Coordination of Iron(III) Cations to β-Keto Esters as Studied by Electrospray Mass Spectrometry: Implications for Iron-Catalyzed Michael Addition Reactions

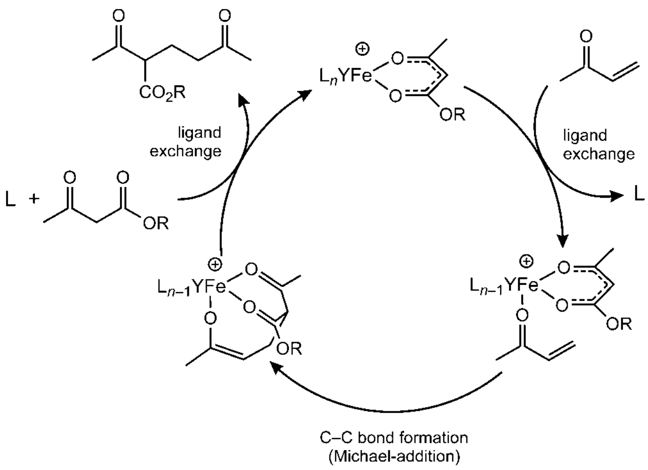
Claudia Trage, Detlef Schröder, and Helmut Schwarz*[a]

Abstract: Solutions of Fe^{III} salts and β-keto esters have been investigated by means of electrospray ionization mass spectrometry. The complexes formed in such solutions have been considered previously as active intermediates in Fe^{III}-catalyzed Michael additions. By using different Fe^{III} salts with a set of β-keto esters, cation and anion mass spectra were analyzed and the effects of ester concentration, the role of the counterion, and the structure of the ester employed are discussed. Depending on the basicity of the ester, an increase of its concentration may lead to a decrease in the concentration of iron complexes observed in the mass spectra. Counterions with strong binding affinities to iron are found to capture the metal as ferrates, thereby removing the metal from the catalytic cycle.

Keywords: electrospray ionization · enolates · iron · keto esters · mass spectrometry · Michael addition

Introduction

The Michael addition is a classical reaction for C–C bond formation in organic chemistry. Coupling of a nucleophile (usually an enolate such as a deprotonated 1,3-dicarbonyl compound) and α,β-unsaturated ketones or esters is generally achieved by using stoichiometric amounts of a base. Recently, a catalytic form of the Michael reaction mediated by iron(III) chloride was reported.[1] Broad screening of β-keto esters and α,β-unsaturated ketones has proven the practicability of C–C coupling for a wide range of reactants.[2–7] Furthermore, kinetic investigations and a suitable choice of substrates have provided evidence that corroborates the proposed mechanism of a one-center template reaction, in which the iron is assumed to act as a Lewis acidic center to facilitate both deprotonation of the coordinated dicarbonyl compound and coupling by means of template effects (Scheme 1).[8] While these mechanistic proposals are in accordance with experimental observations, direct experimental evidence for the active species within the catalytic cycle and the intermediates is lacking so far. However, theoretical investigations support the proposed mechanism and shed light on the effect of the counterion on the reaction rate.[8]



Scheme 1. Proposed mechanistic scheme for the catalytic cycle of the iron(III)-catalyzed Michael addition. Y stands for an additional anionic ligand and L for a neutral ligand. The number *n* of neutral ligands depends on the hapticity of L to afford an octahedral coordination sphere of the metal center.

Nevertheless, three crucial points remain to be solved:

1) Which complexes are present in a solution of Fe^{III} salts and β-keto esters?
2) What exactly is the role of the counterion?
3) What influence does the structure of the ester have on the complex formation?

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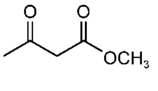
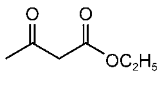
Electrospray ionization mass spectrometry (ESI-MS) provides a powerful tool for answering these questions, as this technique is particularly suitable for transferring ions present in solution more or less directly into the gas phase followed by mass analysis.[9,10] The aim of the present work is to determine the species present in solution. Furthermore, the effects of the structural nature and the concentration of the ester as well as nature of the counterion on the ion formation are investigated. These results may provide a valuable aid for determination of the catalytically active species in future reactivity studies in the gas phase.[10]

Results and Discussion

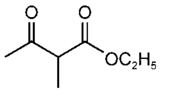
In terms of the esters investigated in this work compound **1a** is the simplest β-keto ester and **1d** is the compound most successfully employed by Christoffers in condensed-phase experiments.[2] Compounds **1b** and **1c** allow a study of the structural influence of the ester on the ions formed. Furthermore, comparison of **1a**, **1b**, and **1e** permits the investigation of possible steric effects of the ester group. Based on the synthetic procedures developed in the condensed phase,[8] the counterion of FeX_3 was selected to study the observed acceleration of the Fe-mediated Michael addition when the counterion is changed from chloride to perchlorate.



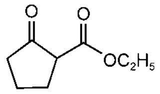
1a



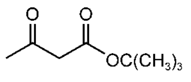
1b



1c



1d



1e

This section is organized as follows: a detailed discussion of the cation and anion spectra formed from **1a** and $Fe(ClO_4)_3$ is followed by investigations of concentration effects, the influence of the counterion of the Fesalt, and the role of the ester structure on the ions formed.

ESI mass spectra of $Fe(ClO_4)_3$ and 1a: The cations observed in all solvents used can be divided into two major categories: Fe-containing ions and metal-free ions, whereby the latter are of remote interest in this study and are only mentioned where necessary.

The evolving singly charged, mononuclear complexes of the first category are iron(III) compounds with the general formula $[FeY_2L_n]^+$, whereby Y is an anionic ligand, that is, E^- (the deprotonated form of the ester EH) or the counterion of the Fe salt, X^- ($X = ClO_4$ or Cl), and L is any neutral closed-shell ligand like the β-keto esters **1a–e** or a solvent molecule. Likewise, $[FeYL_n]^{2+}$ stands for the corresponding dicationic complexes. These Fe complexes can be further divided into three subgroups: cations in which both anionic ligands Y are represented by the deprotonated ester E^-, leading to an FeE_2^+ core; the second group consists of Fe complexes bearing a mixed $FeEX^+$ core; and the third group in which both anionic ligands correspond to the monodentate X counterions, thus containing an FeX_2^+ core.

In the cation ESI spectra of $Fe(ClO_4)_3$ and the methyl ester of 3-oxobutanoic acid (**1a**) dissolved in CH_2Cl_2, ions of the first category, that is, with an FeE_2^+ core, are most prominent. At low cone voltages, corresponding to gentle ionization conditions and thus low internal energies of the ions formed, the mass spectra are dominated by $[FeE_2(EH)]^+$ signals. As expected, this complex loses the neutral ligand EH upon increase of internal energy, thus giving rise to the unsolvated $[FeE_2]^+$ ions. The formal exchange of one E^- by ClO_4^- results in the second category: ions with an $FeEX^+$ core, such as $[FeEClO_4(EH)]^+$ and $[FeEClO_4(EH)_2]^+$. Due to the weaker coordination ability of perchlorate compared to E^-, the intensities of these ions are low relative to the $[FeE_2(EH)_n]^+$ ions ($n = 0$, 1), as long as an EH:Fe ratio ≥ 3 is maintained. The only ion observed in the third category in which the metal bears two perchlorate ligands is $[Fe(ClO_4)_2(EH)_2]^+$. Consistent with a low coordination ability of perchlorate, the abundance of this complex is also very low. Under soft ionization conditions, the dicationic complex $[FeE(EH)_2]^{2+}$ is also observed in a significant amount, as clearly demonstrated by the characteristic isotope pattern with spacings of a half mass unit (Figure 1).[11] It remains to be mentioned that the solvent's coordination ability is so poor that no complexes with dichloromethane as a neutral ligand are observed.

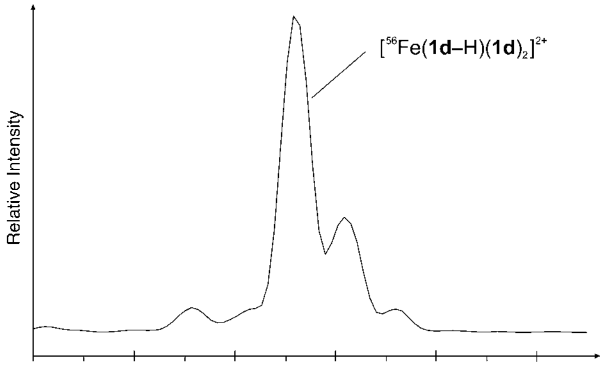


Figure 1. Dicationic $[FeE(EH)_2]^{2+}$ observed in the cation ESI spectrum of a dilute solution of $Fe(ClO_4)_3$ and **1d** in CH_2Cl_2.

The abundant $[FeY_2(EH)_n]^+$ complexes observed at low cone voltages illustrate the basic principle that iron favors coordination numbers high enough to saturate its six free coordination sites, thereby forming 17-electron complexes.

Although the high-spin d^5-configuration of Fe^{III} confers no energetic advantage by virtue of crystal-field stabilization on an octahedral arrangement of the coordinating ligands,[12] related tris(β-diketonato)iron(III) complexes are known to adopt a typical pseudo-octahedral symmetry.[12–14] Therefore, the cationic complexes under study are also assumed to be 17-electron complexes with quasi-octahedral symmetry. With increasingly harsher ionization conditions, successive ligand losses occur, leading to complexes with lower coordination numbers.

Interestingly, the number of neutral ligands L is influenced by the nature of the counterions. Both, the β-keto ester EH as a neutral ligand L and the deprotonated form E^- as an anionic ligand Y^- act as bidentate ligands. In the case of the complexes with an FeE_2^+ core, only two coordination sites remain for neutral ligands L to reach an octahedral coordination sphere. The evident neutral ligand potent enough to form such a bond is the bidentate ester EH, thereby explaining the formation and the predominance of the experimentally observed $[FeE_2(EH)]^+$ complex. In complexes with an FeX_2^+ core in which both anionic ligands stem from the monodentate counterions of the Fe salt, two additional coordination sites are available, allowing for a second ester EH group to act as a neutral ligand resulting in a pseudo-octahedral environment of $[FeX_2(EH)_2]^+$. A different situation exists for the ions with a mixed $FeEX^+$ core. With the anionic ligands E and X occupying three coordination sites, an odd number of free coordination sites remains to be saturated by neutral ligands in order to achieve a sixfold coordination of the complex. Alternatively, it is possible that the two additionally bound ligands lead to a coordination number of seven.[15] We return to these options later.

The second category of cations observed in the ESI mass spectra comprises protonated organic molecules and their clusters. One of them is the protonated ester **1a** $(EH)H^+$ and the respective proton-bound dimer $(EH)_2H^+$. Furthermore, the spectra indicate the occurrence of some reactions that lead to new organic compounds, such as an aldol addition, an aldol condensation, and a methyl transfer among others. As a key aim of this study is to investigate which ions are present in solution of the iron-mediated Michael addition, the origin of these organic ions needs some further consideration. To this end, two additional experiments were carried out to probe whether or not these ions are relevant in this context. In a first experiment, the ESI mass spectra of **1a** in dichloromethane were recorded in the absence of iron. These spectra show the formation of the same organic cations, indicating that their occurrence is by and large independent of the presence of iron. This finding leads to the question of whether these side reactions take place in solution or whether they are a result of the ionization process. To further elucidate this aspect, a solution of $Fe(ClO_4)_3$ with ester **1a** in methanol was refluxed for 24 h. After distillation, the resulting reaction mixture was investigated by NMR spectroscopy. The NMR spectra only show, beside keto-enol tautomerism, signals for a reaction in which a methyl-transfer[20] has taken place, which leads to an enol ether. Signals corresponding to aldol-related reactions or any other side reaction are not observed and indicate that the additionally observed organic cations in the mass spectra do not form in solution, but are a side product of the electrospray ionization process. Hence, they are of only remote interest for this study and will not be pursued any further, except noting that these side products are also able to serve as ligands for the iron center. The observed enol ether, for example, can act as an additional ligand resulting in a mass shift of $\Delta m = +14$ relative to the ester complexes under investigation.[21]

The ESI mass spectra of solutions of $Fe(ClO_4)_3$ and **1a** in the negative ion mode show only metal-free anions over the entire range of cone voltages. Under soft ionization conditions, clusters of the type $HClO_4{\cdot}ClO_4^-$ and even $(HClO_4)_2{\cdot}ClO_4^-$ dominate the spectra. With increasing cone voltage, the perchlorate clusters $(HClO_4)_n{\cdot}ClO_4^-$ dissociate giving rise to free perchlorate. Further increase of the cone voltage leads to successive fragmentation of ClO_4^- thereby giving rise to ClO_3^-, ClO_2^-, ClO^-, and eventually Cl^-. No metal- or ester-containing anions are observed in significant intensities.

Concentration effect: The initially colorless esters adopt a rich color upon complexation with iron. In all samples investigated in CH_2Cl_2, an increase of the ester concentration in solution eventually leads to a color change. This change of color is most distinct for EH = **1c** with a switch from blue to red. With such visual evidence that the concentration of the ester affects the sample, it seems astounding that the resulting ESI mass spectra are almost unchanged. While the spectra remain qualitatively the same, counterintuitively, an *increase* of ester concentration results in a *decreasing* intensity of the iron–ester complexes. This seemingly contradictory observation together with the fact that the eye-catching color change is not reflected directly in the mass spectra may be explained by the possibility that the increased concentration of ester leads to the formation of *neutral* iron–ester complexes. These neutral complexes are discriminated in ESI-MS, because the electrospray ionization process is known to favor intrinsically charged particles and to strongly discriminate neutral analytes present in the same sample.[10,22]

To rationalize the effects of increased ester concentration on the solution, a closer look at the way the cations are formed is necessary. The iron salt FeX_3 added to the ester (in solvent or neat) is dissolved by successive replacement of X^- by the β-keto ester. The exchange of ionic X^- by a neutral ligand leads to a build-up of charge density in the complex that is unfavorable. To circumvent this situation, deprotonation of the coordinated ester ligand takes place. Removal of the acidic hydrogen at C(2) is rather facile due to the two adjacent carbonyl groups in β-keto esters, and becomes even easier upon coordination of a Lewis acidic metal center. Under the given conditions, two possible bases are available to accept the liberated proton. One is the X^- ion co-generated upon heterolysis of FeX_3 and which can act as a base by forming its conjugate acid HX. A second possibility arises from the amphoteric character of the ester. The proton released from the coordinated ester can be stabilized by coordination to a free ester to yield $(EH)H^+$ or preferably the proton-bound dimer, $(EH)_2H^+$, by coordination with an additional ester molecule. If the amphoteric character of the ester plays a marked role, that is, the free ester acts as a base to deprotonate the ester molecules coordinated to the Lewis acidic iron, the ratio of ester to X^- concentration is expected to have an effect on the resulting spectra. However, because the ester acts both as ligand and as base, the influence of the above-mentioned ratio is more subtle than expected. If the ester plays a marked role as a base, absence of a sufficient amount of free ester to form the proton-bound dimer suppresses the deprotonation of cationic $[FeY_2L_n]^+$ complexes. Thus, the metal fragment remains charged, thereby allowing its detection in the mass spectrometer (Figure 2A). Increase of concentration of the free ester in turn allows the complete deprotonation of the $[FeY_2L_n]^+$ complexes to generate neutral metal complexes $[FeY_3L_{n-1}]$ (Figure 2B).

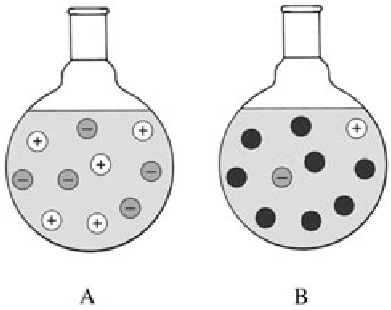


Figure 2. Schematic representation of the possible situation in solution after dissolving an FeX_3 salt and ≥ 3 equivalents of ester in dichloromethane. A: solution with predominantly charged complexes. B: solution with predominantly neutral complexes and only small amounts of ions. ⊖ represents any negatively charged particles in solution, ⊕ any positively charged particles and ● any neutral complexes.

To further clarify the situation, let us consider the two extreme cases. Equation (1) involves only the minimum number of ester molecules necessary for the exchange of all X^- ligands to form the neutral octahedral FeE_3 complex. This can only be achieved if all esters are deprotonated by X^-. In comparison, nine equivalents of ester were needed to form the same complex with EH acting as a base as shown in Equation (2).

$$FeX_3 + 3\,EH \rightarrow FeE_3 + 3\,HX \qquad (1)$$

$$FeX_3 + 9\,EH \rightarrow FeE_3 + 3\,(EH)_2H^+ + 3\,X^- \qquad (2)$$

Influence of the counterion: Upon changing from X = ClO_4 to X = Cl the counterion's coordination ability becomes strong enough to compete with E^- as a ligand; this in turn leads to more abundant cation complexes with $FeEX^+$ and FeX_2^+ cores. Hence, with $FeCl_3$ instead of $Fe(ClO_4)_3$, in addition to $[FeE_2(EH)_n]^+$ (n = 0, 1) the complexes $[FeClE(EH)_n]^+$ (with n = 0–2) and $[FeCl_2(EH)_n]^+$ (with n = 1, 2) are generated.

Beside the changes in ion abundances, the nature of the counterion has a further influence on the complexes with an $FeEX^+$ core. These ions represent a unique case in that of all iron–ester complexes discussed so far, only those with an $FeEX^+$ core possess an odd number of free coordination sites to be saturated by neutral ligands in order to reach a pseudo-octahedral geometry. Since the alternative, a coordination number of seven, results in an unfavorable 19-electron complex, the two following scenarios exist to circumvent the problem (Figure 3): 1) one of the neutral ester ligands may act as a monodentate ligand, which would allow for an octahedral coordination sphere; and 2) an almost symmetrical octahedral coordination sphere is achieved by arranging the three esters to build a dicationic $FeE(EH)_2^{2+}$ core, thereby forming a noncovalently bound dication/anion pair with X^-, held together by Coulomb attraction. In case of X = Cl, one would expect the chloride anion to enter the core and compete for a coordination site at the metal center due to the high coordination ability of the chloride ligand (Figure 3, left). In contrast, a "free" chloride anion (Figure 3 right) is unfavorable due to the high charge density on Cl^-. Precisely the opposite holds for X = ClO_4. Perchlorate is able to delocalize the negative charge resulting in a lower charge density, which makes it more favorable as a loosely bound counterion of an $[FeE(EH)_2]^{2+}$ ion. Due to this lower charge density and a higher steric demand, the perchlorate's coordination ability is weaker, which makes a competition with the oxygen atoms of the ester ligand for the sixth coordination site less efficient. Therefore, the $FeE(EH)_2^{2+}/X^-$ case appears a conceivable option for X = ClO_4.

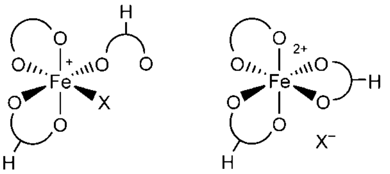


Figure 3. Structural options for $[FeEX(EH)_2]^+$ complexes to adopt a pseudo-octahedral geometry. Left: One of the neutral ester ligands acts as a monodentate ligand only and the anionic ligand X^- is covalently bound to the metal center. Right: All ester ligands (neutral and anionic) act as bidentate ligands forming a quasi-symmetrical coordination sphere of $[FeE(EH)_2]^{2+}$ with X^- kept in proximity to the dicationic core by Coulomb attraction without direct coordination to the metal center.

Indeed, for X = Cl, the first option seems to prevail, as the CID spectra show loss of EH, whereas expulsion of HCl is not observed at all (Figure 4a). The latter is expected to compete with EH-loss in the $FeE(EH)_2^{2+}/Cl^-$ situation: apparently, Cl^- is able to vie successfully for coordination sites with E^-. In marked contrast to the X = Cl case, the CID spectrum of $[FeEX(EH)_2]^+$ with X = ClO_4 (Figure 4b) shows loss of $HClO_4$ as an additional fragmentation pathway. This

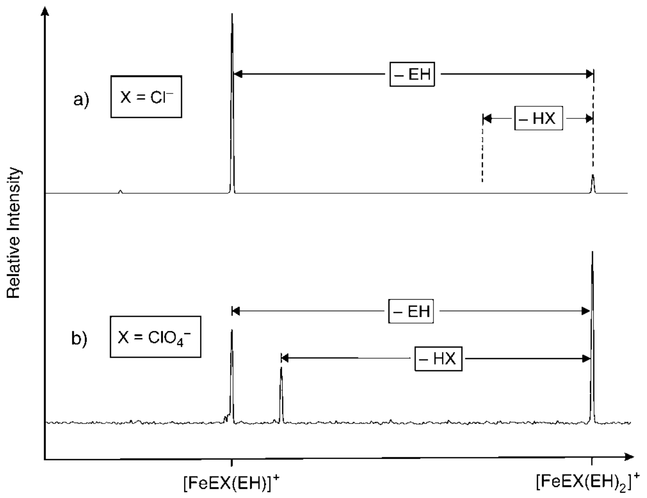


Figure 4. CID spectra of $[FeEX(EH)_2]^+$ with $X={}^{35}Cl$ ($E_{CM}=1.2$ eV) and ${}^{35}ClO_4$ ($E_{CM}=1.0$ eV) and EH = **1a**.

finding lends support to the assumption that due to the weaker coordination ability of ClO_4^- an $FeE(EH)_2^{2+}/X^-$ bonding situation is more likely than a covalent $Fe{-}OClO_3$ bond with one ester acting as a monodentate ligand only. Another indication supporting the proposal of such a dication "in disguise" is the fact that the corresponding free dication $[FeE(EH)_2]^{2+}$ is also observed in the ESI spectra for $X=ClO_4$ (Figure 1).

Having discussed the influence of the counterions on the *cation* spectra, the respective influence on the *anion* spectra is considered. The ESI mass spectra obtained in the negative ion mode differ markedly for $X=ClO_4$ and $X=Cl$. Due to the higher coordination ability of chloride, the metal-containing ions $[Fe_mCl_n]^-$ dominate the mass spectra throughout the entire range of cone voltages. Under gentle ionization conditions, the iron(III) species $[FeCl_4]^-$ and $[Fe_2Cl_7]^-$ prevail, and with increasingly harsher ionization, expulsion of atomic chlorine becomes feasible leading to $[FeCl_3]^-$ and $[Fe_2Cl_6]^-$, respectively, at elevated cone voltages. The only metal-free anion of noteworthy intensity is $HCl{\cdot}Cl^-$. As with the solutions of $Fe(ClO_4)_3$, anions bearing an ester molecule play no appreciable role. Hence, the change from $X=Cl$ to $X=ClO_4$ has a substantial influence on the resulting anion spectra: the metal-free anion spectra of solutions of $Fe(ClO_4)_3$ contrast those of $FeCl_3$, which are dominated by chloro ferrates, that is, metal-centered ions.

The counterion effects observed in the anion mass spectra provide an additional explanation for the acceleration of the Fe-catalyzed Michael addition by about one order of magnitude when the counterion is changed from chloride to perchlorate. In previous work, van Wüllen and co-workers proposed two possible explanations for why the reaction proceeds faster in the absence of Cl^-. In the first, the catalytically active species possesses no chloride but only water and ester ligands.[8] Therefore, it would be necessary that the chloride ligands present at iron be removed prior to the formation of the active catalyst. In the case of $Fe(ClO_4)_3$, heterolysis is more facile due to the lower charge density and coordination ability of the counterion. In the second, for the Cl^--containing complexes the chloro ligand hampers deprotonation of the ester relative to chloride-free complexes.[23] As the deprotonation of the ester is crucial for the desired Michael addition, this also hints towards a drawback of Cl^- as a counterion.

While these two scenarios provide working models for the experimentally observed changes in rate constants, the counterion effect on the anion spectra presented here implies yet an additional explanation. Even if the active catalyst species is presumably chloride-free, the presence of chloride ions can still influence the reactivity. This effect is indirect in that solvolysis to afford free Cl^- can be assumed to be rapidly followed by coordination of the chloride ion to neutral $FeCl_3$ to yield $[FeCl_4]^-$ and its clusters at higher $FeCl_3$ concentrations. Chloride ions can therefore be regarded as a kind of general catalyst poison, as they lower the concentration of the iron-containing species by trapping the metal as chloro ferrate $[Fe_nCl_{3n+1}]$,$^-$ such that the iron is no longer available for catalysis.

Structural influence of the ester on the complexes formed Qualitatively, for the set investigated, the ester structure does not influence the type of ions formed. Upon closer inspection, however, the structure of the ester influences the abundances of the various iron-containing complexes. A quantitative evaluation of these effects is, however, complicated and in part even impossible because of the complex nature of ion formation in ESI. Change of one keto ester to another may, for example, not only affect the tendency for the formation of a particular iron complex in solution, but also affect droplet formation, solvent evaporation, proton- and electron-transfer reactions, and so forth.[24]

To achieve a more detailed insight into the effect of substitution of the keto ester, two esters were simultaneously added to solutions of FeX_3 in solvent thereby allowing both to compete with each other in the coordination to iron. Let us first consider the esters **1b**, **1c**, and **1d**. A variation of the substitution pattern of the ester, while keeping the alkoxy moiety constant, allows a systematic investigation of the structural influence of backbone substituents. Accordingly, comparison of **1b** and **1c** reveals the influence of alkylation in the α-position. Comparison with **1d**, the substrate most successfully employed by Christoffers in condensed-phase experiments,[2] reveals the influence of incorporating a cyclic structure. In the experiments reported here, equimolar solutions of two esters in CH_2Cl_2 are mixed with a small amount of FeX_3. The resulting distribution patterns of the (mixed) $[FeE_2]^+$ and $[FeE_2(EH)]^+$ ions permit conclusions with respect to the relative formation tendencies. If, for example, an equimolar mixture of two esters AH and BH in a dilute Fe^{III} solution is subjected to the ESI mass spectrometer, a 1:2:1 distribution would be expected for the series of $[FeE_2]^+$ complexes ($[FeA_2]^+$:$[FeAB]^+$:$[FeB_2]^+$) if both esters bind equally strongly to the iron center (Figure 5, left). Any deviation from the 1:2:1 pattern indicates a pref-

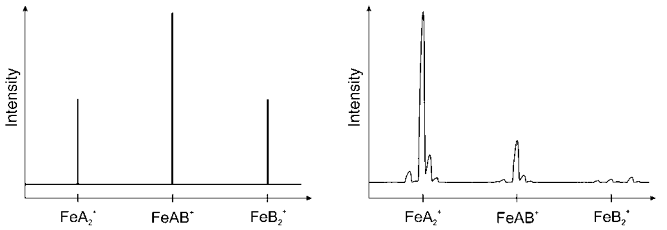


Figure 5. Comparison of a hypothetical 1:2:1 distribution pattern expected for a 1:1 mixture of equally bound esters AH and BH (left) with the actual distribution pattern observed in the case of AH = **1b** and BH = **1c** at a cone voltage of 50 V (right).

erence of one ester over the other. In case of **1b** and **1c**, for example (Figure 5, right) a marked preference of **1b** over **1c** can be observed. Likewise, a comparison of the remaining ester pairings (**1b**/**1d** and **1c**/**1d**) leads to a qualitative Fe affinity scale of the esters as: **1c** < **1b** < **1d**.

The distributions show only a weak cone-voltage dependence, which can be attributed to sequel fragmentations that may influence the $[FeE_2]^+$ abundances. Furthermore, a quantitative analysis shows that α-methylation (**1b** versus **1c**) is accompanied by a decrease in Fe affinity by about a factor of 5.8 ± 1.0. In contrast, incorporation of a cyclic carbon backbone, as in **1d**, increases the Fe affinity by a factor of 5.3 ± 0.8 relative to **1b** and by a factor of 32 ± 5 relative to **1c**.

A second possibility to determine the Fe-affinity of the different esters is to investigate the fragmentation pattern of the mixed $[FeE_2(EH)]^+$ complexes with CID. At moderate collision energies, the only fragmentation channel observed in these complexes is the loss of the neutral ester ligand EH. Let us now consider the expected fragmentation pattern of $[FeA_2B(H)]^+$ complexes. If the Fe affinities of the two esters are equal, a $-$BH/$-$AH ratio of 1:2 is expected (Figure 6, left). Any deviation from this ratio would indicate a preferential binding of one ester relative to the other. The example CID spectrum of $[FeA_2B(H)]^+$ with AH = **1b** and BH = **1c** (Figure 6, right) shows a $-$BH/$-$AH ratio that implies a stronger bond between iron and **1b** than iron and **1c**. A quantitative analysis reveals a ratio of $-$BH/$-$AH = 2.2 ± 0.2. After consideration of the statistical effects (two **1b** ligands and only one **1c** ligand in the parent ion) the preference of **1b** over **1c** equates to a factor of 4.3 ± 0.4.

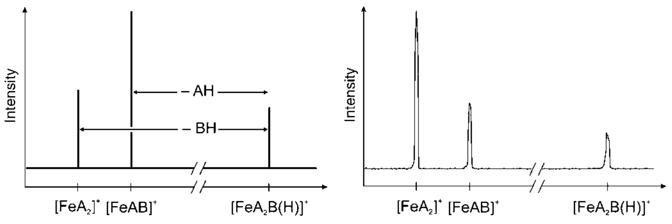


Figure 6. Comparison of a hypothetical 1:2 fragmentation pattern expected for the collision induced dissociation of an $[FeA_2B(H)]^+$ complex with equally bound esters AH and BH (left) with the actual fragmentation pattern observed in the case of AH = **1b** and BH = **1c** at a collision energy of $E_{CM} = 3.3$ eV (right).

The corresponding analysis of the CID spectrum of $[FeAB_2(H)]^+$ is hampered by an isobaric overlap by an ethyl-transfer product,[20,21] which also coincides in the *m/z* ratio of one of the fragments. Nevertheless, a $-$BH/$-$AH ratio of 6.2 ± 1.3 is obtained, which after statistical corrections results in an Fe-affinity 3.0 ± 0.6 times larger for **1b** than **1c**. Certainly, analysis of the $[FeA_2B(H)]^+$ and $[FeAB_2(H)]^+$ complexes is supposed to give the same Fe affinities, but due to the above-mentioned isobaric interference, the $-$BH/$-$AH ratio of 6.2 ± 1.3 obtained for $[FeAB_2(H)]^+$ is underestimated.[25] Qualitatively, the Fe affinities of the esters **1b**, **1c**, and **1d** derived from the source spectra agree with those deduced from CID. However, a more quantitative analysis reveals some discrepancies. These deviations can be attributed to two problems of the analysis of the CID spectra that have not been addressed so far. Firstly, analysis according to the kinetic method[26] not only requires a barrierless dissociation of the competing ligands, but in this case also a complete and rapid equilibration of the proton. The latter situation might not be the case, which would affect the results obtained with the kinetic method in this work. Furthermore, the effective temperature (T_{eff}) operative in ion dissociation is a priori unknown. Therefore, we restrict ourselves to the consideration of the source spectra as a monitor of the situation in solution.

It is astounding that the comparably small structural changes in the substrate (e.g., **1b** vs **1c**) have such distinct effects. When looking for an explanation, the first physical property likely to have an influence on the ion formation is the acidity of the β-keto ester. Amongst others this is an important aspect, because the formation of iron–ester complexes involves deprotonation of one or more ester molecule and is facilitated with increasing acidity of the ester. Indeed, the stability series described above correlates qualitatively with the acidities of the corresponding esters in water.[27–30] Alkylation in the α-position goes along with a destabilization of the resulting carbanion[31] and, therefore, with a substantial decrease in acidity ($pK_a[\mathbf{1b}_{aq}] = 10.65$, $pK_a[\mathbf{1c}_{aq}] = 12.25$),[28] which is reflected in the decrease in Fe affinity by a factor of 5.8 ± 1.0. However, if alkylation is concomitant with incorporation into a five-membered ring such as in **1d**, the ester is considerably more acidic than comparable open-chain α-substituted β-keto esters. This is due to the fact that the enolic form of the cyclic ester is especially favorable in the carbanion form.[32] Hence, the acidity of the cyclic ester is slightly higher than that for the nonalkylated case ($pK_a[\mathbf{1b}_{aq}] = 10.68$, $pK_a[\mathbf{1d}_{aq}] = 10.52$).[27] A direct quantitative correlation between the Fe affinities and the pK_a values is not expected, however, as several other factors are likely to contribute as well. One of them is the proton affinity of the ester, provided the ester also acts as a base. Notwithstanding, the qualitative agreement achieved indicates that the acidity represents a very important parameter.

Another structural influence is the steric demand of the ester. Comparison of the complementary series of esters **1a**, **1b**, and **1e** allows for an investigation focussed on steric effects, because variation of the alkoxy group is expected to barely change the acidity of the ester.[29,30] Considering the methyl ester (**1a**), the sterically slightly more demanding ethyl ester (**1b**) and the bulky *tert*-butyl ester (**1e**), a competition experiment between two different esters for the metal center, as described above, may provide a probe for the sensitivity towards purely steric factors in ion formation. It should be noted first that all esters readily form the corresponding $[FeE_2(EH)]^+$ complexes. Even for the *tert*-butyl ester the steric demand is, therefore, not so large that formation of these complexes is inhibited. When the esters compete for the iron (in experiments analogous to the ones described above) any deviation from the 1:2:1 distribution pattern points to the operation of a steric effect. Unfortunately, two problems arise that complicate the analysis. The first is that the methyl transfer described earlier leads to a mass overlap in the comparison of **1a** and **1b**. In the case of **1a** (116 amu), methyl transfer leads to a potential ligand with 130 amu, which coincides with the molecular weight of **1b**. The second is that, in addition to ligand loss, the complexes of the *tert*-butyl ester **1e** undergo facile fragmentation with expulsion of *iso*-butene upon CID and in the source spectra at elevated cone voltages.

Analysis of the iron competition experiments for **1a** and **1b** leads to a formal steric effect of about 1.5 ± 0.15. However, against intuition, the analysis attributes ester **1b** a *larger* Fe affinity than **1a**. In any case, no big influence is expected by comparison of a methyl ester with an ethyl ester, but *if* a steric effect were to be observed, then it would be expected to be reverse, that is, the methyl ester should bind better to iron than the ethyl ester.[33] Note that the pK_a values of **1a** and **1b** coincide within the experimental error ($pK_a[\mathbf{1a}_{aq}] = 10.61 \pm 0.03$, $pK_a[\mathbf{1b}_{aq}] = 10.63 \pm 0.03$).[30] Even if one would want to argue with the small difference in the absolute pK_a values of the methyl and ethyl esters, a reverse trend would be expected. The observed Fe affinities can therefore not be attributed to the different acidities of **1a** and **1b**. The methyl-transfer product of **1a** may further lead to an overestimation for the isobaric complexes of **1b**, which have both the same *m/z* ratio.

The other experiments are subject to a second problem, the instability of **1e** at elevated cone voltages (and upon CID), leading to an underestimation of its Fe affinity. Hence, comparison of the ethyl ester with the *tert*-butyl ester shows a relatively strong dependence on the cone voltage. A formal increase of Fe affinity of **1b** relative to **1e** is observed with increasing internal energy. This can, however, be attributed to the fact that with increased internal energy the fragmentation of **1e** is more pronounced, which amplifies the underestimation of **1e**. The Fe affinity of **1b** is about 2.8 ± 0.5 times higher than that of **1e**. However, due to the reasons mentioned above, this value is overestimated. The according comparison of **1a** with **1e** is less affected by this interference and reveals an Fe affinity ratio of 1.2 ± 0.4 in favor of the methyl ester, which shows no steric effect within the experimental error. Unfortunate as the observed interferences may be, they nonetheless illustrate that if there is any steric effect operative, it is not large.

Conclusion

Electrospray mass spectra of mixtures of Fe^{III} salts and β-keto esters (EH) in various solvents indicate that the metal favors the formation of cationic complexes with a coordination number of six and a pseudo-octahedral geometry. Irrespective of the solvent, the monocationic complexes obey the general formula $[FeY_2L_n]^+$, in which n depends on the ionization conditions as well as the nature of the anionic ligand, Y, and L is the free β-keto ester, EH in most cases. The iron-containing cations can be assigned to three different groups: 1) cations with an FeE_2^+ core, in which E stands for the deprotonated β-keto ester; 2) cations consisting of a mixed $FeEX^+$ core, in which X is the counterion of the FeX_3 salt used; and 3) complexes with an FeX_2^+ core, in which both anionic ligands are provided by the counterion.

Quite surprisingly, an increase in ester concentration leads to a decreased abundance of the iron–ester complexes in the ESI mass spectra. This phenomenon can be attributed to the amphoteric character of the ester, which may also act as a base when present in high concentration. As a result, the formation of neutral FeE_3 complexes, which remain undetected in ESI-MS, is suggested. As far as the counterion X is concerned, its coordination ability determines the relative intensities of complexes with FeE_2^+, $FeEX^+$, and FeX_2^+ cores with the last being much more pronounced for $X = Cl$ than for $X = ClO_4$.

Although the types of complexes are the same for all β-keto esters examined, competition experiments with mixtures of β-keto esters establish a relative Fe affinity scale. The trends observed correlate with the acidities of the esters, in that more facile deprotonation favors the formation of the corresponding FeE_2^+ complexes. Interestingly, the Fe-affinity series $\mathbf{1c} < \mathbf{1b} < \mathbf{1d}$ derived from mass spectrometric experiments qualitatively correlates with the chemical yields obtained in the condensed phase Michael reactions of these particular esters with methyl-vinyl ketone ($\mathbf{1c} = 87\% < \mathbf{1b} = 90\% < \mathbf{1d} = 97\%$).[2] Furthermore, the ESI mass spectra obtained in the negative ion mode provide an alternative explanation for the deceleration of the Fe^{III}-catalyzed Michael addition in case of $X = Cl$,[8] in that a considerable amount of the employed iron is trapped as chloroferrates $[Fe_nCl_{3n+1}]^-$ and is therefore no longer available for catalysis.

Experimental Section

The mass spectrometric experiments were carried out on a commercial VG BIO-Q mass spectrometer which has been described in detail previously.[42] In brief, the VG BIO-Q consists of an ESI source combined with a tandem mass spectrometer of QHQ configuration (Q: quadrupole, H: hexapole, Figure 7). In the present experiments, the sample solutions were prepared by mixing FeX_3 salts ($X = Cl$, ClO_4) and β-keto esters (**1a**–**e**) in dichloromethane, methanol, or ethanol,[43] or as the neat ester. The resulting solutions were introduced through a syringe pump (flow rate $10\,\mu L\,min^{-1}$) into the fused-silica capillary of the ESI source. Nitrogen was used as drying gas and as a nebulizer gas. The source tempera-

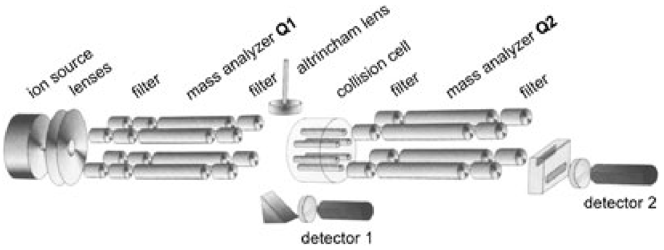


Figure 7. Setup of the VG BIO-Q mass spectrometer.

ture was varied between 60 °C and 190 °C depending on the solvent composition. The cone voltages applied in the desolvation zone of the differentially pumped ESI source were systematically varied for the ions of interest (see below), which were then selected at unit mass resolution by means of Q1.

The cone voltage U_C determines the amount of collisional activation of the ions evolving from solution in the differential pumping system of the ESI source. At low cone voltages, multiply solvated ions are formed, which then lose the weakly bound solvent molecules at increased U_C, followed by losses of more strongly bound ligands including the cleavage of covalent bonds, electron-transfer processes etc. Finally, atomic metal cations are obtained at high cone voltages.[44] Collision-induced dissociation (CID) experiments were performed with xenon at various collision energies ($E_{lab} = 0–30$ eV) and a pressure of approximately 3×10^{-4} mbar, which is considered to correspond to single-collision conditions.[42] The collision energies were converted to the center-of-mass frame, $E_{CM} = [m/(M+m)]E_{lab}$, in which m and M are the masses of the collision gas and the ionic species, respectively. The product ions formed in the hexapole were then analyzed by scanning Q2. Isotope patterns of all ions described below agreed with expectation on the basis of natural isotope abundances.[45] Finally, note that all mass-to-charge ratios given in this work refer to the complexes of the most abundant ^{56}Fe isotope.

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it has to be taken into account that the proton affinities mentioned here refer to the gas phase where no solvation effects are operative. These three effects cause a further stabilization of the coordinated proton and hence increase its proton affinity. Therefore, the influence of the alkoxy moiety alone on the proton affinity for the esters **1a**, **1b**, and **1e** is expected to be less pronounced than for the respective alkyl acetates. Consequently, proton affinities of the esters **1a**, **1b**, and **1e** can only be estimated and the difference in PAs is not expected to be large. Moreover, the expected trend will be opposed to the steric effect and both trends might therefore by and large cancel each other.

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