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Iron(I)-Induced Diastereoselective C–H Bond Activation in Nonrigid Molecules[1]

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Abstract: The Fe(I)-mediated introduction of a terminal C–C double bond by gas-phase dehydrogenation of 3-methylpentan-2-one is subject to diastereoselective discrimination of the hydrogen atoms of C(4). This unprecedented effect in gas-phase organometallic chemistry results most likely from the formation of chairlike intermediates bearing an axial or an equatorial methyl substituent, depending on the relative configuration of C(3) in the acyclic substrate. The latter reaction path is favored by a factor of 1.5, and a kinetic isotope effect $k_{H_2}/k_{HD} = 2.13$ is associated with the reductive elimination of molecular hydrogen.

While there exist numerous reports on the reactions of bare and partially ligated transition-metal ions with organic substrates in the gas phase,[2] detailed studies on the *stereochemical* course of the metal-mediated C–H bond activation are scarce. Hitherto these studies were limited to cyclic systems, in which the metal was either bound to the π-system of an aromatic ring or chelated by multidentate ligands.[3,4]

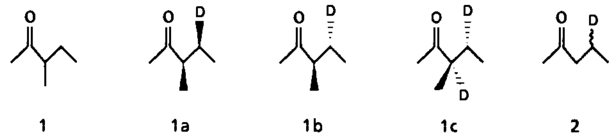
In previous studies,[5] we have examined the C–H and C–C bond activation of aliphatic ketones by bare Fe$^+$ cations, and these reactions were described in terms of the remote functionalization concept (Scheme I).[6] In the gas-phase reactions of dialkyl ketones with Fe$^+$, even a consecutive remote functionalization of the two flexible chains was observed.[5] By labeling experiments and the analysis of intramolecular kinetic isotope effects, associated with the regiospecific dehydrogenation of the alkyl chain, it was demonstrated that the reductive elimination of molecular hydrogen (step III) corresponds to the rate-determining step in the overall reaction; possible contributions of the CH insertion (step I) or the β-H transfer (step II) to the kinetic isotope effects are negligible.[5] However, if steps I and II are reversible within the time scale of the experiment, H/D equilibration is expected to precede the dissociation; this has not been observed in the experiments.

In this contribution, we will not only resolve this dilemma but also address successfully, for the first time, the as yet unresolved problem of *diastereoselective* activation of aliphatic C–H bonds by bare Fe$^+$.

Experimental Section

The metal complexes were generated by 100-eV electron bombardment of 1/1 mixtures of Fe(CO)$_5$ and the organic substrates of interest in the chemical ionization source of a four-sector BEBE mass spectrometer (B stands for magnetic and E for electrostatic analyzers), which has been described in detail elsewhere.[7] The 8-keV beam of Fe$^+$(ketone) ions was mass-selected ($m/\Delta m \approx 3000$) by means of B(1)E(1), and the unimolecular dissociation occurring in the field-free region preceding B(2) was monitored by scanning of B(2). Between 5 and 20 scans were averaged, all spectra were on-line processed with the AMD-Intectra data system, and the data given are averages of at least three independent measurements.

Chart I



Ketones **1** and **2** (Chart I) were synthesized by standard laboratory procedures, purified by preparative gas chromatography, and characterized by spectroscopic means. The diastereospecifically labeled ketones **1a–c** were prepared via the following routes: The monodeuterated compounds **1a** and **1b** were prepared from the starting compounds *cis*-2-butene (Linde AG, 99% purity, >99% *Z*-isomer) and *trans*-2-butene (Linde AG, 99% purity, >99% *E*-isomer), respectively, by (a) epoxidation of the olefins, (b) reduction of the epoxides with LiAlD$_4$ (Janssen Chimica, >98 atom % D), (c) tosylation of the corresponding [3-^{2}H$_1$]-2-butanols and subsequent nucleophilic displacement with CN$^-$ to yield the diastereomeric 2-methyl-[3-^{2}H$_1$]-butyronitriles,[8] and (d) conversion of the nitriles to the racemic methyl ketones **1a** and **1b**, respectively, by reaction with methylmagnesium iodide in benzene (Scheme IIa) for the synthesis of *rac*-**1a**. For the generation of *rac*-**1b** the reaction commenced with *trans*-2-butene.[9] Since enolization involving C(3) would result in a loss of stereochemical information, the last step in the synthesis is crucial with respect to the steric homogeneity of **1a** and **1b**. Furthermore, as **1a** and **1b** are prone to acid- and base-catalyzed, facile racemization, the study of **1c** is of prime importance in the present context, as this stereoisomer can be used as a probe. This follows directly from the fact that racemization of **1c** in solution is invariably accompanied by a deuterium/hydrogen exchange at C(3); consequently, the investigation of mass-selected, D$_2$-containing Fe$^+$ complex of **1c** is not likely to be subject to any stereoisomerization at C(3) prior to the mass-spectrometric experiment and, thus, serves as a control test for the study of **1a** and **1b**. Ketone **1c** was prepared via an independent synthesis starting from tiglic acid (Janssen, 98%) by (a) *syn*-deuteration with [^{2}H$_2$]-diimide to [2,3-^{2}H$_2$]-2-methylbutyric acid[10] and (b) conversion to the corresponding methyl ketone with an excess of etheral methyllithium (Scheme IIb).[11]

[⊛] Abstract published in *Advance ACS Abstracts*, September 1, 1993.

(1) Dedicated to Professor Dr. h.c. Rudolf Wiechert, Schering AG, on the occasion of his 65th birthday.

(2) For a review, covering more than 700 references, see: Eller, K.; Schwarz, H. *Chem. Rev.* **1991**, *91*, 1121.

(3) For an investigation of the *face-selctivity* of metal ion induced single and double dehydrogenations of tetraline, see: (a) Seemeyer, K.; Prüsse, T.; Schwarz, H. *Helv. Chim. Acta* **1993**, *76*, 113. See also: (b) Whitesides, T. H.; Arhart, R. W. *Tetrahedron Lett.* **1972**, 297. (c) See: Meyer, K.; Schwarz, H. *Helv. Chim. Acta*, in press.

(4) For a detailed study on the *regioselectivity*, *stereoselectivity*, and *isotopically sensitive branching* in the Fe(I)-mediated dehydrogenation of octane-1,8- and hexane-1,6-diol in the gas phase, see: (a) Prüsse, T.; Fiedler, A.; Schwarz, H. *Helv. Chim. Acta* **1991**, *74*, 1127. (b) Seemeyer, K.; Prüsse, T.; Schwarz, H. *Helv. Chim. Acta* **1993**, *76*, 7632. (c) Also see: Nekrasov, Y. S.; Zagorevskii, D. V. *Org. Mass Spectrom.* **1991**, *26*, 733.

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(6) Review: Schwarz, H. *Acc. Chem. Res.* **1989**, *22*, 282.

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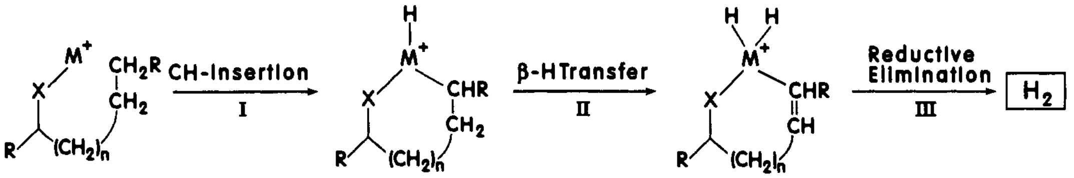
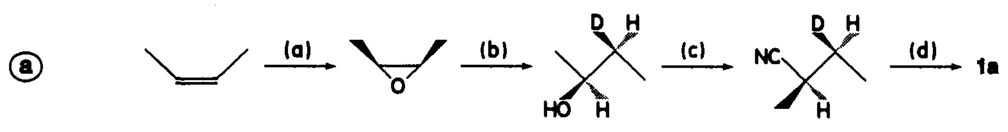
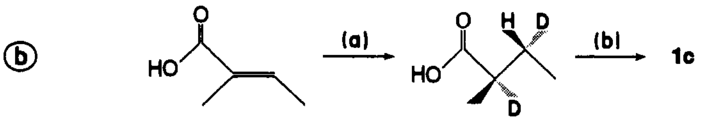
Scheme I



Scheme II

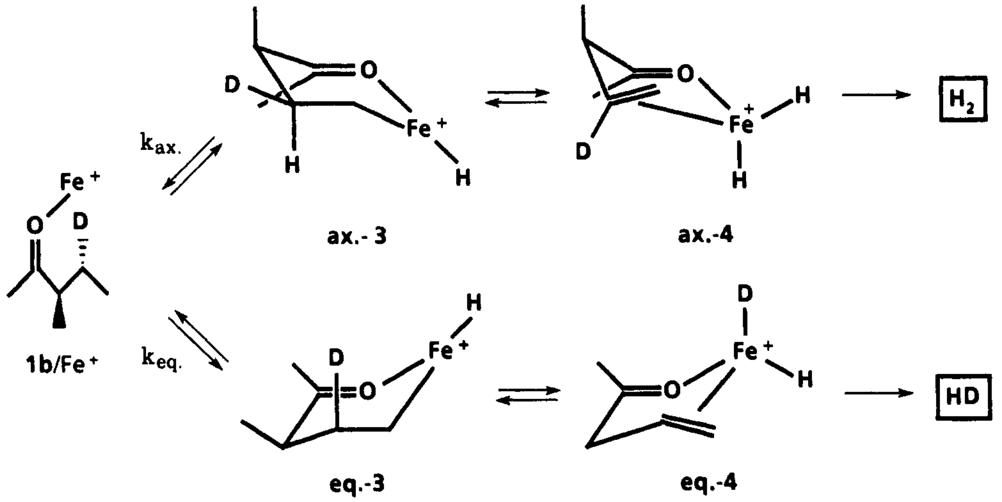


(a) 1.)NBS/H_2O;2.)3n NaOH
(b) 1.)$LiAlD_4/Et_2O$;2.)aq.NH_4Cl
(c) 1.)TosCl/py;2.)NaCN/DMSO/130°C
(d) 1.) MeMgI/C_6H_6;2.)cold 2n HCl



(a) 1.)CH_3OD(3x);2.)KOOC-N=N-COOK/CH_3OD/CH_3COOD
(b) 1.)CH_3Li/Et_2O;2.)cold 2n HCl

Scheme III



The similarity of the ratio of H_2 and HD losses from **1b** and **1c** indicates that enolization in their syntheses is indeed negligible. In order to further test the efficacy of the diastereoselectivity, and to check for internal consistency of our data analysis, **1c** was converted to a mixture of all possible stereoisomers of $[3\text{-}^2H_1]$-2-methylbutan-2-one by H/D exchange and equilibration of the C(3) position in an aqueous K_2CO_3 solution at 100 °C; the Fe^+ complex of the so-formed mixture of **1a** and **1b** gave an H_2/HD ratio of 2.23 ± 0.05, as expected for an equimolecular mixture of all stereoisomers.[12]

Table I. Unimolecular Dehydrogenation (MI Mass Spectra) of the Fe^+ Complexes of **1a–c**[a]

precursor[b]	H_2	HD	H_2/HD
1a	76	24	3.13 ± 0.08
1b	61	39	1.56 ± 0.09
1c	59	41	1.41 ± 0.05

[a] Data are normalized to the sum of molecular hydrogen losses = 100%. [b] The diastereoisomers **1a–c** have been measured as racemic pairs.

Results and Discussion

The metastable ion (MI) mass spectrum[7] of the Fe^+ complex of 3-methylpentan-2-one (**1**) is dominated by the loss of molecular hydrogen (90%), and the study of the isotopomers of **1** demonstrates (Table I) that the reaction follows the previously described concept of remote C–H bond activation,[13] involving specifically the $\omega/\omega - 1$ positions of the alkyl chain. From the investigation of the Fe^+ complex of **2**, a kinetic isotope effect (KIE) $k_{H_2}/k_{HD} = 2.13$ emerges for the dehydrogenation. This value is in line with results from other Fe^+(ketone) complexes, for which it has been demonstrated that the isotope effect is almost exclusively due to the reductive elimination of molecular hydrogen.[5]

Quite remarkable is the unprecedented diasteroselectivity operative in the dehydrogenation of the racemic pairs of **1a**–Fe^+ versus the Fe^+ complexes of **1b** and **1c**. For the former, the ratio of H_2/HD loss (3.13 ± 0.08) is significantly larger than that of the latter (**1b**; 1.56 ± 0.09; **1c**, 1.41 ± 0.05). A straightforward,

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(13) Additional MI processes of **1**–Fe^+ correspond to the formations of C_2H_4 (6%) and of CH_4 (4%).

internally consistent analysis of these findings is provided by assuming the reaction sequence depicted in Scheme III.[14] This analysis takes into account the coupled operation of an intramolecular kinetic isotope effect (favoring loss of H_2 versus HD) and the energetics of the cyclic diastereoisomers generated en route to the product formation. For example, for **1b** and **1c**, loss of H_2 will invariably proceed via a conformation having an energetically unfavorable axial CH_3 group (**ax-3**). As a consequence, the system will "bypass" this intermediate by populating the equatorial intermediate **eq-3**, although this path suffers from the isotope effect associated with the loss of HD. On the other hand, for the complex **1a**–Fe^+, elimination of H_2 versus HD is favored both in terms of a preferred conformation and in terms of the isotope effect. From a simple algebraic analysis,[15] it follows that, in the overall effect, the kinetic isotope effect amounts to $k_{H_2}/k_{HD} = 2.1$ and the conformational preference of an equatorial versus an axial CH_3 ligand in the intermediates **3** and **4** is as large as 1.5. Furthermore, the effects imply that the intermediates have a chairlike structure, as depicted in Scheme III, rather than a boat conformation, for which the ratio of H_2 to HD should be small for **1a** and enlarged for **1b** and **1c**. In addition, the formation of *cyclic* intermediates, whose conformational interconversion by a pseudorotation process is energy-demanding, is most likely the origin for the observed absence of H/D scrambling in the activation of carbon–hydrogen bonds of *acyclic* substrates by bare metal ions.[5]

It should be mentioned that the results reported here are not confined to ketone **1**; similar effects, in terms of both diastereoselectivity and kinetic isotope effects, also hold true for larger ketones (e.g. heptan-2-one) or α-methyl-substituted carboxylic acids.[12]

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[14] For the sake of clarity, in Scheme III only the reactions of **1b**–Fe^+ are presented. For **1c** all the essential features are identical, and the stereochemical properties of **1a** are obtained by simply exchanging the H/D substituents of the stereocenter C(4).

[15] In the analysis,[12] it is assumed that the KIE's associated with the reductive elimination of molecular hydrogen from **ax-4** and **eq-4** are identical.