A Mechanistic Study of the FeO^+-Mediated Decomposition Pathways of Phenol, Anisol, and Their Thio Analogues

Mark Brönstrup, Detlef Schröder, and Helmut Schwarz*[a]

Dedicated to Dr. Pol Bamelis on the occasion of his 60th birthday

Abstract: The gas-phase oxidations of phenol, anisol, thiophenol, and thioanisol by 'bare' FeO^+ are examined by using Fourier transform-ion cyclotron resonance (FT-ICR) and tandem mass-spectrometry. Reaction mechanisms are derived on the basis of isotope-labeling experiments, MS/MS studies, and comparison with structural isomers, that is ions formed by independent routes. The chemistry of all substrates is determined by the functional groups, whereas reactions typical of unsubstituted benzene with FeO^+ are suppressed. For phenol and thiophenol, four-membered metallacycles are obtained concomitant with a regioselective loss of water, which involves the O atom from the FeO^+ entity and hydrogen atoms originating from the functional group and from the *ortho* position of the ring. C–H bond cleavage of the methoxy group ($k_H/k_D = 2.0$) is rate-contributing for the degradation of metastable anisol/FeO^+, which is featured by highly regioselective losses of H_2O, HCO, H_2CO, and $[C,H_2,O_2]$. In the oxidation of thioanisol, two different C–H bond activation mechanisms are operating, resulting in the elimination of [Fe,H,O,S] concomitant with the formation of the benzyl cation ($k_H/k_D = 4.7$), and loss of water ($k_H/k_D = 2.5$). The reactions of independently generated, formal *S*- and *C*-oxidation intermediates of thioanisol indicate the occurrence of extensive structural isomerizations prior to dissociation. For anisol and thioanisol, analogies and differences between oxidation reactions catalyzed by the enzyme cytochrome P-450 in the condensed phase and those observed for the gas-phase model FeO^+ are discussed.

Keywords: anisol • cytochrome P-450 • gas-phase chemistry • iron oxide • mass spectrometry • phenol

Introduction

A large variety of aromatic compounds stemming from natural as well as from anthropogenic sources is present in ecosystems; therefore, the determination of their fate in the environment and their chemical behavior is of profound interest.[1] In the metabolism of arenes, important routes involve oxidations catalyzed by transition metals incorporated in intra- and extracellular enzymes such as cytochrome P-450 and other powerful oxidation catalysts.[2, 3] The present study comprises the monosubstituted aromatic compounds phenol (**1**), thiophenol (**2**), anisol (**3**), and thioanisol (**4**). The last two substrates are degraded by iron-containing enzymes by oxidative O-dealkylation [Reaction (1)] and stereoselective sulfoxidation [Reaction (2)], respectively.[4–7]

$$C_6H_5OCH_3 \longrightarrow C_6H_5OCH_2OH \longrightarrow C_6H_5OH + CH_2O \quad (1)$$

$$C_6H_5SCH_3 \longrightarrow C_6H_5S(O)CH_3 \quad (2)$$

One way to elucidate mechanistic details of metal-mediated reactions is to perform experiments in the diluted gas phase in a mass spectrometer. In these studies, the complexity of the activated heme-system that mediates the decomposition of arenes is reduced to a single FeO^+ unit as the simplest conceivable model system.[8] This approach allows one to uncover the intrinsic chemical behavior of the reactive metal–oxo species under rigorous exclusion of many surrounding parameters such as solvent effects, counterions, ligands, or enzyme backbones. It should be pointed out that owing to the dramatic differences to real systems mentioned above, gas-phase studies will never account for the precise mechanisms, energetics, and kinetics relevant in the condensed phase.[8] Notwithstanding, the knowledge of the reactivity patterns of these model systems may enable one to assess the relevance of the environment present in the condensed phase, as has been demonstrated recently.[9] The reactions of FeO^+ with benzene,[10, 11] alkylbenzenes,[10b,12] substituted anilines,[13] and some aromatic heterocycles[14] have been studied in detail recently. The present paper extends this series by investigating the FeO^+-mediated dissociation pathways of **1**–**4** by a combination of mass spectrometric studies and isotopic labeling (see below).

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[a] Prof. Dr. H. Schwarz, Dipl.-Chem. M. Brönstrup, Dr. D. Schröder
Institut für Organische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-10623 Berlin (Germany)
Fax: (+49)30-314 21102
E-mail: schw0531@www.chem.tu-berlin.de

Experimental Section

Substrates: Most unlabeled compounds are commercially available and were used without further purification. *ortho*-Phenylenecarbonate was obtained by reacting catechol with carbonyldiimidazol.[15] 2-(Phenylthio)-acetic acid was prepared from thiophenol and bromoacetic acid under basic conditions.[16] [4-D_1]phenol (**1b**) was synthesized by addition of three equivalents of *n*-butyllithium to a solution of 4-bromophenol in tetrahydrofuran at $-40\,^{\circ}C$, followed by deuterolysis with D_2O at room temperature and rapid workup with H_2O to re-exchange the phenolic hydrogen. [3,5-D_2]-Phenol (**1c**) was prepared from [3,5-D_2]aniline by thermal decomposition of the corresponding diazonium salt in water.[17] [3,5-D_2]Aniline was made by threefold D/H exchange of [2,3,4,5,6-D_5]aniline in an excess of water catalyzed by diluted H_2SO_4.[18] [2,3,4,5,6-D_5]Aniline was obtained in two steps by 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.[19] Deuterium-labeling of the hydroxy group and of *ortho* and *para* positions was achieved by H/D exchange reactions following standard laboratory procedures.[18] [^{18}O]Phenol (**1f**) was obtained by decomposing dry phenyldiazoniumtetrafluoroborate (0.90 g, 4.7 mmol) in a suspension of $H_2{}^{18}O$ (0.40 g, 20 mmol) in Et_2O (4 mL) in 20% yield (5% yield based upon $H_2{}^{18}O$); the yield can be increased to 39% (10% based upon $H_2{}^{18}O$) by a significant scale-up.[20] [1-$^{13}C_1$]Phenol (**1g**) was synthesized by first preparing [1-$^{13}C_1$]-4-nitrophenol from [2-$^{13}C_1$]acetone and nitromalonaldehyde monohydrate (50% yield) and subsequently removing the nitro group by reduction with $NaBH_4$ on Pd/C, diazotation, and reaction with hypophosphorous acid (65% yield).[18] [2-$^{13}C_1$]Acetone was obtained by pyrolysis of [1-$^{13}C_1$]acetic acid at 450 °C in 90% yield.[18] Labeled anisols and thioanisols were obtained from the corresponding phenols and thiophenols by methylation with (labeled) iodomethane in dimethyl sulfoxide.[18] [D_2]iodomethane was prepared by iodine–magnesium exchange of CD_2I_2 with isopropylmagnesium bromide and subsequent quenching of the carbenoid with methanol.[21, 22] Oxidation of labeled thioanisols with Br_2/H_2O yielded the corresponding methylphenyl sulfoxides.[23] All labeled compounds were purified by chromatography and characterized by ^1H NMR spectroscopy and GC/MS.

Sector MS: Most of the mass spectrometric experiments reported here 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 through the heated septum inlet system in a ratio of about 10:1:1; phenol was introduced through the solid-probe inlet system. The mixture was ionized by a beam of electrons (100 eV) in a chemical ionization source (repeller voltage about 0 V). The ions of interest were accelerated to 8 keV and mass-selected by means of B(1)/E(1) at a resolution of $m/\Delta m > 3000$. 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 comparative collisional activation (CA) studies, the precursors were selected by means of B(1)/E(1)/B(2) and collided with helium between B(2) and E(2) at 80% transmission of the incident ion beam; this corresponds to an average of 1.1–1.2 collisions.[25] 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 by 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). All spectra were on-line processed with the AMD-Intectra data system; 5–40 scans were accumulated to improve the signal-to-noise ratios. The reported kinetic isotope effects (KIEs) are associated with an error of ±10%.

FTICR-MS: A few additional experiments were performed with a Spectrospin CMS 47X FT-ICR mass spectrometer that has been described previously.[26, 27] Briefly, Fe^+ ions were generated by laser desorption/laser ionization by focusing the beam of a Nd:YAG laser (Spectron Systems, $\lambda = 1064$ nm) onto an iron target. The ions were extracted from the source, transferred into the analyzer cell by a system of electrostatic potentials and lenses, decelerated, and trapped in the field of a superconducting magnet (maximum field strength 7.05 T). Prior to ion–molecule reactions, the $^{56}Fe^+$ isotope was mass-selected by using the FERETS technique,[28] a computer-assisted protocol that combines frequency sweeps and single-frequency ion-ejection pulses to optimize ion isolation. FeO^+ was generated by pulsing-in N_2O, thermalized with pulsed-in argon, and subsequently mass-selected. Organic substrates were continuously leaked-in up to a pressure of $5-10 \times 10^{-9}$ mbar. Ionic reaction products were monitored as a function of reaction time and reactant pressure. The data were accumulated and processed by means of an ASPECT 3000 minicomputer.

General considerations: Let us briefly mention some characteristics of the experiments that illustrate the need for two different mass spectrometric approaches. At first, the substrates have significant memory effects in high-vacuum devices due to adsorption in the device itself as well as in the inlet systems. Second, the deuterium-labeled phenols applied in this study are sensitive to H/D exchanges with themselves, upon contact with the walls of the inlet systems or the machinery, as well as with background gases (e.g. moisture). Both effects cause serious problems in the FTICR. The performance of sector MS is superior in these respects, because the operating pressure (ca. 10^{-4} mbar) is about four orders of magnitude higher than that of typical ICR conditions (ca. 10^{-8} mbar), thereby increasing the neutral flows and hence reducing H/D exchange. Nevertheless, some amount of H/D scrambling in the labeled phenols is inevitable, and the selectivities derived below should be regarded as lower limits. Thus, the reactions of all substrates were screened using sector MS, and the ICR technique was used for those experiments that require exact mass measurements of ionic products or the investigation of consecutive reactions with a second substrate. Prime advantages of FTICR-MS compared to chemical ionization in sector MS are that it provides full control of the ions' histories and relatively narrow distributions of their internal energy, that is the reactions occur under well-defined conditions at ambient temperatures.[29] Another general consideration is fundamental for making a comparison with the results obtained with these different mass spectrometric techniques: Under ICR conditions, the full complexation energy gained upon interaction of FeO^+ with the substrate is available for chemical processes. In contrast, metastable arene/FeO^+ complexes examined in sector MS are formed in a chemical ionization plasma, which allows collisional cooling prior to unimolecular dissociation. Therefore, it is fair to assume that the metastable ions formed upon chemical ionization in the sector MS have lower average internal energies than the encounter complexes formed under ICR conditions.[30] Note that in the MI experiments, the low-energy fraction of ions do not react within the sampled time window, whereas highly energetic ions dissociate prior to mass selection. Thus, only the small fraction of the ion population which undergoes unimolecular decay in the μs regime is sampled.

Results and Discussion

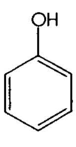
The reaction pathways for the substrates **1**–**4** will now be considered separately. The substrates with hydrogen–heteroatom bonds (phenol, thiophenol) and those with methylated heteroatoms (anisol, thioanisol) are grouped together according to their reactivity patterns.

Phenol: Loss of H_2O is the by far prevailing dissociation process for metastable **1**/FeO^+ complexes, accompanied by traces of decarbonylation [Reaction (3)].

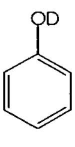
$$\mathbf{1}/FeO^+ \longrightarrow [Fe,C_6,H_4,O]^+ + H_2O \quad 100\% \tag{3a}$$

$$\mathbf{1}/FeO^+ \longrightarrow [Fe,C_5,H_6,O]^+ + CO \quad \approx 1\% \tag{3b}$$

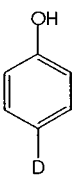
The regioselectivity of Reaction (3) has been elucidated by deuterium- and ^{18}O-labeling experiments (see Table 1). The dominant losses are H_2O from **1b**/FeO^+ and from **1c**/FeO^+, HDO from **1a**/FeO^+ and from **1d**/FeO^+, and D_2O from **1e**/FeO^+. Accordingly, the majority of the water molecules generated bear one hydrogen atom from the hydroxy group and one from the *ortho* position of the ring. However, the



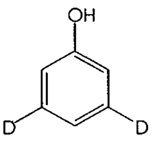
1



1a



1b



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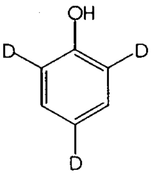
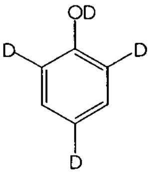


1d



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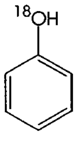

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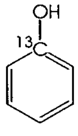
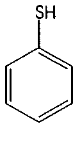


1g



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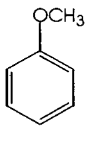

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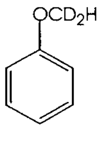
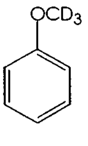
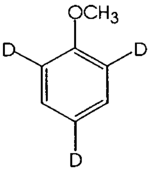


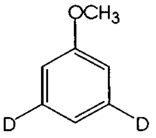
3a



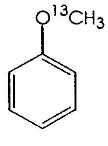
3b



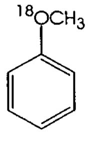
3c



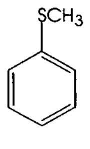
3d



3e



3f



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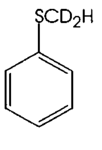
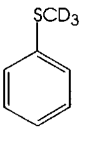
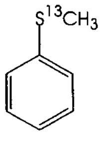


4a



4b



4c

Table 1. Neutral fragments in the metastable ion spectra of phenol/FeO$^+$ complexes obtained by chemical ionization with $Fe(CO)_5$ and N_2O.

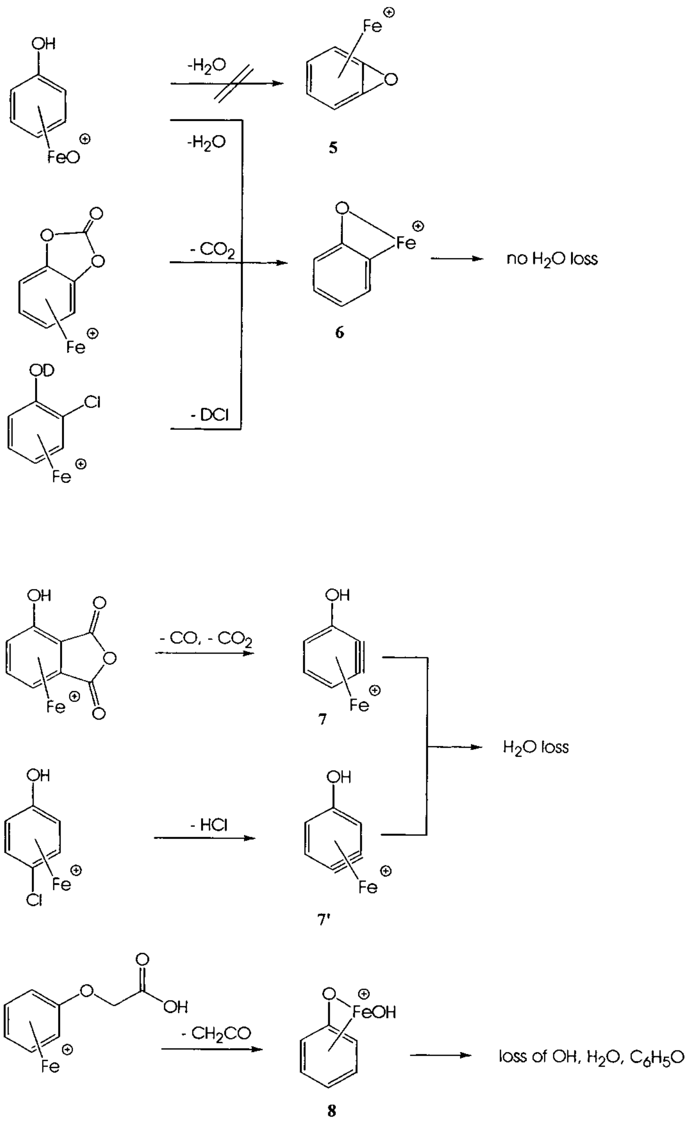
	Neutral losses[a]					
Substrate	H_2O	HDO	$D_2O/H_2{}^{18}O$	CO	^{13}CO	$C^{18}O$
1	100			2		
1a	20	100				
1b	100	6				
1c	100	3		1		
1d	4	100	15	1		
1e	2	12	100	1		
1f	100		2	3[b]		0.1[b]
1g	100			0.3[b]	4[b]	

[a] Intensities are given relative to the base peak = 100 %. [b] Product ratio relative to H_2O loss determined by ICR-MS.

minor HDO losses from **1b**/FeO$^+$ and **1c**/FeO$^+$ demonstrate that the *meta* and *para* positions also participate to a small extent in the reaction. For **1a**, **1d**, and **1e**, the observed selectivity is even lower, which can be rationalized i) by the operation of kinetic isotope effects (KIE) and ii) by the fact that partial H/D exchange processes in the ion source between background water and the labile *ortho*, *para*, and hydroxy positions cannot be avoided (see above). One additional experiment with regard to the H/D regioselectivity should be mentioned: Among many other fragments, collisional activation of **1**/FeO$^+$ yields a FeOH$^+$ signal (m/z 73; 4 % relative to the base peak), but only negligible amounts of $Fe(H_2O)^+$ (m/z 74).[31] In contrast, only FeOD$^+$ (m/z 74) is produced upon CA of **1a**/FeO$^+$. Further, collisional activation of **1f**/FeO$^+$ only gives rise to $Fe^{16}OH^+$ (m/z 73), but not to $Fe^{18}OH^+$ (m/z 75). These results very much corroborate an initial O–H bond activation of phenol by FeO$^+$ (see below).

Interestingly, ^{18}O-labeling in **1f**/FeO$^+$ yields losses of $H_2{}^{16}O$ and $H_2{}^{18}O$ in a 98:2 ratio, thus revealing that the oxygen atom involved in the formation of water stems almost exclusively from the oxo unit of the FeO$^+$ ion. As the nonequivalence of oxygen atoms is crucial for the reaction analysis, the bimolecular reaction of FeO$^+$ with **1f** has been also examined by using FT-ICR mass spectrometry, and losses of $H_2{}^{16}O$ and $H_2{}^{18}O$ in a 97:3 ratio fully confirm the results obtained with sector-MS. Accordingly, any mechanistic path involving a symmetric intermediate with respect to the oxygen atoms, for example arene hydroxylation, must be disputed for the gas-phase reaction.

CA/CA experiments have been applied to elucidate the structure of the ionic product of Reaction (3a) having the elemental composition $[Fe,C_6,H_4,O]^+$ (Scheme 1, Table 2). The CA/CA spectrum of [**1**/FeO$^+$ – H_2O] is dominated by losses of carbon monoxide, $[C_3,H_2,O]$, and the entire ligand $[C_6,H_4,O]$, whereas dehydration is not observed. First, we have investigated whether an iron-bound benzooxirene[32] **5** is produced in Reaction (3a). To this end, [**1g**/FeO$^+$ – H_2O] complexes have been submitted to a CA/CA experiment, which yields only losses of ^{13}CO and not of ^{12}CO. This finding demonstrates that the ^{13}C–O bond of phenol remains intact. In addition, it rigorously excludes structure **5** for the $[Fe,C_6,H_4,O]^+$ ions by symmetry arguments. In order to reveal whether the metallacycle **6** or rather the iron-bound hydroxyarynes **7** and/or **7′** result from the **1**/FeO$^+$ decomposition, these three structures are accessed from different precursors (Scheme 1). Ionizing a mixture of [O-D]-2-chlorophenol and $Fe(CO)_5$ is presumed to give **6** upon elimination of DCl. Alternatively, **6** is likely to be formed from *ortho*-phenylenecarbonate and $Fe(CO)_5$. The hydroxyaryne complexes **7** and **7′** are approached using 3-hydroxyphthalic acid anhydride and 4-chlorophenol, respectively. The collision-



Scheme 1.

induced fragmentation patterns of the $[Fe,C_6,H_4,O]^+$ ions formed by these routes all display losses of CO, $[C_3,H_2,O]$, and $[C_6,H_4,O]$, but differ in one significant respect: Whereas water eliminations occur using precursors that can be assumed to yield iron-bound hydroxyarynes, no such processes are observed from precursors that are presumed to give **6** (Table 2). Accordingly, two facts strongly support the assumption that **6** represents the structure of the $[Fe,C_6,H_4,O]^+$ ions produced in Reaction (3a). i) The CA/CA spectrum of these ions is characterized by the absence of water loss. ii) As hydrogen atoms from *meta* and *para* positions participate only to a minor extent in Reaction (3a), an iron-bound hydroxyarylyne can only be realized after extensive structural rearrangements. Such a rearrangement sequence, which does not involve H/D scrambling, is hardly conceivable. In contrast, the mechanism for formation of **6** can be described in a straightforward manner (see below).

Table 2. Characteristic neutral fragments in the CA mass spectra of $[Fe,C_6,H_4,O]^+$ ions obtained by chemical ionization of different precursors with $Fe(CO)_5$.

Substrate	Neutral losses[a] H_2O	 CO	 $[C_3,H_2,O]$	 $[C_6,H_4,O]$
phenol/N_2O		100	27	22
[O-D]-2-chlorophenol		100	11	4
ortho-phenylene carbonate		100	6	5
3-hydroxyphtalic acid anhydride	4	100	5	4
4-chlorophenol	31	100	11	9

[a] Intensities are given relative to the base peak = 100%.

Let us now discuss the decarbonylation of **1**/FeO^+ in Reaction (3b). The rather low intensity of Reaction (3b) and a mass overlap with $Fe(CO)_4{}^+$ ions present in the CI source, which undergo facile decarbonylation, obscures a quantitative description of the reaction with sector-MS. Therefore, we have investigated the related bimolecular reaction of isolated FeO^+ ions and phenol in the FT-ICR spectrometer, where $[Fe,C_5,H_6,O]^+$ ions are obtained with an intensity of 4% relative to the base peak.[33] When FeO^+ is allowed to react with **1f** under FT-ICR conditions, the ratio of $C^{16}O$ loss versus $C^{18}O$ loss equals 3:97. Likewise, ^{12}CO and ^{13}CO are lost in a 8:92 ratio from **1g**. The minor amounts of $C^{16}O$ loss in both experiments require the formation of a new carbon–oxygen bond by an oxidation of phenol to a dihydroxybenzene, in which the $^{16}O/^{18}O$ and $^{12}C(OH)/^{13}C(OH)$ labels have lost their positional integrity. However, the vast majority of carbon monoxide is cleaved-off from phenol starting from the carbon–oxygen bond already present in the substrate.

The FT-ICR experiments provide further information by approaching Reaction (3a) from the product side. $[Fe,C_6,H_4,{}^{18}O]^+$ ions produced from **1f** and FeO^+ in Reaction (3a) are found to add background water to give a complex with the elemental composition $[Fe,C_6,H_6,{}^{16}O,{}^{18}O]^+$ under ICR conditions. The latter complex was mass-selected and characterized by a collision-induced dissociation (CID) experiment, which yields losses of $H_2{}^{16}O$ (35%), $[C,H_2,{}^{16}O,{}^{18}O]$ (35%), $[C_6,H_5,{}^{18}O]$ (100%), and $[C_6,H_6,{}^{16}O,{}^{18}O]$ (90%). Evidently, the oxygen atoms remain nonequivalent in the experiment (see below).

Finally, a complex putatively isomeric to **1**/FeO^+ has been generated by ionizing a mixture of $Fe(CO)_5$ and phenoxyacetic acid $C_6H_5OCH_2CO_2H$ in the sector-field instrument. As $C_6H_5OCH_2CO_2H/Fe^+$ complexes undergo unimolecular elimination of CH_2CO,[34] we presume that the so-formed $[Fe,C_6,H_6,O_2]^+$ ions have a $C_6H_5O\text{-}Fe^+\text{-}OH$ connectivity **8** (Scheme 1). This is confirmed by the collisional activation spectrum of the compound, which displays significantly higher fractions of losses due to OH and C_6H_5O compared to **1**/FeO^+.[31, 35] Note that the MI spectrum of **8** is practically identical to that of **1**/FeO^+, that is only products corresponding to formation of water (100%) and CO (<1%) are present.

On the basis of the experimental findings, the following mechanism for the reaction of FeO^+ and phenol is proposed (Scheme 2). In the initial encounter complex of **1** and FeO^+, π coordination of the aromatic ring to FeO^+ is probably more stable than σ coordination of the hydroxy group according to typical Fe^+–ligand binding energies.[36, 37] The first step of bond activation involves the transfer of the hydroxylic hydrogen to the metal–oxo unit to give **8**. This conjecture is supported by the $FeOD^+$ signal observed in the CA spectra of the [O-D] labeled complexes **1a**/FeO^+ and **1e**/FeO^+. Fur-

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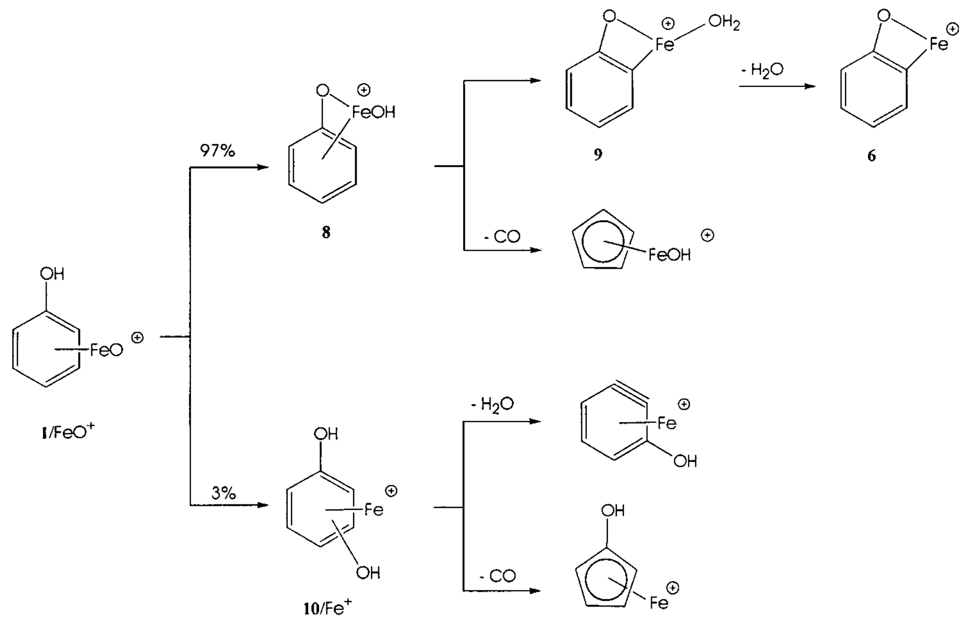
thermore, a plausible sequence for CO loss can be derived from **8** (Scheme 2). Finally, the fact that the MI spectrum of an independently generated structural isomer that is likely to have structure **8** is identical to that of **1**/FeO$^+$ strongly suggests that **8** is a central intermediate of Reaction (3). As the majority of water loss involves the *ortho* position of the arene, and as the final product is the metallacycle **6** (see above), **8** and **6** are linked by a regioselective C–H bond activation to give **9**. The fact that CID of [Fe,C$_6$,H$_6$,^{16}O,^{18}O]$^+$ ions formed under FT-ICR conditions (see above), gives rise to H$_2$^{16}O (being characteristic for **9**) as well as to C$_6$H$_5$^{18}O (being characteristic for **8**) indicates that an interconversion of **8** and **9** is facile.



Scheme 2.

The minor participation of hydrogens from *meta* and *para* positions in the water losses and the negligibly small amount of C^{16}O from **1 f**/FeO$^+$ and of ^{12}CO from **1 g**/FeO$^+$ show that oxidation of phenol to a dihydroxybenzene **10** only takes place in a side reaction. Such a formal oxygen-atom transfer from FeO$^+$ to an arene is reported to be feasible in the gas phase.[10] The resulting **10**/Fe$^+$ complexes are known to lose water and carbon monoxide in a 97:3 ratio.[38] This ratio nicely agrees with the approximate 95:5 ratio for the fragments H$_2$^{18}O and C^{16}O found in FT-ICR experiments with **1 f**/FeO$^+$, which are indicative for ring oxidation. We would like to point out that ring oxidation to yield intermediate **10**/Fe$^+$ from **1**/FeO$^+$ occurs only to a minor extent (ca. 3 %) according to the labeling experiments, while the major reaction pathway (ca. 97 %) is the highly selective formation of **6** by the sequence outlined in Scheme 2.

Thiophenol: The almost exclusive dissociation process of metastable thiophenol/FeO$^+$ complexes corresponds to the elimination of water (reaction 4).[39, 40] Minor products arising from losses of H$_2$, CO, and CS with relative intensities of less than 1 % are detected, but not pursued any further.

$$\mathbf{2}/\mathrm{FeO}^+ \longrightarrow [\mathrm{Fe,C_6,H_4,S}]^+ + \mathrm{H_2O} \qquad (4)$$

When [Fe,C$_6$,H$_4$,S]$^+$ ions generated from Reaction (4) are dissociated by means of a CA/CA experiment, a broad, unspecific fragmentation pattern is obtained; the most abundant ions correspond to elimination of CS (35 %), C$_2$H$_3$ (65 %), Fe (100 %), C$_6$H$_4$ (40 %) and [C$_6$,H$_4$,S] (75 %). Two complexes putatively isomeric to **2**/FeO$^+$ are generated independently. First, ionizing a mixture of 2-(phenylthio)acetic acid and Fe(CO)$_5$ is presumed to give C$_6$H$_5$S-Fe$^+$-OH upon loss of CH$_2$CO.[41] Second, a mixture of ethylphenyl sulfoxide and Fe(CO)$_5$ is ionized to give either sulfenic acid/Fe$^+$ or thiophenol-*S*-oxide/Fe$^+$ complexes upon loss of C$_2$H$_4$ from the organic compound. [Fe,C$_6$,H$_6$,O,S]$^+$ ions from both precursors show only loss of water in the MI spectrum, analogous to **2**/FeO$^+$.

We propose that a mechanism completely analogous to the phenol reaction is operating in the dissociation of **2**/FeO$^+$. Water loss involves activation of the S–H bond and of one C–H bond in the *ortho* position of the aromatic ring. The mechanism is further supported by the observation that ions with a presumed C$_6$H$_5$S-Fe$^+$-OH connectivity also yield an exclusive loss of water. While we have not performed labeling experiments with **2**, the generation of water arising from dehydrogenations of two aromatic positions without participation of the thiol group is considered as being improbable. If the functional group plays only a spectator role, the overall product distribution should resemble the one obtained for FeO$^+$ and unsubstituted benzene. In the latter system, water loss accounts for only 5 % of the products, while the main channels are due to the evaporation of CO, HCO, and [C$_6$,H$_6$,O].[10] This marked difference can only be rationalized by an active participation of the functional group in **2**. In spite of the overall similarity, **1**/FeO$^+$ and **2**/FeO$^+$ differ in two particular respects. i) Whereas the elimination of a C–X fragment (X = O, S) from the substrate is observed for phenol in Reaction (3b) and dominates the consecutive decay of [Fe,C$_6$,H$_4$,O]$^+$ ions, the analogous CS losses from **2**/FeO$^+$ and [Fe,C$_6$,H$_4$,S]$^+$ are much less pronounced. This difference is in line with thermochemical data that predict a much higher endothermicity for the metal-free reaction $\mathrm{C_6H_5SH \rightarrow C_5H_6 + CS}$ ($\Delta_r H = 68\,\mathrm{kcal\,mol^{-1}}$) compared to $\mathrm{C_6H_5OH \rightarrow C_5H_6 + CO}$ ($\Delta_r H = 28\,\mathrm{kcal\,mol^{-1}}$).[42] Thus, the differences in reactivity simply reflect the relative instability of the CS fragment compared to CO. ii) Metastable [Fe,C$_6$,H$_6$,O,S]$^+$ complexes with an intact S–O bond as obtained from ethylphenyl sulfoxide and Fe(CO)$_5$ also eliminate water exclusively. This finding implies an interconversion between the **2**/FeO$^+$ and C$_6$H$_5$SOH/Fe$^+$. The question whether the water loss, which follows a mechanism analogous to the one outlined in Scheme 2, is preceded by an initial, reversible *S*-oxidation of thiophenol by FeO^+ is treated in further detail in the section about thioanisol/FeO^+ (see below).

Anisol: The MI spectrum of **3**/FeO^+ is characterized by the generation of H_2O, HCO, H_2CO, and $[C,H_2,O_2]$ [Reactions (5a – 5d)].

$$\mathbf{3}/\mathrm{FeO}^+ \begin{cases} \rightarrow [\mathrm{Fe,C_7,H_6,O}]^+ + \mathrm{H_2O} & (75\,\%) & (5a) \\ \rightarrow [\mathrm{Fe,C_6,H_7,O}]^+ + \mathrm{HCO} & (100\,\%) & (5b) \\ \rightarrow [\mathrm{Fe,C_6,H_6,O}]^+ + \mathrm{H_2CO} & (15\,\%) & (5c) \\ \rightarrow [\mathrm{Fe,C_6,H_6}]^+ \quad + [\mathrm{C,H_2,O_2}] & (60\,\%) & (5d) \end{cases}$$

In order to obtain further mechanistic insight into the reaction mechanism, a series of labeling experiments and studies with isomeric ions have been performed (Table 3 and Table 4, Scheme 3 and Scheme 4). Let us first discuss the individual dissociation channels and products separately. On the basis of the experimental findings, an overall reaction mechanism is derived further below.

Reaction (5a): Complete deuterium labeling of the methyl group (**3b**) gives rise to losses of H_2O, HDO, and D_2O in a 4:25:71 ratio. Thus, more than 83 % of the hydrogen atoms in the water loss stem from the substituent, although some scrambling with ring positions occurs. Even *meta* positions of the ring participate to a minor extent in the scrambling process, as indicated by the formation of H_2O and HDO in a 97:3 ratio from **3d**/FeO^+. Note that any unintended H/D exchange of the neutral precursor in the ion source can safely be excluded for **3d**. The extent of scrambling is subject to isotope effects, as 95 % of hydrogen atoms stem from the methoxy group for ring-labeled **3c**/FeO^+. The origin of the oxygen atom involved in dehydration is determined from **3f**/FeO^+, which yields exclusive losses of $H_2{}^{16}O$; the ^{18}O label is completely retained in the substrate.

Table 3. Neutral fragments in the MI mass spectra of $[Fe,C_7,H_8,O_2]^+$ ions and their isotope-labeled analogues obtained by chemical ionization of different precursors with $Fe(CO)_5$.

	Neutral losses[a]										
Substrate	H_2O	HDO	D_2O	CO	HCO	H_2CO, DCO, $H^{13}CO$	$HC^{18}O$, HDCO, $H_2{}^{13}CO$	D_2CO, $H_2{}^{18}CO$	$[C,H_2,O_2]$	$[^{13}C,H_2,O_2]$ $[C,H,D,O_2]$	$[C,H_2,O,^{18}O]$ $[C,D_2,O_2]$
3/N_2O	75				100	15			60		
3a/N_2O	13	56	9		26	100	7	7	2	48	12
3b/N_2O	3	18	51		6	100	[b]	20		4	40
3c/N_2O	58	6			100	12			54	2	
3d/N_2O	89	2			100	14			59		
3e/N_2O	59					100	19			58	
3f/N_2O	68						100	11			56
$C_6H_5OCH_2CO_2H$	95			2	50	1			100		
$C_6H_5CO_2H/H_2CO$	95			35[c]	50	25[c]			100		
C_6H_5OH/H_2CO				3		100					
C_6H_5CHO/H_2O	100										
$C_6H_6/CO/H_2O$	100			57							
C_6H_6/HCO_2H	5			3					100		

[a] Intensities are given relative to the base peak = 100 %. [b] Taking into account the signal-to-noise ratio, traces of HDCO (< 5 % relative to D_2CO) cannot be excluded. [c] Upper limit; an overestimate due to interference signals from ^{58}Fe- and ^{18}O-isotopomers of $Fe(C_6H_5CO_2H)(CO)^+$ is possible.

Table 4. Characteristic neutral fragments in the CA/CA spectra of ionic products from **3**/FeO^+ and in the CA spectra of $[Fe,C_7,H_6,O]^+$ and $[Fe,C_6,H_7,O]^+$ ions obtained by chemical ionization of different precursors.

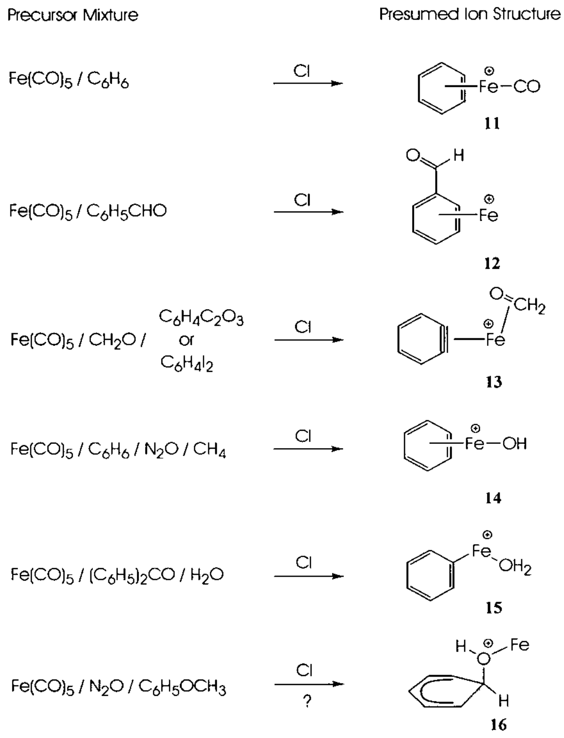
	Neutral losses[a]												
	CO	HCO, ^{13}CO	H_2CO, $H^{13}CO$, DCO	H_3CO, HDCO	$[C_3,H_3,O]$	$[C_3,H_4,O]$	FeH	FeD	C_6H_4	FeCHO	FeCDO	$[C_7,H_6,O]$	$[C_7,H_5,D,O]$, $[C_6,^{13}C,H_6,O]$
[**3**/FeO^+ – H_2O]	100	15	12		7		15			5		40	
[**3b**/FeO^+ – D_2O]	100	[b]	20	15			5	10			5		55
[**3e**/FeO^+ – H_2O]		100	[b]			20	15						70
$Fe(CO)_5/C_6H_6/CO$	100	7	1		2	1	1					10	
$Fe(CO)_5/C_6H_5CHO$	100	18	6		6	3	8			5		40	
$Fe(CO)_5/C_6H_4C_2O_3/H_2CO$	95	8	100	4		9	9		6			10	

	Neutral losses[a]									
	OH	H_2O/OD	$[H_3,O]$/HDO	$[H,D_2,O]$	CO	C_6H_5	C_6H_5D	C_6H_6	$[C_6,H_7,O]$	$[C_6,H_5,D_2,O]$
[**3**/FeO^+ – HCO]	30	20	20					100	30	
[**3b**/FeO^+ – DCO]	10	20	10	20			100			30
$Fe(CO)_5/N_2O/C_6H_6/CH_4$	100	20	5		10			50	35	
$Fe(CO)_5/(C_6H_5)_2CO/H_2O$	2	100	9		6	5		8	13	

[a] Intensities are given relative to the base peak = 100 %. [b] Determination not possible due to overlap with adjacent signals.

The structure of the dehydration product formed in Reaction (5a) with the elemental composition $[Fe,C_7,H_6,O]^+$ has been further elucidated by CA/CA experiments, in which losses of CO (100%), HCO (15%), H_2CO (12%), FeH (15%), and $[C_7,H_6,O]$ (40%) are observed (Table 4). For [**3b**/$FeO^+ - D_2O$], DCO and HDCO instead of HCO and H_2CO are produced in the analogous CA/CA experiment. Furthermore, the experiment with [**3e**/$FeO^+ - H_2O$] yields losses of ^{13}CO, $H^{13}CO$, $H_2{}^{13}CO$ etc., demonstrating that the ejected carbon atom stems only from the methyl group of anisol and not from the aromatic ring.

These fragmentation patterns can be compared to three well-defined isomeric $[Fe,C_7,H_6,O]^+$ ions generated by independent routes (Scheme 3). First, chemical ionization (CI) of a mixture of $Fe(CO)_5$, benzene, and CO is assumed to yield the $Fe(CO)(C_6H_6)^+$ complex **11**. Second, chemical ionization of $Fe(CO)_5$ with benzaldehyde gives rise to $[Fe,C_7,H_6,O]^+$ ions that presumably have the $Fe(C_6H_5CHO)^+$ structure **12**. Finally, structure **13** was approached by ionizing a mixture of $Fe(CO)_5$, phthalic acid anhydride $C_6H_4C_2O_3$, and formaldehyde. Taking 1,2-diiodobenzene instead of phthalic acid anhydride as the aryne precursor gives rise to an identical spectrum. The following differences between the spectra of these three reference isomers should be pointed out. Only the $[Fe,C_7,H_6,O]^+$ ions obtained from $Fe(CO)_5/H_2CO/C_6H_4C_2O_3$ show pronounced losses of formaldehyde and C_6H_4, in line with the presumed structure **13**. $[Fe,C_7,H_6,O]^+$ ions obtained from $Fe(CO)_5/C_6H_5CHO$ can be differentiated from those made by $Fe(CO)_5/C_6H_6/CO$ by i) the presence of a $C_6H_5CO^+$ ion (concomitant with the formation of neutral FeH) and by ii) a more pronounced signal for Fe^+ (concomitant with elimination of neutral C_7H_6O) relative to CO loss (Table 4). Both features confirm the proposed ion structures **11** and **12**, respectively, as a benzoyl cation is indicative for the presence of a benzaldehyde unit, and as the ratio of $[C_7,H_6,O]$ loss versus CO loss is expected to be higher for $Fe(C_6H_5CHO)^+$ than for $Fe(C_6H_6)(CO)^+$ complexes.



Scheme 3.

In comparison, the dissociation pattern of $[Fe,C_7,H_6,O]^+$ ions obtained by dehydration of **3**/FeO^+ is much more similar to that of **12** than to that of **11** and **13** with respect to the structure-indicative fragments mentioned above. We therefore propose that the ionic product of Reaction (5a) corresponds to the iron–benzaldehyde complex **12**. An iron–(phenoxy)carbene structure would also rationalize the labeling experiments for the water loss; an experimental investigation of this structure was not feasible due to the lack of appropriate precursors. However, the formation of an iron–(phenoxy)carbene cation from **3**/FeO^+ is considered to be unlikely, because among the reactions of a large variety of substrates with FeO^+, a 1,1-dehydrogenation of a carbon center has not been observed for kinetic reasons.[43] One might argue that for **3**/FeO^+, the formation of the iron–carbene complex is facilitated by the heteroatom. Nevertheless, substrates structurally similar to **3** such as dimethyl ether do not react with FeO^+ via carbene formation, but undergo only single C–H bond activation, followed by C–O bond activation.[44] Exactly this sequence is also proposed for **3**/FeO^+ and directly leads to the formation of **12** in Reaction (5a), as demonstrated below.

Reaction (5b): Loss of the formyl radical involves the methoxy group. Thus, **3e**/FeO^+ and **3f**/FeO^+ show exclusive losses of $H^{13}CO$ and $HC^{18}O$, respectively. However, H/D equilibration precedes dissociation to a minor extent as demonstrated by the 6:94 ratio of HCO:DCO generated from **3b**/FeO^+. Assuming that the participation of ring protons is similar for **3a**/FeO^+, we can use the experimentally observed HCO:DCO ratio of 21:79 to deduce an estimate for the kinetic isotope effect of Reaction (5b) of $k_H/k_D = 2.8 \pm 0.5$.[45, 46]

The product of Reaction (5b) with the elemental composition $[Fe,C_6,H_7,O]^+$ preferentially loses C_6H_6 in a CA/CA experiment, whereas formations of OH, H_2O, and $[H_3,O]$ occur to a comparable extent (Table 4). With $[Fe,C_6,H_5,D_2,O]^+$ ions arising from the DCO loss of **3b**/FeO^+, the fragments OD and $[H,D_2,O]$ are eliminated instead of OH and $[H_3,O]$.

This dissociation pattern is compared to that of $[Fe,C_6,H_7,O]^+$ ions generated independently by chemical ionization (CI) from different precursors (Scheme 3). First, an iron hydroxide cation ligated by benzene **14** was approached by ionizing a mixture of $Fe(CO)_5$, N_2O, benzene, and methane. Second, structure **15** was approached by ionizing $Fe(CO)_5$, benzophenone $(C_6H_5)_2CO$, and water. The former two components are assumed to give the phenyliron cation,[47] which is then complexed with water.

The collisional activation spectra of these $[Fe,C_6,H_7,O]^+$ ions generated by three different routes are distinctly different from each other. The spectrum obtained from $Fe(CO)_5/H_2O/(C_6H_5)_2CO$ is dominated by water loss and shows a characteristic signal due to the elimination of C_6H_5; these results are in keeping with the assumed structure **15**. As far as the other two $[Fe,C_6,H_7,O]^+$ ions are concerned, a structural assignment is less straightforward. For the $Fe(CO)_5/N_2O/C_6H_6/CH_4$ mixture, the following observations support the assignment of a $(C_6H_6)FeOH^+$ connectivity: i) Bare FeO^+ can be converted completely to $FeOH^+$ in an excess of CH_4 and N_2O.[48] ii) A mixture of $Fe(CO)_5$, C_6H_6, and N_2O is known to produce a complex with $(C_6H_6)FeO^+$ connectivity at m/z 150.[10b] iii) When CH_4 is added to a mixture of $Fe(CO)_5$, C_6H_6, and N_2O, the signal at m/z 150 disappears, while a new signal at m/z 151 appears. iv) Ionizing a mixture of CH_4, $Fe(CO)_5$, C_6D_6, and N_2O gives a complex at m/z 157, which loses OH (100%), OD/H_2O (20%), and $HDO/[H_3,O]$ (15%) upon collisional activation, demonstrating that the hydrogen atom from methane is transferred to the oxygen atom of $(C_6D_6)FeO^+$, whereas transfer to the ring is negligible. Thus, the mode of generation and the dominant losses of OH and C_6H_6 are in favor of the assumed $(C_6H_6)FeOH^+$ connectivity. However, the preference of elimation of OH over that of C_6H_6 contradicts the binding energies, as $D(Fe^+{-}OH) = 87.5 \pm 2.9\,kcal\,mol^{-1}$ is much larger than $D(Fe^+{-}C_6H_6) = 49.6 \pm 2.3\,kcal\,mol^{-1}$;[36] it might be that the dissociation of the former ligand is preferred on dynamic grounds because of more favorable statistical factors arising from the higher number of low-frequency modes in $Fe^+{-}(C_6H_6)$ compared to $Fe^+{-}OH$. Another reason for the counterintuitive ratio of OH and C_6H_6 losses arises from the consideration of spin multiplicities. Bare $FeOH^+$ is known to have a $^5A'$ ground state[49] and $Fe(C_6H_6)^+$ is a quartet.[53] In **14**, however, the benzene ligand may force the system to the triplet surface.[50] Accordingly, dissociation at a putative triplet state of **14** would be spin allowed, but loss of benzene would lead to $FeOH^+$ in an excited triplet state.[51] This would thereby result in a discrimination of C_6H_6 loss and could thus explain the experimental results. Finally, it should be pointed out that knowledge about structural properties of the monoligated species $FeOH^+$ and $Fe(C_6H_6)^+$ does not suffice to predict the actual structure of a bisligated $(C_6H_6)FeOH^+$ complex, because recent quantum chemical studies[11, 52] demonstrate that transition metals might adopt unexpected hapticities towards π ligands upon oxidation. For example, oxidation of $(C_6H_6)Fe^+$ to $(C_6H_6)FeO^+$ is associated with a change from a η^6 coordination[53] to a η^2 coordination[11] of the metal to the arene.

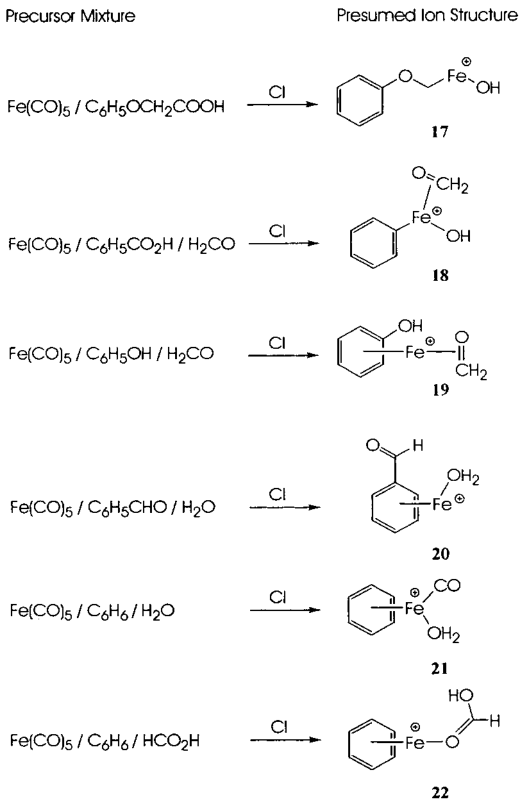
The analysis of the CA/CA spectrum of $[Fe,C_6,H_7,O]^+$ ions obtained from Reaction (5b) has to account for two remarkable features: Elimination of C_6H_6 is very facile, and losses of H_xO ($x = 1-3$) are nonspecific. Therefore, metallacyclic structures in which iron forms part of the ring appear quite unlikely. Most surprisingly, the C_6H_6 loss proceeds much easier than in the complex with presumed $(C_6H_6)FeOH^+$ connectivity. A weakly bound benzene unit might be realized by a η^1 coordination of the ring by the hydroxy group as displayed in structure **16**. The structure is in line with the observed CA/CA spectrum, as it rationalizes the facile formation of C_6H_6 as well as the nonspecific eliminations of H_xO ($x = 1-3$). Although structures similar to **16** have been proposed by theoretical calculations to be of relevance for cytochrome P-450 chemistry,[54] it is obvious that more detailed experimental and computational work on $[Fe,C_6,H_7,O]^+$ isomers is indispensable to check the above structural proposals. These are, however, beyond the scope of the present study.

Reaction (5c): Exclusive losses of D_2CO, $H_2{}^{13}CO$, and $H_2C^{18}O$ from **3b**/FeO^+, **3e**/FeO^+, and **3f**/FeO^+ demonstrate that only atoms from the methoxy group of anisol participate in Reaction (5c). Accordingly, the 1:1 ratio of HDCO and D_2CO formations from **3a**/FeO^+ implies a kinetic isotope effect of $k_H/k_D = 2.0$ operative in Reaction (5c). Unfortunately, the intensity of $[Fe,C_6,H_6,O]^+$ ions did not suffice to carry out CA/CA experiments, thereby preventing a structural comparison of the product ion with reference isomers.

Reaction (5d): Metastable **3**/FeO^+ complexes yield $[Fe,C_6,H_6]^+$ concomitant with loss of neutral $[C,H_2,O_2]$. The high regioselectivity of this process is demonstrated by labeling experiments with **3b**/FeO^+, **3e**/FeO^+, and **3f**/FeO^+, which yield neutral $[C,H,D,O_2]$ and $[C,D_2,O_2]$ in a 9:91 ratio and exclusive losses of $[^{13}C,H_2,O_2]$ and $[C,H_2,O,^{18}O]$, respectively. As the CA/CA spectrum of $[Fe,C_6,H_6]^+$ ions produced by Reaction (5d) cannot be distinguished from the CA spectrum of an independently generated complex of iron with benzene, we suggest that Reaction (5d) also yields $Fe(benzene)^+$ as the final ionic product.

So far, different isomers have served to elucidate the product structures of Reaction (5). The dissociations of isomeric ions with the elemental composition $[Fe,C_7,H_8,O_2]^+$ generated from six different precursors might help to understand the first rearrangement steps of **3**/FeO^+ to intermediate structures *prior to* dissociation (Table 3, Scheme 4). First, we attempted to approach structure **17** by ionizing phenoxyacetic acid and $Fe(CO)_5$, taking into account the fact that phenoxyacetic acid/Fe^+ complexes undergo decarbonylation.[34] The generation of **18** was attempted by ionizing a mixture of benzoic acid, formaldehyde, and $Fe(CO)_5$. Benzoic acid and $Fe(CO)_5$ are known to undergo multiple CO losses under CI conditions to yield a complex with C_6H_5-Fe^+-OH connectivity,[10b] which might then be ligated with formaldehyde to give presumably **18**. α-Elimination of iron from **18** would yield the $Fe(C_6H_5OH)(H_2CO)^+$ complex **19**. We tried to generate **19** by ionizing a mixture of $Fe(CO)_5$, phenol, and formaldehyde. Ionization of a mixture of $Fe(CO)_5$, H_2O, and benzaldehyde presumably yields the bisligated complex $Fe(H_2O)(C_6H_5CHO)^+$ **20**. A mixture of $Fe(CO)_5$, C_6H_6, and H_2O is ionized in order to afford the trisligated complex $Fe(CO)(C_6H_6)(H_2O)^+$ **21**. Finally, ionization of $Fe(CO)_5$, C_6H_6, and formic acid HCO_2H presumably yields the complex **22** with a $Fe(C_6H_6)(HCO_2H)^+$ connectivity.

In general, the fragmentation patterns of the $[Fe,C_7,H_8,O_2]^+$ ions formed from these precursor mixtures are in good agreement with the proposed connectivities (Table 3). Specifically, intense losses of H_2CO are only observed for the ions formed from $Fe(CO)_5/C_6H_5CO_2H/H_2CO$ and from $Fe(CO)_5/C_6H_5OH/H_2CO$, thus in keeping with structures **18** and **19**. The fact that metastable ions from a $Fe(CO)_5/C_6H_5CHO/H_2O$ mixture lose only water is in line with the assumed connectivity **20**. The absence of an arene ligand loss reflects the

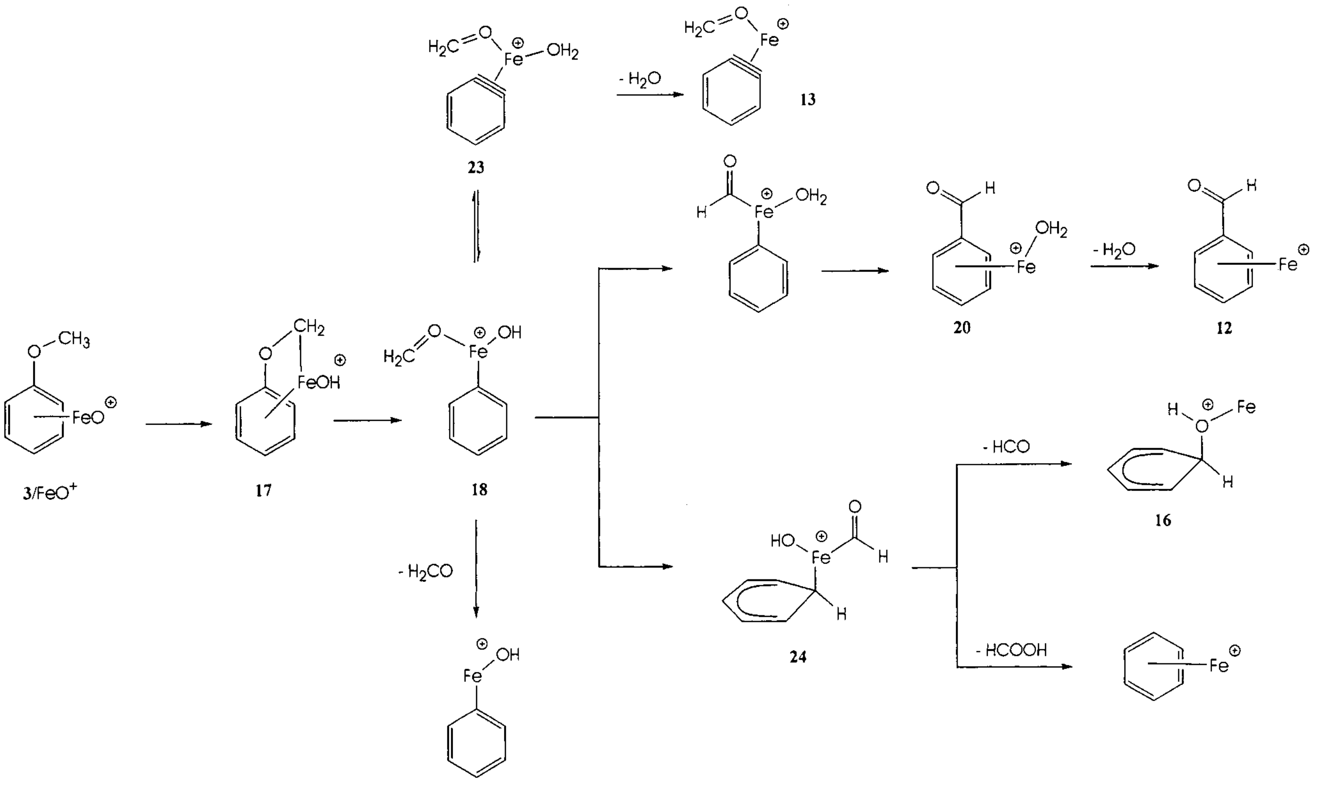


Scheme 4.

fact that $D(\mathrm{Fe^+{-}C_6H_5CHO}) \approx 48\,\mathrm{kcal\,mol^{-1}}$[55] largely exceeds $D(\mathrm{Fe^+{-}H_2O}) = 30.6\,\mathrm{kcal\,mol^{-1}}$.[36] Likewise, the assumption that ions obtained from $\mathrm{Fe(CO)_5/C_6H_6/H_2O}$ have structure **21** is supported by the observed formations of water and CO. The ratio of H_2O versus CO loss is again in line with the order of binding energies for the monoligated species ranging from $D(\mathrm{Fe^+{-}H_2O}) = 30.6\,\mathrm{kcal\,mol^{-1}}$ and $D(\mathrm{Fe^+{-}CO}) = 31.3\,\mathrm{kcal\,mol^{-1}}$ to $D(\mathrm{Fe^+{-}C_6H_6}) = 49.6\,\mathrm{kcal\,mol^{-1}}$.[36] For ions generated from $\mathrm{Fe(CO)_5/C_6H_6/HCO_2H}$, the dominant loss of HCO_2H fully confirms the proposed structure **22**.

Let us now compare the MI-dissociation pattern of **3**/FeO$^+$ with that of the six $[\mathrm{Fe,C_7,H_8,O_2}]^+$ ions described above, thereby relating the six ions to their assumed structures **17**–**22**. Structures **19**, **20**, and **22** are product complexes and the direct precursors for the dissociations of H_2O [Reaction (5a)], H_2CO [Reaction (5c)], and $[\mathrm{C,H_2,O_2}]$ [Reaction (5d)]. The barriers for reverse reactions from the product complexes are high compared to the exit channels, as **19**, **20**, and **22** show almost exclusively the expected specific ligand losses. As **3**/FeO$^+$ complexes do not loose CO, **21** is not supposed to play any role in the FeO$^+$-mediated decomposition of anisol. Starting from **17** and **18**, channels (5a), (5b), and (5d) can be reached, which suggests that **17** and **18** are intermediate structures for several dissociation channels of **3**/FeO$^+$. Both ions loose H_2O and $[\mathrm{C,H_2,O_2}]$ in the same ratio as observed for **3**/FeO$^+$, but both do not show the preference of **3**/FeO$^+$ for formyl loss. This either indicates that a different intermediate structure is relevant for formyl loss, which has not been generated here. Alternatively, the product ratio might depend on the way the intermediate is generated due to molecular dynamic effects.[56]

On the basis of the experimental data presented above, let us now develop a reaction mechanism that rationalizes the product formation (Scheme 5). The difference in ionization energies of anisol and FeO (IE = 8.21 eV for anisol[42] vs.



Scheme 5.

8.8 eV for FeO[57]) suggests that electron density is transferred from **3** to FeO^+, resulting in an enhanced acidity of the methyl protons as well as an enhanced basicity of the iron–oxo unit. Thus, hydrogen transfer from the substrate to FeO is likely to occur to give **17**. The charge in **17** is mainly located in the organic π system rather than on the FeOH unit, as suggested by IE(FeOH = 7.9 eV) > IE($H_3COCH_2^{\bullet}$ = 6.9 eV).[42] However, precise information about the suite of elementary steps (electron transfer/proton transfer vs. hydrogen atom transfer)[2] is not provided in the experiment. Insertion of iron into the C(phenyl)–oxygen bond leads to structure **18**. Direct loss of the formaldehyde ligand from **18** accounts for the absence of H/D scrambling in Reaction (5c). The kinetic isotope effect associated with Reaction (5c) of $k_H/k_D = 2.0$ derived from **3a**/FeO^+ then corresponds to the primary C–H bond activation of the methoxy group in anisol.

The mechanism leading to loss of water [Reaction (5a)] has to comply with the labeling distribution observed for the deuterium-labeled anisols. As mentioned above, the hydrogen atoms involved in this process stem mainly from the methoxy group. Starting from the intermediate **18**, a further hydrogen shift from the formaldehyde ligand to the hydroxy group followed by reductive elimination gives **20** as a direct precursor for H_2O loss as demonstrated by the CA/CA experiments. Partial H/D scrambling with the *ortho* positions might occur by a reversible aryne formation from **18** to **23** as depicted in Scheme 5. This process rationalizes the formation of HDO and H_2O from **3b**/FeO^+ complexes as well as the minor HDO loss from **3d**/FeO^+. As the D_2O:HDO:H_2O ratio is higher than any value obtained by assuming statistical H/D equilibration with one or more ring hydrogens, the rate constants leading to product formation are higher than those for H/D scrambling. The fact that the degree of H/D scrambling is higher for Reaction (5a) than for Reactions (5b)–(5d) may suggest that **23** is also involved as a possible intermediate for the dehydration.

Prior to loss of HCO [Reaction (5b)], a hydrogen atom has to be shifted from the formaldehyde ligand of the intermediate **18**. However, this atom is *not* transferred directly to the hydroxy group before HCO loss, as the CA/CA spectrum of $[Fe,C_6,H_7,O]^+$ molecules generated in Reaction (5b) is different from that of **15** (Scheme 3). Instead, either a transfer to the aromatic ring to give **24** or a β-hydride transfer to the metal is conceivable. However, due to the somewhat obscure connectivity of $[Fe,C_6,H_7,O]^+$ product ions (see above), the sequence depicted in Scheme 5 is not more than a proposal. The fact that the HCO:DCO ratio is far from being statistical demonstrates that cleavage of the formyl radical is faster than the exchange of hydrogen atoms from the methoxy group with those from the ring positions.

The central question with respect to Reaction (5d) concerns the structure of the neutral fragment(s) with the elemental composition $[C,H_2,O_2]$. Is formic acid generated in Reaction (5d), or are two distinct molecules lost consecutively? In particular the combinations HCO + OH and H_2O + CO appear reasonable, because HCO and H_2O fragments are actually lost in the MI spectrum. However, the former combination can be excluded, as the $[Fe,C_6,H_7,O]^+$ ions formed in Reaction (5b) hardly lose OH upon collisional activation. Expulsion of H_2O followed by that of CO can be discarded on the basis of two arguments. i) The intensity of CO loss from metastable $[Fe,C_7,H_6,O]^+$ ions produced in Reaction (5a) in an MI/MI experiment is only 0.3% of the signal for the $[Fe,C_7,H_6,O]^+$ parent ion. Thus, the small amount of $[Fe,C_6,H_6]^+$ ions produced by consecutive losses of H_2O and CO cannot account for the intensity ratio of 56:44 observed for channels (5a) and (5d). ii) If $[Fe,C_6,H_6]^+$ ions were formed by consecutive losses of H_2O and CO, the degree of H/D-scrambling would have to be identical for channels (5a) and (5d). However, whereas H_2O, HDO, and D_2O are lost in a ratio of 4:25:71 from **3b**/FeO^+, the $[C,H_2,O_2]$:$[C,H,D,O_2]$:$[C,D_2,O_2]$ pattern is < 1:9:91. Other combinations for a consecutive elimination of two molecules are conceivable, for example $H_2 + CO_2$, $CO_2 + H_2$, or CO + H_2O. However, note that peaks due to losses of H_2, CO_2, or CO are not observed in the MI spectrum. This means that the rate constant for the second fragmentation would have to be higher than that for the first process by several orders of magnitude. Consequently, formation of formic acid as an intact $[C,H_2,O_2]$ neutral is implied. Although neither of the two possibilities can be strictly ruled out, only the more likely loss of formic acid is included in Scheme 5. Note that the proposal of **24** as a common intermediate for Reactions (5b) and (5d) is further supported by the fact that the observed degrees of H/D scrambling in **3a**/FeO^+ and **3b**/FeO^+ are similar in these pathways.

Thioanisol: Whereas the reactivity of thiophenol and phenol towards FeO^+ is similar, thioanisol exhibits distinctly different behavior compared to anisol. Four dissociation processes take place according to Reaction (6).

$4/FeO^+ \longrightarrow [Fe,C_7,H_6,S]^+ + H_2O$ 100% (6a)
$4/FeO^+ \longrightarrow [Fe,C_7,H_6,O]^+ + H_2S$ 8% (6b)
$4/FeO^+ \longrightarrow [Fe,C_6,H_6,O]^+ + H_2CS$ 10% (6c)
$4/FeO^+ \longrightarrow C_7H_7^+ + [Fe,H,O,S]$ 40% (6d)

Dehydration [Reaction (6a)] constitutes the dominant dissociation pathway; in marked contrast to anisol/FeO^+, ring hydrogens participate to a large extent, because H_2O, HDO, and D_2O are lost in a 3:89:8 ratio from **4b**/FeO^+ (Table 5). A kinetic isotope effect of $k_H/k_D = 2.5 \pm 0.5$ associated with Reaction (6a) is derived from **4a**/FeO^+.[45, 58] The product of Reaction (6a) with the elemental composition $[Fe,C_7,H_6,S]^+$ has been submitted to a CA/CA experiment, yielding a rather broad distribution of fragmentations dominated by losses due to C_2H_2 (100%), CS (75%), H_2CS (80%), Fe (50%), C_6H_6 (95%), and $[C_7H_6S]$ (60%).

The formation of $C_7H_7^+$ [Reaction (6d)] hardly involves ring positions according to deuterium-labeling experiments. The kinetic isotope effect for Reaction (6d) amounts to $k_H/k_D = 4.7$ as derived from **4a**/FeO^+. This value is almost identical to the KIE observed for the generation of $C_7H_6D^+$/$C_7H_5D_2^+$ concomitant with loss of DS/HS from metastable, thioanisol radical cations **4a**$^{\bullet+}$ ($k_H/k_D = 4.9$);[59] possible mech-

Table 5. Neutral fragments in the MI spectra of $[Fe,C_7,H_8,O,S]^+$ ions obtained by chemical ionization of different precursors with $Fe(CO)_5$.

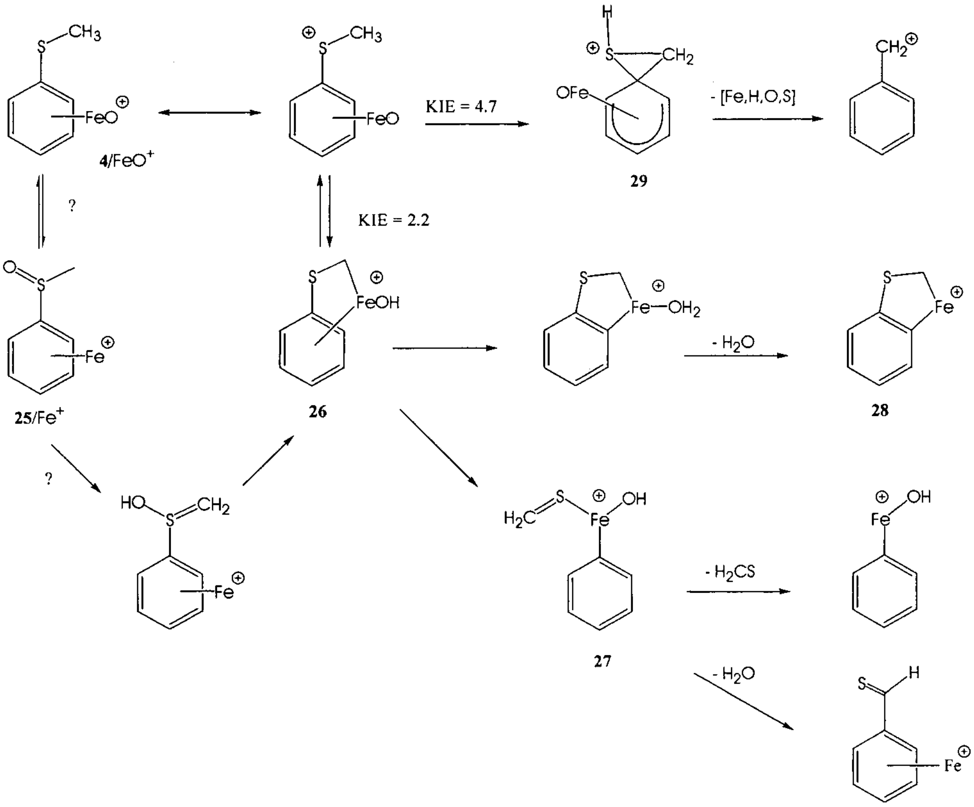
	Neutral losses[a]										
Substrate	H_2O	HDO	D_2O	H_2S	HDS	D_2S	H_2CS	HDCS, $H_2{}^{13}CS$	D_2CS	[Fe,H,O,S]	[Fe,D,O,S]
4/N_2O	100			8			10			40	
4a/N_2O	100	90	4		10			1	1	47	20
4b/N_2O	4	100	9			2			3	4	50
4c/N_2O	100			5				3		31	
$C_6H_5S(O)CH_3$	100			4			3				52
$C_6H_5S(O)CHD_2$	100	100	7		4	1		6	4	71	38
$C_6H_5S(O)CD_3$	5	100	11			1		1	4	2	45
$C_6H_5SCH_2CO_2H$	100			9							50

[a] Intensities are given relative to the base peak = 100%.

anistic implications of this finding are discussed below. Let us now address the question of the structural connectivity of $C_7H_7^+$ ions formed in Reaction (6d). It has been demonstrated previously that a benzylium or a tropylium connectivity can be distinguished experimentally in the gas phase by reacting $C_7H_7^+$ with toluene.[60] Whereas benzylium ions react efficiently with toluene to yield xylenium ions and benzene, the isomeric tropylium ions are unreactive towards toluene. We have applied this test by monitoring the bimolecular reaction between isolated FeO^+ and leaked-in **4** in an FT-ICR spectrometer. The $C_7H_7^+$ ions obtained under these conditions are isolated and subsequently allowed to react with pulsed-in [D_8]toluene. A $[C_8,H_2,D_7]^+$ ion (m/z 112) is formed predominantly. Weaker signals at m/z 111 (10%) and m/z 113 (10%) are identified as $[C_8,H_3,D_6]^+$ and $[C_7,{}^{13}C,H_2,D_7]^+$ using high-resolution FT-ICR mass spectrometry; these ions can by and large be attributed to the incompleteness of deuterium labeling and the natural abundance of ^{13}C, respectively, in [D_8]toluene. This result demonstrates unambiguously that the $C_7H_7^+$ ions formed by the FeO^+-mediated decomposition of thioanisol have the benzylium structure. Only *one* neutral molecule [Fe,H,O,S] is formed in Reaction (6d), as the generation of two separate neutrals like FeO + SH, FeS + OH, or FeH + SO is predicted to be endothermic relative to **4** + FeO^+ by 20, 29, and 49 kcal mol^{-1}, respectively.[36, 42] The structure of [Fe,H,O,S] cannot be determined, however, due to the lack of any thermochemical data. We note in passing that the product distribution obtained in the unimolecular dissociation of metastable **4**/FeO^+ in sector MS differs significantly from that of the bimolecular reaction under FTICR-MS conditions, where H_2O (7%), H_2CS (15%), H_2COS (10%), FeO (100%), FeOH (9%), and [Fe,H,O,S] (77%) are lost as neutral fragments. Thus, the increased average internal energy compared to sector MS gives rise to processes like electron transfer and hydride abstraction that are fast, but have a moderate exothermicity; on the other hand, reactions with entropically restricted transition states like loss of water become less pronounced. In sector MS, dissociative ET or hydride abstraction reactions certainly also occur in the ion source, but are not observed for the low-energy fraction of complexes sampled by the MI experiment on energetic grounds. Instead, these ions undergo entropically demanding isomerizations to the energetically favorable exit channels (6a)–(6d).

Two $[Fe,C_7,H_8,O,S]^+$ complexes generated from different precursors are examined for comparison by sector MS. Interestingly, the unimolecular dissociation pattern of Fe^+-complexed methylphenyl sulfoxide **25** is almost superimposable to that of **4**/FeO^+ (Table 5).[61] Furthermore, also the labeling distributions are identical within experimental error for **4b**/FeO^+ and ([D_3]methyl)phenyl sulfoxide/Fe^+. KIEs have been derived from ([D_2]methyl)phenyl sulfoxide/Fe^+ complexes. For the generation of $C_7H_6D^+$/$C_7H_5D_2{}^+$, a somewhat lower isotope effect compared to **4a**/FeO^+ is obtained ($k_H/k_D = 3.7$ vs. 4.7); the KIEs associated with losses of H_2O/HDO are identical, however. Second, a mixture of 2-(phenylthio)acetic acid $C_6H_5SCH_2CO_2H$ and $Fe(CO)_5$ is ionized to give $[Fe,C_7,H_8,O,S]^+$ ions, which are assumed to have a $C_6H_5SCH_2$-Fe-OH^+ connectivity **26**.[41] Again, the unimolecular losses are almost identical to those arising from **4**/FeO^+ and **25**/Fe^+.

Let us now consider the mechanism of Reaction (6) on the basis of the experimental findings presented above (Scheme 6). Any proposal has to comply with the remarkable feature of **4**/FeO^+ (and also of **25**/Fe^+) that the isotope effect associated with Reaction (6d) (KIE = 4.7) is significantly larger than that of Reaction (6a) (KIE = 2.2), although both processes require the cleavage of only one C–H bond. Therefore, Reactions (6a) and (6d) must have different elementary steps for the C–H bond activation from the methyl group, assuming that secondary isotope effects cannot account for the difference. Another central mechanistic topic concerns the question of initial *S*- vs. *C*-oxidation of **4** by FeO^+. The similarities in product distributions and isotope effects strongly suggest that **4**/FeO^+ and **25**/Fe^+ either equilibrate or both collapse to a common intermediate. According to thermochemical data,[42] the *S*-oxidation of **4** by FeO^+ to **25** and Fe^+ is associated with a moderate exothermicity of about 8 kcal mol^{-1} and therefore feasible under ICR conditions. On the other hand, theoretical calculations predict the *C*-oxidized intermediate $C_6H_5SCH_2OH$ to be 27 kcal mol^{-1} more stable than its isomer **25**.[4] None of the products obtained in Reaction (6) indicates an initial *S*-oxidation; furthermore, losses of H_2O, H_2S, and H_2CS from **25**/Fe^+ require the *cleavage* of the S–O bond. Despite numerous examples for *S*-oxidations by metal–oxo species in the condensed phase, no evidence for an equivalent process in the gas phase has been obtained yet.[14, 62] Thus, the observed products can only be rationalized by a *C*-oxidation; an initial, reversible *S*-oxidation preceding product formation, however, cannot be rigorously ruled out. For a *C*-oxidation, the first mechanistic steps are analogous to the sequence



Scheme 6.

derived for anisol. Electron density is transferred from thioanisol to FeO$^+$, followed by proton transfer from the methyl group to oxygen to yield **26**. These assumptions are supported by the significant differences in IEs (8.8 eV for FeO vs. 7.94 eV for thioanisol)[42] as well as by the observation that neutral FeO and FeOH are formed in the bimolecular reaction of FeO$^+$ and **4** under ICR conditions. The C–H bond activation is subject to an isotope effect of $k_H/k_D = 2.5$ according to the ratio of H_2O/HDO losses from **4a**/FeO$^+$. Note that from a precursor that supposedly gives **26**, an identical MI dissociation pattern is obtained, thus supporting the view that **26** is a central reaction intermediate. From **26**, H_2CS is eliminated after insertion of iron into the C(phenyl)–sulfur bond [Reaction (6c)] to **27**. Loss of H_2CS is less abundant compared to that of H_2CO from **3**/FeO$^+$, and elimination of HCS is not observed at all. These differences can by and large be attributed to the relatively low stabilities of C–S multiple bonds.[63]

Loss of water from **26** involves a C–H bond activation from the *ortho*-position of the ring, giving the metallacycle **28** as the major ionic product. The small degree of H_2O elimination observed for **4b**/FeO$^+$ indicates that the activation of aromatic C–H bonds is reversible; however, dissociation is much faster than H/D equilibration. The fact that more D_2O than H_2O is lost from **4b**/FeO$^+$ indicates the presence of a minor, competing mechanism for water loss that involves only the methyl group; this side reaction is proposed to follow a mechanism similar to the one derived for **3**/FeO$^+$. Note however that the ratios of ring participation vs. twofold substituent activation for water losses differ significantly for **3**/FeO$^+$ and **4**/FeO$^+$. The reluctance of **4**/FeO$^+$ to undergo twofold substituent activation is ascribed to the instability of the putative intermediate **27** containing an unfavorable C–S multiple bond.

According to the observed KIEs, the conversion of **4**/FeO$^+$ to **26** does *not* comprise the C–H bond activation step responsible for Reaction (6d). As the KIE for $C_7H_7^+$-formation from **4**/FeO$^+$ is identical to that found from **4**$^{\cdot+}$, we suggest that a mechanism similar to that for HS loss from the bare radical cation is operating. Thus, starting from **4**/FeO$^+$, a hydrogen atom is shifted from carbon to sulfur without metal assistance. Model calculations on $H_3CSCH_3^{\cdot+}$ predict a barrier of about 48 kcal mol^{-1} for the migration step.[64] A lower barrier is expected for **4**/FeO$^+$, as the migration is facilitated by anchimeric assistance of the aromatic ring through the bridged intermediate **29**. However, the energy regimes of the experiments are likely to be high enough to overcome even a barrier of 50 kcal mol^{-1}.

How can the [Fe,C_7,H_8,O,S]$^+$ potential-energy surface be entered starting from **25**/Fe$^+$? A spectator role of iron during rearrangements of the organic core can be excluded, as the dissociation of bare **25**$^{\cdot+}$ is distinctly different.[65] The possible collapse of **25**/Fe$^+$ into **4**/FeO$^+$ by an iron-mediated cleavage of the S–O bond would rationalize the identity of product distributions from both [Fe,C_7,H_8,O,S]$^+$ precursors. Alternatively, **25**/Fe$^+$ might be directly converted to **26** by a 1,3-hydrogen-shift from carbon to sulfur, followed by insertion of iron into the S–OH bond. No matter which of the central intermediates is accessed first, the fact that the final product distribution is independent of the entry to the energy surface demonstrates that extensive equilibration of intermediate structures precedes any dissociation process.

Conclusion

General reactivity trends of complexes between donor-substituted arenes and FeO$^+$ as revealed by the present experiments can be summarized as follows: Although the ionization energy of FeO$^+$ (8.8 eV)[57] is significantly higher than that of the four substrates phenol (8.47 eV), thiophenol (8.30 eV), anisol (8.21 eV), and thioanisol (7.94 eV),[42] dissociative electron transfer processes are absent for arene/FeO$^+$ complexes with low internal energy as sampled with sector MS and account for 5 % (phenol) to 45 % (thioanisol) of the products in FT-ICR reactions sampling a higher average internal energy. This finding indicates that the exit channels observed with sector MS are hampered kinetically, but lower in energy than the (barrierless) dissociative electron transfer. The substituent does not only tune the electrophilic properties of the aromatic ring, but actively participates in all reactions. Although aromatic C–H bonds can be activated by bare FeO$^+$ efficiently, this process is almost completely absent and discriminated against oxidation of the substituents, a feature that is also found for the analogue enzymatic reactions in solution mediated by, for example, cytochrome P-450. Furthermore, the presumed initial steps are rather similar for the condensed phase and our gas-phase model. For example, the oxidation of anisol involves the activation of the $C_6H_5OCH_2$-H bond in both environments, and the putative intermediate **17** would rapidly collapse to a hemiacetal and finally to the *O*-dealkylated product under aqueous conditions. The fact that the final products in the gas phase differ from those in the enzymatic system is attributed to the absence of a reactive environment (e.g. water), thereby rendering unimolecular rearrangement pathways possible. The present study has demonstrated that these rearrangement paths can be followed to some extent by mass spectrometric techniques. Although experiments in the gas phase differ fundamentally from those in the condensed phase in their reaction profiles due to solvation, the intrinsic reactivity of the iron oxide core probed in this study might guide the interpretation of metabolistic studies.

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[31] Collisional activation of **1**/FeO$^+$ yields losses of OH (4 %), H_2O (100 %), CO (5 %), [C,H_2,O_2] (3 %), C_6H_5O (4 %), and [C_6,H_6,O_2] (2 %).

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[34] The MI spectrum of phenoxyacetic acid/Fe$^+$ complexes shows eliminations of CH_2CO (100 %) and CO (13 %).

[35] Collisional activation of [Fe,C_6,H_6,O_2]$^+$ ions, which are generated from Fe(CO)$_5$ and phenoxyacetic acid, yields: OH (32 %), H_2O (100 %), [H_3,O] (8 %), CO (5 %), [C,H_2,O_2] (15 %), C_6H_5O (15 %), and [C_6,H_6,O_2] (3 %).

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[44] The reaction of FeO^+ with dimethylether under ICR conditions yields losses of CH_3 (50%), $[C_2,H_5,O]$ (15%), and FeOH (35%). D. Schröder, H. Schwarz, unpublished results.

[45] A more precise determination of the KIE is hampered by the presence of minor H/D scrambling processes. For the fraction of ions that undergoes scrambling, statistical isotope distributions are assumed.

[46] According to the ratio of HCO:DCO of 6:100 observed for **3b**/FeO^+, 9% of the ion population participates in statistical scrambling.

[47] The CA spectrum of $[Fe,C_6,H_5]^+$ ions generated by this procedure is featured by the elimination of $H^\bullet$ (100%), CH_2 (25%), C_2H_2 (45%), C_2H_3 (30%), C_2H_4 (25%), C_4H_4 (70%), and C_6H_5 (70%), which are in line with a $Fe^+{-}C_6H_5$ connectivity.

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[58] According to the ratio of H_2O:HDO:D_2O losses observed for **4b**/FeO^+, 10% of the ion population participates in statistical scrambling (see text), and 7% undergo a twofold activation of the methyl group.

[59] Metastable $PhSCH_3^{\bullet+}$ radical cations loose H (15%), CH_3 (3%), HS (100%), and H_2CS (35%). A KIE of $k_H/k_D = 2.4$ associated with loss of H_2CS is derived from **4a**$^{\bullet+}$.

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