, we can by and large rule out the participation of meta and para positions in the

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[35] The following neutral fragments are formed upon metastable dissociation of $C_6H_5OC(O)Cl/Fe^+$ complexes: −CO (100%); $-CO_2$ (8%).

Table 4. Neutral Fragments in the Metastable Ion Spectra of C_6H_5X/FeO^+ Complexes Obtained upon Chemical Ionization of C_6H_5X with $Fe(CO)_5$ and N_2O (X = F−I)

substrate	CO	HX	X	C_6H_5O	[C,O,X]
C_6H_5F (**2**)	32	100			
C_6H_5Cl (**1**)	100	75			
C_6H_5Br (**3**)	100	1			
C_6H_5I (**4**)	100		74	10	7

dissociation of **1**/FeO$^+$ for three reasons. (i) All metastable meta and para isomers of $[Fe,C_6,H_5,Cl,O]^+$ undergo unimolecular losses of water. Therefore, any participation of meta and para positions in the dissociation of **1**/FeO$^+$ should be reflected by loss of water in the metastable ion spectra. This process is completely *absent* for **1**/FeO$^+$, however. (ii) All intermediates of an oxidation of meta and para positions yield by far more HCl than CO; none of the meta and para intermediates can rationalize the CO:HCl ratio of 100:75 observed for **1**/FeO$^+$, taking into account that about 33% ipso substitution occurs (see data for **1f**/FeO$^+$). (iii) As mentioned above, it can be ruled out that formation of HCl in reaction 1b is preceded by oxidation of the meta or para positions to the corresponding chlorophenols or their keto forms. Thus, while [*m*-**9**/Fe$^+$-HCl], [*m*-**10**/Fe$^+$-HCl], [*p*-**9**/Fe$^+$-HCl], and [*p*-**10**/Fe$^+$-HCl] complexes show characteristic losses of water upon collisional activation, [*o*-**9**/Fe$^+$-HCl], [*o*-**10**/Fe$^+$-HCl], and [**1**/FeO$^+$-HCl] complexes do not (Table 2).[36] In addition, a meta or para oxidation would not rationalize the substantial amount of ^{13}CO loss from [**1f**/FeO$^+$-HCl].

Other Phenyl Halides. In the following section, we discuss the effect of varying the halogen substituent X on the dissociation pattern of C_6H_5X/FeO^+ complexes. For this purpose, the unimolecular reactions of FeO$^+$ complexed with fluorobenzene (**2**), bromobenzene (**3**), and iodobenzene (**4**) have been investigated (Table 4). Whereas loss of HX is the dominant process for X = F, it becomes less relevant for X = Cl, is hardly detectable for X = Br, and is completely absent for X = I. Is HX formation really becoming more difficult, or is the decreasing relative intensity merely a consequence of the fact that the competing process, i.e., CO formation, becomes easier? An answer is given by the MI spectrum of 4-chlorofluorobenzene/FeO$^+$, which is featured by eliminations of HF (100%), HCl (40%), and CO (16%). The product ratio demonstrates that HF loss is actually preferred compared to that of HCl. A direct bond cleavage of the phenyl−halide bond as the rate determining step appears improbable, given that $D(C_6H_5\text{-}F) = 125.7$ kcal mol^{-1} largely exceeds $D(C_6H_5\text{-}Cl) = 95$ kcal mol^{-1}.[37] A possible rationale for the observed reactivity is obtained by considering the coordination modes. According to recent quantum chemical calculations,[11] FeO$^+$ prefers a η^2-coordination at benzene rather than the η^6-coordination known to be prevalent for many other metal atoms.[38] Therefore, the FeO$^+$ unit in 4-chlorofluorobenzene/FeO$^+$ may be directed toward one of the halides to form an unsymmetrical complex with FeO$^+$ bound to the halide substituent, whereas the other, uncomplexed halide atom is not accessible for activation and subsequent HX loss. Assuming that the FeO$^+$ unit is directed toward fluorine due to its higher negative partial charge, the HF/HCl ratio is determined by the preference for F coordination in the initial encounter complex.

We note in passing that complexes of 4-chlorofluorobenzene with bare Fe$^+$ lose HF (6%), HCl (100%), FeClF (40%), and C_6H_4ClF (20%). Thus, taking Fe$^+$ instead of FeO$^+$ a dramatic reversal of the HF: HCl ratio occurs, thereby demonstrating the decisive role of the oxo unit for the course of the reaction. As Fe$^+$ prefers η^6-coordination at the arene,[38] both halogens are accessible for HX elimination, and the cleavage of the weaker carbon−chlorine bond is preferred.

For C_6H_5I/FeO^+, the product distribution differs from that obtained for the lighter halides in that C−H bond activation is absent; expulsions of CO, C_6H_5O, I, and [C,I,O] are observed instead. We suggest that the elimination of neutral [C,I,O] is actually due to a consecutive loss of atomic iodine and CO rather than an intact ICO$^\bullet$ radical. As the CA/CA spectrum of [**4**/FeO$^+$-I] is by and large dominated by loss of CO, and as the CA/CA spectrum of [**4**/FeO$^+$-CO] displays intense losses of I (70%) and of C_5H_5 (100%), both orders for the consecutive reactions (first CO, then I loss, and vice versa) are possible. The fact that expulsion of X, C_6H_5O, and X/CO is only observed for X = I is in line with thermochemical data. For the formation of $FeX^+ + C_6H_5O$, the reaction exothermicity relative to the separated reactants $FeO^+ + C_6H_5X$ is largest for X = I ($\Delta H_r < -51$ kcal mol^{-1}) and smallest for X = F ($\Delta H_r = -23$ kcal mol^{-1}). Although absolute values for the generation of $[Fe,C_6,H_5,O]^+ + X$ are not available, thermochemical data predict the reaction to be as much as 60 kcal mol^{-1} more favorable for X = I than for X = F.[37] All neutral fragments generated from **4**/FeO$^+$ indicate C−X bond activation, whereas initial C−H bond cleavage is completely discriminated against. The present trends for **1**/FeO$^+$ to **4**/FeO$^+$ suggest a correlation between increasing C−X bond strengths and the extent to which the C−H bond activation path is followed; a mechanistic rationale is given below. Note that none of the phenyl halides undergoes water loss, which is characteristic for phenol formation. In analogy to the scenario derived for **1**/FeO$^+$, this result indicates that initial docking at the halogen prevails such that the meta and para positions cannot effectively participate in subsequent bond activation processes.

On the basis of all experimental data, a mechanistic scenario is proposed for **1f**/FeO$^+$ that takes two different activation steps into account (Scheme 3). The coordination of FeO$^+$ at chlorine ("docking") is a common, initial step for both pathways, thereby limiting the number of accessible sites of the arene. Path A involves the attack of the aromatic π-system at the ortho position to form a σ-complex. A shift of hydrogen to the adjacent ipso position concomitant with C−Cl bond cleavage gives intermediate **12a**, which can eliminate ^{12}CO with a carbon atom originating from the ortho position of the ring. For such a hydroxylation-induced, intramolecular migration of hydrogen, the term NIH-shift was coined.[7a] In path B, a formal Cl$^-$ abstraction yields **13**, the phenyl cation bound to FeOCl. This conjecture is supported by the fact that $C_6H_5^+$ is observed upon collisional activation of **1**/FeO$^+$ and also as a primary product under FT-ICR conditions.[30] A formal substitution of chlorine by oxygen yields intermediate **12b**, which mainly expels ^{13}CO. Alternatively, the ortho position of the ring in **13** can be deprotonated by the basic FeOCl unit to give **14**, from which HCl is eliminated. The symmetric intermediate **14** also explains the exchange of carbon atoms involving the ipso and one ortho position from [**1f**/FeO$^+$−HCl]. Assuming that the acid−base

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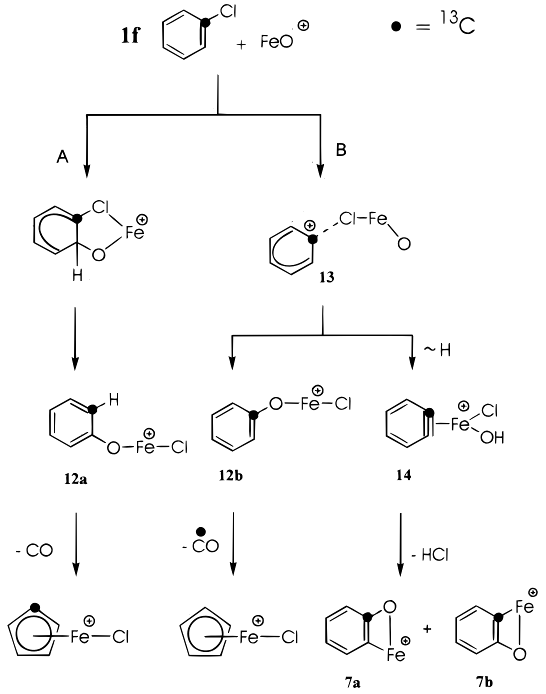
[36] The ion current of [**11**/Fe$^+$-HCl] complexes was not sufficient to perform CA/CA experiments on these isomers.

[37] Lias, S. G.; Liebmann, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, 695.

[38] (a) Bauschlicher, C. W.; Partridge, H.; Langhoff, S. R. *J. Chem. Phys.* **1992**, *96*, 3273. (b) Stöckigt, D.; Hrušák, J.; Schwarz, H. *Int. J. Mass Spectrom. Ion Processes* **1995**, *149/150*, 1. (c) Dunbar, R. C.; Klippenstein, S. J.; Hrušák, J.; Stöckigt, D.; Schwarz, H. *J. Am. Chem. Soc.* **1996**, *118*, 5277. (d) Hertwig, R. H.; Seemeyer, K.; Schwarz, H.; Koch, W. *Chem. Eur. J* **1997**, *3*, 1315. (e) Yang, C.-N.; Klippenstein, S. J. *J. Phys. Chem. A* **1999**, *103*, 1094. (f) Dargel, T. K.; Hertwig, R. H.; Koch, W. *Mol. Phys.* **1999**, *96*, 583.

Scheme 3



reaction from **13** to **14** is partly reversible, this would explain the minor degree of H/D-scrambling associated with reaction 1b. The two different activation mechanisms (paths A and B) are proposed to rationalize (i) the HCl/CO ratio observed for **1**/FeO$^+$ and (ii) the ^{12}CO/^{13}CO ratios, which differ for **1f**/FeO$^+$ and for [**1f**/FeO$^+$-HCl]. According to the data for **1f**/FeO$^+$, the branching ratio between path A and path B is about 1:1.6. *o*-**9** is not considered to be involved in reaction 1, as HCl expulsion from *o*-**9** is probably not accompanied by any loss of the positional integrity of carbon atoms.[14] Compared to unsubstituted benzene, the moderate alteration of the aromatic ring, introduced by substitution of chlorine for hydrogen, induces a complete change in reactivity toward FeO$^+$, in that direct ring hydroxylation is thoroughly suppressed.

Conclusions

The present study demonstrates for the first time that FeO$^+$ activates the ipso and ortho positions of **1**, and probably also those of the phenyl halides **2**−**4**, whereas formation of the corresponding substituted phenols is absent. In marked contrast, enzymatic systems such as cytochrome P-450 show a preference for oxidations of ortho and para position to yield halophenols.[4−6] This discrepancy between the enzyme and its most simple electronic model[9] is by and large attributed to ligation effects. The chemistry of FeO$^+$ is governed by initial coordination of the metal at the functional group ("docking"), thereby rendering only the adjacent positions accessible for subsequent reactions. In the enzyme, the FeO entity is embedded in a heme system; therefore, a coordination site at the metal next to the oxo unit is not available for the substrate. Consequently, the regioselectivity is not determined by precoordination, but by the electron density distribution of the aromatic ring and/or steric effects. Nevertheless, the gas-phase model and the enzymatic system have one remarkable feature in common: although both systems show an inherently high reactivity toward unsubstituted benzene, a rather moderate alteration of the arene, as given by halide substitution, suffices to induce highly regioselective product formation. It might be an interesting topic for studies on phenyl halides in the condensed phase to further probe the role of ipso substitution, for which precedence is rare so far.[7]

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