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Regio- and diastereoselective C–H bond activation of valeramide and 3-methyl valeramide by bare Fe^+ ions

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Dedicated to the memory of Pierre Longevialle.

Abstract

Mass spectrometric studies of metastable complexes of valeramide (n-$C_4H_9CONH_2$) with Fe^+ cations are used to probe selectivity in metal-mediated C–H– and C–C bond activations. Extensive labeling studies reveal that the dehydrogenation occurs via regioselective activation of the remote C–H bonds at C(4) and C(5). As a side reaction, C(3)–C(4) bond activation leads to loss of ethene concomitant with the formation of propionamide/Fe^+. Introduction of an additional methyl group at the C(3) position allows to probe stereochemical aspects of bond activation in 3-methyl valeramide/Fe^+ complexes by means of diastereospecific labeling. Quantitative analysis of the labeling distributions reveals that the steric effect (SE $= 2.0 \pm 0.1$) due to diastereoselective discrimination is of similar magnitude as the kinetic isotope effect (KIE $= 2.3 \pm 0.1$) associated with remote functionalization of the C(4) and C(5) positions. (Int J Mass Spectrom 217 (2002) 169–177)

Keywords: Fe^+ chemistry; Stereochemistry; C–H bond activation

1. Introduction

While already the mere activation of aliphatic C–H and C–C bonds constitutes a formidable challenge for contemporary chemical research, stereoselective functionalization of non-activated C–H bonds is even more demanding. Nevertheless, continuous progress is achieved, and recent examples concern the stereoselective C–H bond activation of δ-positions in organoboranes [1], the diastereoselective γ-hydroxylation of valine by a modified Shilov system [2], and the enantioselective C–H bond insertions of rhodium-bound carbenes [3]. Following Breslow's seminal studies on biomimetic synthesis [4], selective bond activation of functionalized hydrocarbons has been referred to as *remote functionalization*.

Mass spectrometric studies have amply demonstrated that naked transition-metal cations permit regioselective activations of C–H and C–C bonds in monofunctionalized alkanes far apart from the functional group [5]. In this gas-phase variant of remote functionalization, a reactive, bare or ligated transition-metal cation is first complexed to the functional group and then directed towards a certain region of the aliphatic backbone [5,6]. The product distributions depend on the transition-metal [5,7], the presence of additional ligands [8], the functional group [5], the flexibility and also stereochemical details of the backbone [9,10]. In the present study, we

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focus on the remote functionalization of valeramide (n-$C_4H_9CONH_2$, **1**) by the late transition-metal cation Fe^+, which induces losses of neutral hydrogen and ethene, respectively, from the mass-selected, metastable valeramide/Fe^+ complex. The generalized reaction mechanism involves the following steps [5]: (i) initial coordination of the transition-metal ion M^+ to the functional group, (ii) folding of the aliphatic chain such that remote bonds become accessible for M^+, (iii) C–H or C–C bond activations to yield the corresponding insertion intermediates, and (iv) formation of molecular hydrogen, alkene, or alkane subunits via formal β-H- and β-alkyl migrations in multi-centered [11] transition structures (TSs) with subsequent losses of the so-formed small neutral ligands.

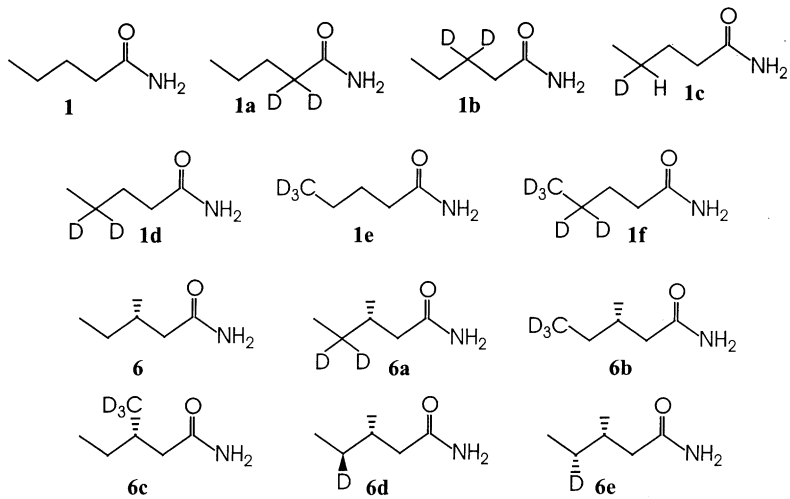
The particular choice of valeramide as the model system was based on the following considerations. (i) Amides belong to an important class of biomolecules, and their reactions with transition-metal cations receive increasing interest [12]. (ii) By definition, remote functionalization requires a certain distance between the functional group and the positions to be activated. (iii) Earlier studies have shown that the Fe^+-mediated C–H bond activation of aliphatic ketones [13] and acids [14] shows largest regioselectivities for n-butyl side chains. While the associated barriers increase for smaller chain lengths, these become more and more similar with extended chains, such that regioselectivities decrease [15]. (iv) For probing diastereoselectivity by mass spectrometric means, it is in turn rather crucial to chose a substrate for which highly selective reactions occur.

2. Experimental details

The experiments were performed with a modified VG ZAB/HF/AMD four-sector mass spectrometer of BEBE configuration (B stands for magnetic and E for electric sectors) which has been previously described [16]. Briefly, the metal complexes were generated in a chemical ionization source (CI, repeller voltage ca. 0 V) by 100 eV electron bombardment of a mixture of $Fe(CO)_5$ and the amide of interest. The ions were accelerated to 8 keV kinetic energy and mass-selected by means of B(1)/E(1) at a resolution of $m/\Delta m = 2000$–3000. Unimolecular fragmentations of metastable ions (MIs) occurring in the field-free region preceding B(2) were recorded by scanning this sector; the last sector E(2) was not used in this study. All spectra were accumulated and on-line processed with the AMD-Intectra data system. The data are given as averages of several independent measurements with a standard deviation of ±1 for the intensities normalized to $\Sigma = 100$. While reactions of electronically excited metal ions may obscure the results for metastable ions, previous studies of nitrile/M^+ systems as well as the relatively high pressure that prevails in the CI source suggest that excited states of M^+ ions are unlikely to participate in the reactions described below [17,18].

For a rough estimation of the bond dissociation energies (BDEs) of acetamide/Fe^+ and valeramide/Fe^+, the kinetic method according to Cooks and co-workers was applied [19]. To this end, mixed bisligand complexes amide/Fe(benzene)$^+$ were generated by chemical ionization in the presence of benzene, B(1)/E(1)-mass-selected, and the unimolecular dissociation monitored by scanning of B(2). The experimentally found ratios of the ligand losses were converted to ΔBDE using the Gibbs–Helmholtz equation $\Delta G = RT_{\text{eff}} \ln[I(\text{amide/Fe}^+)/I(\text{Fe(benzene)}^+)]$ with $\text{BDE}(C_6H_6\text{–Fe}^+) = 49.6 \pm 2.3$ kcal/mol [20] as a reference. As far as the effective temperature T_{eff} employed in the kinetic method is concerned, the ion-source temperature was used as a pragmatic guess for the monocations, i.e., $T_{\text{eff}} = 473 \pm 200$ K [21,22]. While this choice of T_{eff} lacks a concise physical foundation, it turned out reasonable for a variety of metastable metal–ion complexes examined in our laboratory [21–24].

The synthesis of the labeled valeramides (Scheme 1) followed previously described strategies [10,13]. Briefly, the amides were made by ammonolysis of the corresponding esters or acid chlorides. The labeled valeric acids (or their derivatives) were made by either (i) reaction of the dianion of acetic acid with 1-bromopropane (applied for **1a** and **1b**) or



Scheme 1.

(ii) conjugate addition of ethyl magnesium bromide to methyl acrylate (applied for **1c–1f**). The 3-methylvaleric acids **6a–6c** were prepared by conjugate addition of grignard reagents to the corresponding α,β-unsaturated esters (ethyl magnesium bromide + crotonate for **6a** and **6c**, methyl magnesium iodide + pent-2-enoate for **6b**). The diastereoselectively labeled amides **6d** and **6e**[1] were prepared starting from *trans*- and *cis*-butene oxide, respectively, as described previously [10]. The final products were purified by recrystallization from chloroform/hexane and spectroscopically characterized by ^{1}H NMR and GC–MS.

3. Results and discussion

Before addressing the metal-mediated bond activations occurring in metastable valeramide/Fe^+, **1**/Fe^+, the bond dissociation energies (BDEs) of acetamide/Fe^+ and valeramide/Fe^+ were estimated applying Cooks kinetic method [19,25]. To this end, the unimolecular dissociation of the mixed bisligand complexes acetamide/Fe(benzene)$^+$ and **1**/Fe(benzene)$^+$ were examined. In the unimolecular dissociation of acetamide/Fe(benzene)$^+$, competitive ligand losses are observed with a ca. 2:3 ratio in favor of loss of acetamide. Hence, benzene appears to be slightly more strongly bound to Fe^+ than acetamide. With BDE(C_6H_6–Fe^+) = 49.6 ± 2.3 kcal/mol [20] as a reference, this ratio leads to BDE(acetamide–Fe^+) = 49.2 ± 2.5 kcal/mol. This value is significantly larger than the BDEs of related acetyl derivatives, e.g., BDE(acetaldehyde–Fe^+) = 35.7 ± 2.6 kcal/mol and BDE(acetone–Fe^+) = 41.4 ± 3.0 kcal/mol [21], which is consistent with the increase of the associated proton affinities, with PA(acetaldehyde) = 183.9 kcal/mol; PA(acetone) = 194.3 kcal/mol, and PA(acetamide) = 206.6 kcal/mol [26]; a similar order evolves for the corresponding Cu^+ affinities [27]. Nevertheless, in the same vein as protonation occurs at the carbonyl oxygen, the metal ion is assumed to be attached to the oxygen atom. This reasoning is amply supported by theoretical studies of complexes of amides with transition-metal

[1] Note that the synthesis leads to racemic mixtures of diastereomerically pure compounds. Thus, **6d** corresponds to a 1:1 mixture of (*3R,4S*)-3-methyl-[4D$_1$]-valeramide and (*3S,4R*)-3-methyl-[4D$_1$]-valeramide. Likewise, **6e** is a mixture of (*3R,4R*)-3-methyl-[4D$_1$]-valeramide and (*3S,4S*)-3-methyl-[4D$_1$]-valeramide. For the sake of simplicity, only one of the two enantiomers is shown in the mechanistic schemes. Similarly, **1c**, **6a–6c** were studied as racemic mixtures.

cations in which coordination to the keto-group is strongly preferred over that at the amino group for simple carboxamides, such as formamide [28,29].

For metastable **1**/Fe(benzene)$^+$, three dissociation channels (reactions **1a–1c**) are observed in a ca. 1:10:1 ratio.

$$\mathbf{1}/\mathrm{Fe}(\mathrm{C_6H_6})^+ \rightarrow \mathbf{1}/\mathrm{Fe}^+ + \mathrm{C_6H_6} \quad (1a)$$

$$\mathbf{1}/\mathrm{Fe}(\mathrm{C_6H_6})^+ \rightarrow [\mathbf{1}/\mathrm{Fe}\text{–}\mathrm{H_2}] + \mathrm{C_6H_8} \quad (1b)$$

$$\mathbf{1}/\mathrm{Fe}(\mathrm{C_6H_6})^+ \rightarrow \mathrm{Fe} + (\mathrm{C_6H_6})^+ + \mathbf{1} \quad (1c)$$

In most applications of the kinetic method, the occurrence of side reactions is neglected in that only the competitive ligand losses are considered in the quantitative analysis. Hence, the 1:1 ratio of reactions (1a) and (1c) would imply BDE(**1**-Fe$^+$) = BDE(C_6H_6–Fe$^+$). In the present case, the "side" reaction (1b) gives rise to the base peak, however. Further, the nature of the neutral "C_6H_8" product is uncertain. Based on comparison to related ketone/Fe$^+$ complexes [8b,21,30], the most likely assignment is a sequence of consecutive losses of first C_6H_6 and then H_2. Consequently, the sum of reactions (1a) and (1b) has to be considered in the evaluation of the data according to the kinetic method, leading to BDE(**1**-Fe$^+$) = 51.9 ± 2.7 kcal/mol. Similar values have been reported for other Fe$^+$-complexes of aliphatic ketones and nitrile, e.g., BDE(2-hexanone–Fe$^+$) = 47.6 ± 2.7 kcal/mol, BDE(4-heptanone–Fe$^+$) = 47.8 ± 2.6 kcal/mol [21], BDE(nonanitrile–Fe$^+$) = 48 ± 3 kcal/mol [31]. The slight increases compared to the parent systems (BDE(acetone–Fe$^+$) = 41.4 ± 3.0 kcal/mol and BDE(acetonitrile–Fe$^+$) = 41.3 ± 3.0 kcal/mol) [21], can be attributed to internal solvation of the metal cation by recoil of the alkyl chain towards the cationic site [31].

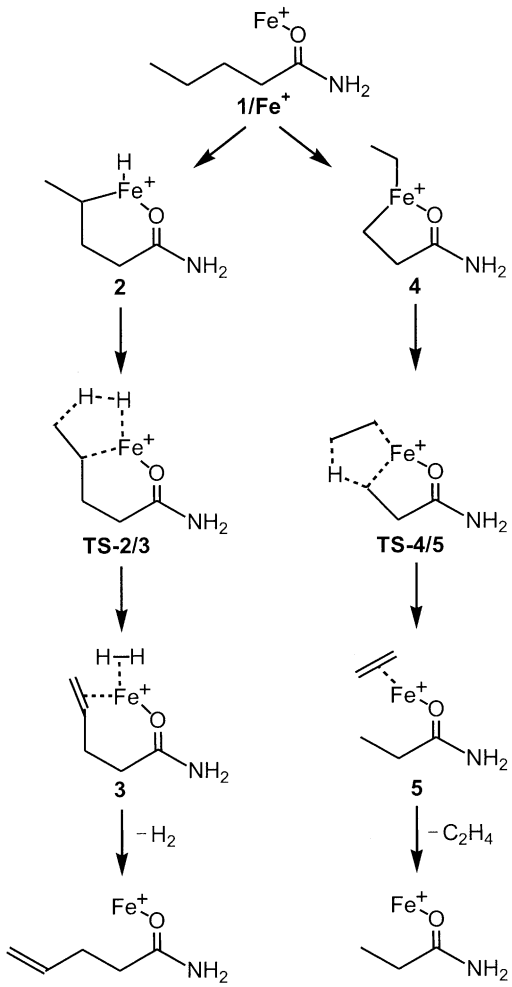
Metastable **1**/Fe$^+$ complexes undergo dissociations resulting in the mass differences $\Delta m = -2$ and -28, respectively (Table 1). While the former can safely be assigned to dehydrogenation, the latter can correspond to losses of CO, C_2H_4, a [C,H_2,N]$^\bullet$ radical, or a mixture of these neutrals. However, the clean shifts to $\Delta m = -29$ for **1c**/Fe$^+$, to $\Delta m = -30$ for **1d** and **1e**, and to $\Delta m = -32$ for **1f** demonstrate that an ethene molecule is lost. Combined with $\Delta m = -28$ observed for **1**/Fe$^+$, **1a**/Fe$^+$, and **1b**/Fe$^+$, it is concluded that the olefin stems from the terminal C(4) and C(5) positions. Dehydrogenation also occurs rather specifically in that only H_2 evolves from **1**/Fe$^+$, **1a**/Fe$^+$, and **1b**/Fe$^+$, whereas the terminally deuterated samples **1d**/Fe$^+$, **1e**/Fe$^+$, and **1f**/Fe$^+$ lose HD and D_2, respectively. Moreover, the exclusive formations of either H_2, HD, or D_2 from these complexes exclude the occurrence of H/D exchange processes prior to dissociation. Hence, Fe$^+$ induces the remote functionalization of one C(4)–H and one C(5)–H in the course of the dehydrogenation reaction, while the expulsion of ethene involves a selective activation of the C(3)–C(4) bond in conjunction with transfer of one H(D) atom from C(5) to the remaining ionic fragment. Note that within the detection limit no other fragments were found such that the reactions are not only selective, but occur regiospecifically. Accordingly, the H_2/HD ratio for the monodeuterated complex **1c**/Fe$^+$ can directly be correlated with the kinetic isotope effects (KIE) associated with dehydrogenation, i.e., KIE(**1c**/Fe$^+$) = I[**1c**/Fe$^+$–H_2]/I[**1c**/Fe$^+$–HD] = 2.52 ± 0.06. By reference to earlier experimental work on Fe$^+$-complexes of related carbonyl compounds conducted in our laboratory [14,32] and the results of ab initio studies [31,33], it is further assumed that the same KIE is operative in the C(5) position because the rate-determining step in metal-mediated dehydrogenation of functionalized alkanes in the gas phase

Table 1
Mass differences (Δm in amu) observed in the MI spectra of isotopologs of valeramide/Fe$^+$ complexes[a]

	−2	−3	−4	−28	−29	−30	−32
1/Fe$^+$	86	–	–	14	–	–	–
1a/Fe$^+$	87	–	–	13	–	–	–
1b/Fe$^+$	87	–	–	13	–	–	–
1c/Fe$^+$[b]	63	25	–	–	12	–	–
1d/Fe$^+$	–	85	–	–	–	15	–
1e/Fe$^+$	–	82	–	–	–	18	–
1f/Fe$^+$	–	–	86	–	–	–	14

[a] Intensities normalized to $\sum_{\text{reactions}} = 100$ with an experimental error of ±1.

[b] The averaged ratio of H_2 and HD losses is 2.52 ± 0.06.



Scheme 2.

corresponds to a multi-centered transition state (TS) in which the H(D) atoms originating from two adjacent carbon atoms equally contribute to the apparent KIE [31]. Based on these previous studies, the mechanism depicted in Scheme 2 is proposed for the C–H and C–C bond activation of the **1**/Fe^+ complex.[2]

Dehydrogenation is initiated by insertion of the metal into a C(4)–H bond, **1**/$Fe^+ \rightarrow$ **2**, from which a multi-centered TS leads first to the product complex **3** and then to dissociation; dihydrido species do not appear to be involved for late transition metal cations [33,34]. Loss of ethene proceeds via initial insertion of Fe^+ into the C(3)–C(4) bond, **1**/$Fe^+ \rightarrow$ **4**, from which metal-assisted hydrogen migration leads to the product complex **5** followed by dissociation. The routes for C–H and C–C bond activations must essentially be uncoupled from each other on the product side in that complexes **3** and **5** do not interconvert; otherwise, H/D equilibration between C(4) and C(5) should have occurred. In contrast, interconversion of **1**, **2**, and **4** is compatible with the experimental results, because reversible bond insertion and reductive elimination has no net effect. This view is consistent with theoretical studies on the activation of alkanes and alkanenitriles by bare Fe^+ in which the formation of the product complexes via multi-centered TSs was found to be rate-determining in both C–H and C–C bond activation [31,33]. As far as competition between the two types of bond activation is concerned, dehydrogenation strongly predominates with C–H/C–C ratios of ca. 87:13 for **1**/Fe^+, **1a**/Fe^+, **1b**/Fe^+, and **1f**/Fe^+. The slight increases of C–C bond activation for **1d**/Fe^+ and **1e**/Fe^+ are attributed to the KIE operative in the dehydrogenation channel (see above).

In conclusion, the dissociation behavior of valeramide/Fe^+ justifies the choice of this particular amide as a model system in that the reactions occur with a remarkable degree of selectivity. Further, the activation barriers associated with C–H and C–C bond activation appear to be quite low with respect to BDE(**1**-Fe^+) $= 51.9 \pm 2.7$ kcal/mol because bond activation exclusively occurs in the metastable ion spectra of **1**/Fe^+ and even upon collisional activation less than one percent of ligand loss leading to bare Fe^+ is observed. Similarly, a barrier of only 12 kcal/mol was estimated to be operative in the C–H bond activation of 4-heptanone/Fe^+ [21], and for Fe^+-complexes of larger dialkyl ketones even consecutive losses of an olefin from one side chain and a hydrogen molecule from the other have been observed [32,35]. While we have not attempted to estimate the activation barriers in the case of **1**/Fe^+, they are likely to fall within the

[2] As discussed in [31], several mechanistic alternatives exist, e.g., initial C(5)–H bond activation followed by *endocyclic* migration of a hydrogen from C(4). For the sake of simplicity, we restrict ourselves to the energetically most favorable route predicted by these ab initio studies.

same margin. These boundaries, high selectivity and low barriers, justify the introduction of an additional stereochemical marker in the valeramide system in the next step, aimed at obtaining information on the stereochemistry of metal-mediated C–H bond activation.

For any substrate, introduction of an additional substituent will inherently affect the chemical behavior of the derivatives in many respects. Even isotopic labeling, as the seemingly most simple substitution, can drastically affect the product distributions when several reactions compete due to isotopically sensitive branching [36]. As far as steric effects are concerned, introduction of bulky substituents appears as an obvious choice. With respect to remote functionalization by transition-metal ions, earlier studies have shown, however, that bulky substituents often do not just modulate the reactivity of the parent system, but heavily disturb the situation. For example, the attempt to probe steric effects in the remote functionalization of heptanenitrile/M^+ by introducing a *tert*-butyl ligand in the ω-position leads to predominant activation of the substituent (loss of CH_4) [37]. Less severe, but still substantial is the change in regioselectivity observed upon introduction of an ω-trimethylsilyl group in the heptanenitrile/Fe^+ system [38]. While these substituent effects are quite interesting in themselves [39], bulky substituents do not seem to be a good choice to probe stereochemical aspects of the remote functionalization in the gas phase. Likewise, changes in the general course of the reactions are expected for aryl- and hetero-substituents because these offer alternative coordination sites for the metal cation. Therefore, we decided for a minimal perturbation by introducing a methyl group at C(3) of valeramide/Fe^+. As shown above, the C(3) position of **1**/Fe^+ does not participate in dehydrogenation, and even if the newly implemented methyl group might undergo initial C–H bond activation, this is not expected to severely disturb the product distribution because an *endocyclic*, energetically demanding TS would be required in the subsequent step [31]. Nevertheless, these arguments are weakened by the fact that methyl substitution leads to a tertiary C–H bond at C(3) and hence a decrease of the C(3)–H bond energy from valeramide to 3-methyl valeramide by about 2 kcal/mol. With these considerations in mind, regioselectivity in the unimolecular reactions of **6**/Fe^+ complexes were examined by means of the deuterated substrates **6a–6c**; afterwards stereochemical aspects were addressed with the diastereospecifically labeled samples **6d** and **6e** (see footnote 1).

Table 2
Mass differences (Δm in amu) observed in the MI spectra of isotopologs of 3-methyl valeramide/Fe^+ complexes[a,b]

	−2	−3	−28	−29	−30
6/Fe^+	95 (95)	–	5	–	–
6a/Fe^+	5 (6)	91 (90)	–	–	4
6b/Fe^+	6 (6)	91 (91)	–	–	3
6c/Fe^+	95 (96)	2 (1)	3	–	–
6d/Fe^+	54 (54)	43 (43)	–	3	–
6e/Fe^+	80 (79)	16 (17)	–	4	–

[a] For the losses of H_2 and HD, the intensities derived from kinetic modeling (see footnote 3) are given in brackets.

[b] Intensities normalized to $\sum_{\text{reactions}} = 100$ with an experimental error of ±1. After re-normalization of the results from Eqs. (2a)–(2e) for the minor loss of ethene.

In perfect analogy to **1**/Fe^+, only losses corresponding to $\Delta m = -2$ and -28 are observed in the MI spectrum of **6**/Fe^+ which can be assigned to the formation of molecular hydrogen and ethene, respectively (Table 2). Interestingly, C–C bond activation is somewhat disfavored upon substitution. Even though the C(3)–C(4) bond might be slightly weakened by methylation of C(3), this effect apparently cannot compete with the increasing steric requirements of the resulting TSs in the route for C–C bond activation. In the MI spectra of **6a**/Fe^+, **6b**/Fe^+, and **6c**/Fe^+, both H_2 and HD losses are observed. Hence, loss of regiospecificity is the price to pay for 3-methyl substitution of valeramide. However, the dehydrogenation of **6**/Fe^+ still proceeds with a rather large selectivity in that activation of the C(4)/C(5) positions includes more than 90% of the products. A quantitative analysis of the regioselectivity must, however, account for the operation of kinetic isotope effects as well as the competition of the various routes which is certainly affected by deuteration due to isotopically sensitive branching. To this end, the data obtained for the substrates **6a–6e** were analyzed by a kinetic modeling which accounts

for both the KIE associated with loss of HD and the effect of competition; perturbation by the minor route via C–C bond activation is, however, neglected. For this purpose, the experimentally observed H_2/HD ratios for **6a–6e**/Fe^+ are partitioned according to the respective positions of the labels and the effects of the KIE. This deconvolution can be done by separating the relative rate constants (with $\sum k_i = 1$) for the various dehydrogenation sites, i.e., $k_{C(4)/C(5)}$ for the two terminal positions, $k_{C(3)/C(4)}$ for the next two C–H bonds, and $k_{C(3)/C(4')}$ as a representative for the involvement of the 3-methyl group; activation of the C(2) position is neglected. Further, the parameter SE is introduced to express the steric effect (SE) operative in the diastereomeric complexes **6d**/Fe^+ and **6e**/Fe^+; by definition, these samples cannot differentiate the SEs associated with $k_{C(4)/C(5)}$ and $k_{C(3)/C(4)}$, such that a single parameter is used. Even when secondary isotope effects are neglected, a strict application of such a treatment would lead the whole system underdetermined, i.e., one variable more than equations. Previous determinations of KIEs in the Fe^+-mediated remote functionalizations of various substrates, closely related to carboxamides (Table 3), suggest that the KIEs do not largely depend on the distance form the functional group. Hence, as an approximation, the same KIE $= k_{H_2}/k_{HD}$ is applied for all positions leading to Eqs. (2a)–(2e).

$$\frac{H_2}{HD}(\mathbf{6a}/Fe^+) = KIE \times \frac{k_{C(3)/C(4')}}{k_{C(3)/C(4)} + k_{C(4)/C(5)}} \quad (2a)$$

$$\frac{H_2}{HD} = (\mathbf{6b}/Fe^+) = KIE \times \frac{k_{C(3)/C(4)} + k_{C(3)/C(4')}}{k_{C(4)/C(5)}} \quad (2b)$$

$$\frac{H_2}{HD}(\mathbf{6c}/Fe^+) = KIE \times \frac{k_{C(3)/C(4)} + k_{C(4)/C(4)}}{k_{C(3)/C(4)} + k_{C(3)/C(4')}} \quad (2c)$$

$$\frac{H_2}{HD}(\mathbf{6d}/Fe^+) = \left[\frac{k_{C(3)/C(4')} + (k_{C(3)/C(4)} + k_{C(4)/C(5)})/2\,SE}{(k_{C(3)/C(4)} + (k_{C(4)/C(5)})/2\,KIE)}\right] \quad (2d)$$

$$\frac{H_2}{HD}(\mathbf{6e}/Fe^+) = \left[\frac{k_{C(3)/C(4')} + k_{C(3)/C(4)} + (k_{C(4)/C(5)})/2}{(k_{C(3)/C(4)} + k_{C(4)/C(5)})/(2KIE \times SE)}\right] \quad (2e)$$

As far as regioselectivities are concerned, the experimental data reported in Table 2 can be modeled reasonably well for KIE $= 2.3 \pm 0.1$ together with the parameters $k_{C(3)/C(4)} = 0.003 \pm 0.003$, $k_{C(3)/C(4')} = 0.027 \pm 0.005$, and $k_{C(4)/C(5)} = 0.97 \pm 0.01$. For the steric effect, a value of SE $= 2.0 \pm 0.1$ is obtained.[3] The magnitude of the KIE is in accord with the data of **1**/Fe^+ and also consistent with previous results for Fe^+ complexes of carbonyl compounds (Table 3). Due to this internal consistency of the solution for Eqs. (2a)–(2e), the relative rate constants

Table 3
KIEs associated with the metal-mediated dehydrogenations of the $\omega/(\omega - 1)$ positions in the unimolecular dissociations of mass-selected complexes of Fe^+ with the carbonyl compounds indicated

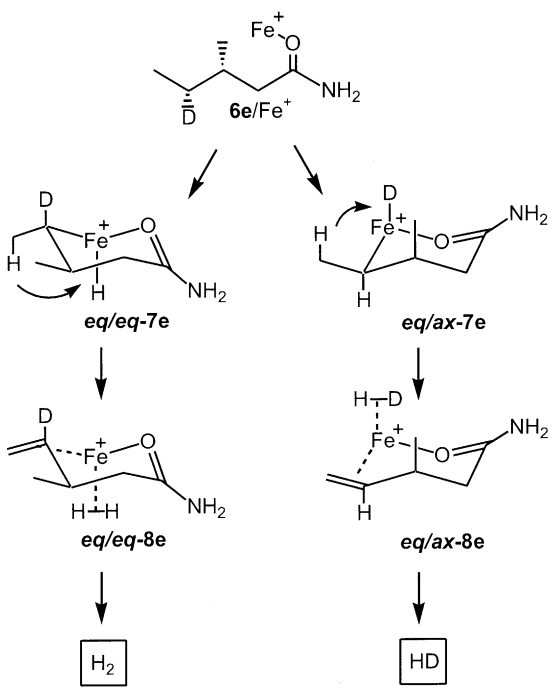
	KIE	References
[4-D_1]-2-Pentanone	2.13 ± 0.04[a]	[9]
[5-D_1]-2-Hexanone	2.76 ± 0.05	[30]
[1,1,1-D_3]-4-Heptanone	2.70 ± 0.04	[41]
[2,2-D_2]-4-Heptanone	2.83 ± 0.04	[41]
[5,5,5-D_3]-3-Ethyl-pentan-2-one	2.97 ± 0.04	[32]
[4,4-D_2]-3-Ethyl-pentan-2-one	2.98 ± 0.04	[32]
[1,1,1-D_3]-5-Nonanone	2.2 ± 0.1[b]	[13]
[2,2-D_2]-5-Nonanone	3.0 ± 0.1[b]	[13]
[4,4,4-D_3]-2-Ethyl-butyric acid	2.58 ± 0.04	[14]
[3,3-D_2]-2-Ethyl-butyric acid	2.55 ± 0.04	[14]
[4-D_1]-Valeramide	2.52 ± 0.06	This work
6/Fe^+	2.25 ± 0.10[c]	This work

[a] Error margin adopted from [14,32,41].
[b] Error margin estimated.
[c] Value derived from kinetic modeling, see text.

[3] With respect to the error margins in the experiments as well as for the sake of readability, only integers are given in Tables 1 and 2. In the explicit kinetic modeling, one more digit was considered, however, which proved significant. The errors of the optimized parameters were assessed by a sensitivity analysis which used the experimental uncertainty of ±1 in the normalized intensities as a cut-off criterion, while varying each variable for the optimized set of parameters. Cooperative effects of the variables might exist, but were not observed during the kinetic modeling when starting from initial values and are therefore neglected.

k_i can be regarded as representatives for the regioselectivities in the Fe^+-mediated C–H bond activations of the various positions of the 3-methyl valeramide. Accordingly, 97% of the dehydrogenation involves $k_{C(4)/C(5)}$ and thus, activation of the two terminal positions.

As far as the diastereomers **6d**/Fe^+ and **6e**/Fe^+ are concerned, inspection of the experimental data reveals a pronounced steric effect. The mere observation of SE $\neq 1$ implies that two different effects determine the activation of the diastereotopic C(4)–H bonds in **6**/Fe^+ upon deuteration. For one diastereomer, KIE and SE amplify each other (here: **6e**/Fe^+), whereas KIE and SE compensate for the other diastereomer (here: **6d**/Fe^+). This relationship is expressed in Eqs. (2d) and (2e) which also acknowledge the competing routes for dehydrogenation. As far as the directionality of the steric effect is concerned, an analogy to the stabilities of six-membered rings in organic chemistry is proposed (Scheme 3). Thus, assuming preferential chair-like conformations of the reaction intermediates and the associated TSs, C(4)–H bond activation of **6e**/Fe^+ leads to the insertion species *eq*/*eq*-**7** in which both methyl groups are in energetically favorable equatorial positions. In contrast, C(4)–D bond activation of **6e**/Fe^+ leads to the intermediate *eq*/*ax*-**7** in which one of the methyl groups must adopt an axial position which is considered unfavorable. Accordingly, both the KIE associated with labeling and the SE due to the axial arrangement disfavor loss of HD, and hence a larger H_2/HD ratio is observed for **6e**/Fe^+. For the diasteromeric complex **6d**/Fe^+, KIE and SE compensate each other leading to a particularly low H_2/HD ratio. Similar considerations evolve from considerations of Newman projections of the C(3)–C(4) bond, which can also be applied to larger rings [10,15,39].



Scheme 3.

4. Conclusions

The observed regiospecific dehydrogenation of valeramide/Fe^+ and the diastereoselective effect of SE = 2.0 in the C–H bond activation of **6**/Fe^+ have two important conclusions. (i) It is usually anticipated (and often true) that polyatomic, metastable ions produced in the ion source of a mass spectrometer have rather large internal energies. The mere observation of a significant SE for a reaction occurring within a flexible alkyl chain implies the opposite, however. Instead, if the internal energy of metastable **6**/Fe^+ were high, a negligible SE and small KIEs are to be expected. The experimental results, therefore, imply that metastable **6**/Fe^+ has a low energy content in conjunction with small activation barriers for both C–H and C–C bond activation. (ii) Highly unsaturated transition-metal ions can be regarded as very reactive reagents being capable to activate a huge manifold of substrates. Nevertheless, the reactions described here proceed with remarkable regio- and diastereoselectivities. Hence, reactive species usually are, but must not necessarily be associated with low selectivities, if pre-coordination of the metal center in conjunction with low activation barriers leads to favorable trajectories for the activation of certain positions within a flexible alkyl backbone [40].

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