106. Definitive Proof for the Operation of Isotopically Sensitive Branching ('Metabolic Switching') in Fe^{I}-Mediated C–H Bond Activation in the Gas Phase

Short Communication

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Dedicated to Professor *M. H. Zenk*, Universität München, on the occasion of his 60th birthday

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Rigorous regio- and stereospecific labeling experiments are performed to demonstrate the operation of the previously suggested operation of 'isotopically sensitive branching' in Fe^{I}-mediated C–H bond activation. For the hexane-1,6-diol/Fe^{+}-complex, it is shown that dehydrogenation involves specifically the central C(3)/C(4) position, and the study of the stereospecifically labeled D,L- and *meso*-[3,4-D_2]-isotopomers **1e** and **1f** demonstrates that dehydrogenation proceedes *via* two competing pathways (*i.e.* '*anti*'- *vs.* '*syn*'-route). The contribution of these routes to the product formation is – due to a kinetic isotope effect – controlled by the *relative configuration at the labeled positions C(3)/C(4)*. For the D,L-form **1e**, we estimate a ratio of 49:1 in favor of the '*anti*'-route; due to an isotope effect, this ratio drops to 4.3:1 for the *meso*-form **1f**.

While isotopically sensitive branching ('metabolic switching') is well-known to exist in enzymatic processes [1], cases in which deuterium isotopic perturbation determines the stereochemical course of a transition-metal-mediated process are scarce. Recently, it was demonstrated that the outcome of metal-complex-induced chain propagation in solution is subject to this effect [2], and a remarkable result was reported for the gas-phase C–H bond activation of *bare* Fe^{+} with octane-1,8-diol[2]). Based on extensive labeling studies, several unusual features were uncovered [4]. Most interesting is the finding that the configurations at C(4)/C(5) in [4,5-D_2]octane-1,8-diol, *i.e.* the D,L- and *meso*-forms, play a pivotal role in the dehydrogenation of the central C(4)/C(5) part. Two reactive conformations are involved: an '*anti*'-conformation of the central C(4)/C(5) bond serves as a precursor to generate a *trans*-fused metallabicyclic intermediate, and the *cis*-fused counterpart is accessible from a '*syn*'-conformation. Unexpected and unprecedented is the result, that the contribution of these two bicyclic intermediates to the product formation is controlled by the relative configuration at the labeled methylene positions C(4)/C(5). The quantitative analysis of the data was hampered, however, by the fact, that the Fe^{I}-mediated dehydrogenation of octane-1,8-diol did not exclusively involve the central C(4)/C(5) positions (80%); rather, the flexibility of the chelate is such that activation of the C(3)/C(4) or the equivalent C(5)/C(6) positions also takes place (20%) with the consequence that extensive algebraic corrections had to be made. Here, we report a clear-cut case which is not subject to this nuisance.

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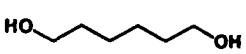
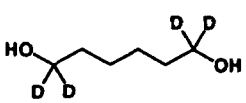
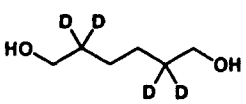
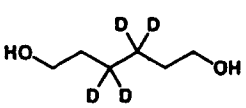
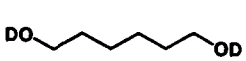
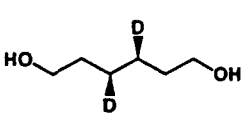
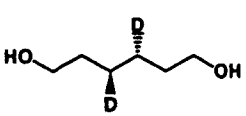
[2]) For a review on C–H/C–C bond activation by bare transition-metal ions, covering more than 700 references, see [3].

If a mixture of hexane-1,6-diol (**1**) and $Fe(CO)_5$ is bombarded with 100-eV electrons in the chemical-ionization source of a four-sector BEBE mass spectrometer[3]), the metastable ion (MI) mass spectrum (unimolecular decomposition) of *B(1)E(1)*-mass selected complexes **1**-Fe^+ reveals the formation of molecular hydrogen, H_2O, and olefins (C_2H_4, C_3H_6). From the study of the specifically labeled isotopomers **1a–f** (*Table 1*), it follows that the olefins are formed in a straightforward manner; in contrast, H_2O loss is preceded by extensive exchange processes involving various sites of the hexane-1,6-diol ligand. These reactions will not be further discussed in the present context. Rather, we will confine ourselves to a discussion of the dehydrogenation reaction to which the concept of 'metabolic switching' applies.

The data given in *Table 1* allow to make the following comments: *i*) Molecular hydrogen originates *exclusively* from the central segment C(3)/C(4) (loss of H_2 from **1a**, **1b**, **1d**, and elimination of D_2 from **1c**). Therefore, we do not have to worry that the analysis of the stereoisomers **1e** and **1f** will be affected by contributions from 'side reactions'. *ii*) As expected from our previous study of the octane-1,8-diol/Fe^+ system [4],

Table 1. *Unimolecular Decomposition of Fe^+-Complexes of Hexane-1,6-diol* (**1**) *and Its Isotopomers* **1a–f**[a])

Precursor		H_2	HD	D_2	H_2O	HDO	D_2O	C_2H_4	$C_2H_2D_2$	C_3H_6	C_3H_5D	$C_3H_4D_2$
	**1**	15	–	–	69	–	–	11	–	5	–	–
	**1a**	19	–	–	64	2	–	–	10	–	–	5
	**1b**	15	–	–	54	5	–	–	21	–	–	5
	**1c**	–	–	2	65	12	–	12	–	–	–	8
	**1d**	17	–	–	–	46	17	13	–	8	–	–
	**1e**[b])	9	0.3	1	67	5	–	11	–	–	6	–
	**1f**	2	6	0.1	69	5	–	11	–	–	6	–

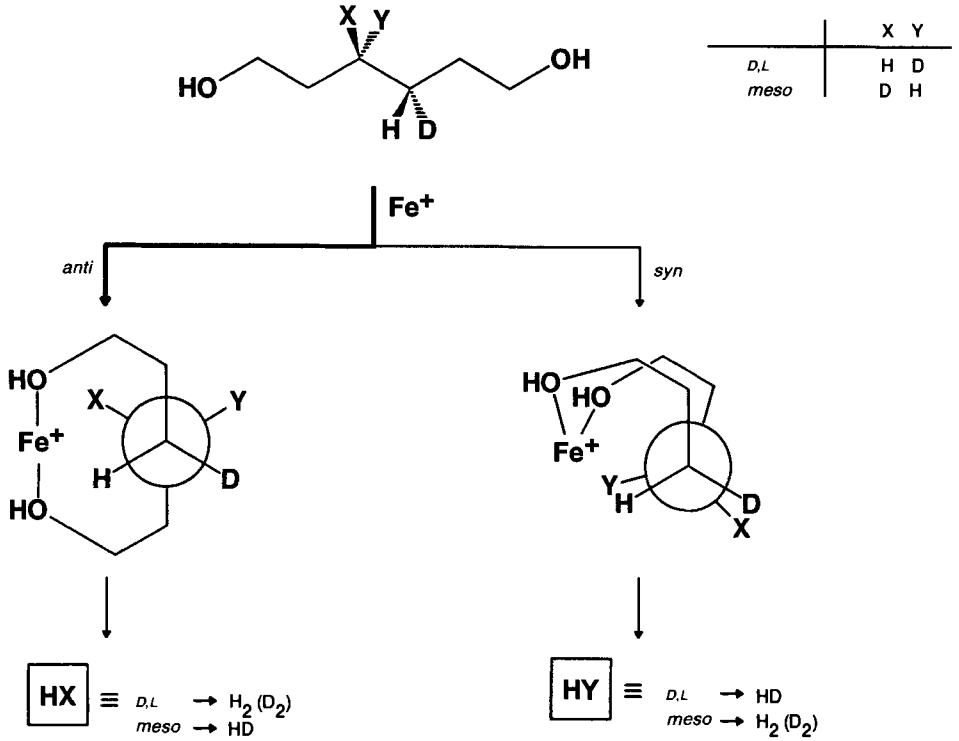
[a]) Intensities are normalized to Σ neutral products = 100%.
[b]) **1e** corresponds to the D,L-form.

[3]) For a detailed description and operation of the machine, see [5]. Experimental details are described in [4] [6].

Table 2. *Fe^{I}-Mediated Dehydrogenation of* D,L- *and* meso-*[3,4-D_2]hexane-1,6-diol*

Precursor	H_2	HD	D_2
1e (D,L)	83	2	15
1f (*meso*)	18	81	1

Scheme



a striking difference is noted for the isotope distribution for the losses of H_2, HD, and D_2 from the two stereoisomers **1e** and **1f**. From the re-normalized data (*Table 2*) in conjunction with the oversimplified mechanism (*Scheme*), we conclude from the ratio $(H_2 + D_2)$/HD that, for the D,L-form **1e**, 98% of the dehydrogenation proceeds *via* the '*anti*'-route (*Scheme*) and only 2% *via* the '*syn*'-path. For the *meso*-form **1f**, however, the numbers are quite different with only 81% involving the '*anti*'- and 19% proceeding *via* the '*syn*'-path (estimated from the ratio $HD/(H_2 + D_2)$). This result is an immediate manifestation of an isotopically sensitive branching: for the *meso*-form **1f**, any conceivable intermediate formed *via* the otherwise favored '*anti*'-route will invariably lead to the generation of HD. Thus, due to the kinetic isotope effects (*Table 1*), the system 'bypasses' this channel and explores to a larger extent the alternative route, which is only disfavored by a factor of 4.3. The opposite situation holds true for the D,L-labeled isotopomer **1e**. Here, the '*anti*'-route has the option to undergo either loss of H_2 and D_2 (favoring the former by a factor of 5.53). Consequently, the need to an isotopically enforced switch to

populate the '*syn*'-path is much less pronounced, and this path is indeed by a factor of 49 less favored than the former. In conclusion, the analysis of the present data lends full support to our previous conclusion [4] that 'metabolic switching', well-known to be operative in enzymatic hydrogen abstractions, has its counterpart in the Fe^{I}-mediated C–H bond activation in the gas phase.

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