106. Regioselectivity, Stereoselectivity, and Isotopically Sensitive Branching in the Fe(I)-Mediated Dehydrogenation of Octane-1,8-diol in the Gas Phase

by **Tilmann Prüsse, Andreas Fiedler**, and **Helmut Schwarz***

Institut für Organische Chemie der Technischen Universität Berlin, Strasse des 17. Juni 135, W–1000 Berlin 12

Dedicated to Prof. *Jürgen Sauer* on the occasion of his 60th birthday

(13.VI.91)

Regio- and stereospecific labeling experiments are conducted to unravel the mechanistic features of the Fe^+-induced dehydrogenation of octane-1,8-diol in the gas phase. With regard to the regioselectivity, *ca.* 20% of molecular hydrogen originates from the C(3)/C(4) or the equivalent C(5)/C(6) positions. The remaining 80% are provided by the C(4)/C(5) methylene units. The steps, preceding the reductive elimination of hydrogen, are irreversible, and the overall reaction follows a 1,2-elimination mode. The loss of HD from C(3)/C(4) is associated with a kinetic isotope effect $k_{H_2}/k_{HD} = 1.68$. Formation of D_2 from the positions C(4)/C(5) has an isotope effect of $k_{H_2}/k_{D_2} = 4.7$; this figure is slightly dependent on the configuration at C(4)/C(5). Most interesting is the finding that the configuration at C(4)/C(5) in [4,5-D_2]octane-1,8-diol, *i.e.* **5c** *vs.* **5d**, plays a pivotal role in the dehydrogenation of the central C(4)/C(5) part. This unexpected and unprecedented result is explained in terms of conformational analysis. A staggered-like conformation serves as a precursor to generate a *trans*-fused bicyclic intermediate **6**. It is this very intermediate from which most of the molecular hydrogen is eliminated. Of minor importance is the *cis*-fused chelate **7**, which is formed from an eclipsed-like conformation of the octane-1,8-diol/Fe^+ complex. *The contribution of* **6** *and* **7** *to the product formation is controlled by the relative configuration at the labeled positions C(4)/C(5).* For the D,L-form **5c**, we estimate a ratio of *ca.* 9:1 for the contribution of **6** *vs.* **7**; due to an isotope effect, this ratio drops to 1.85:1 for the *meso*-form **5d**. This finding constitutes the first example for the existence of isotopically sensitive branching ('metabolic switching') in gas-phase organometallic chemistry.

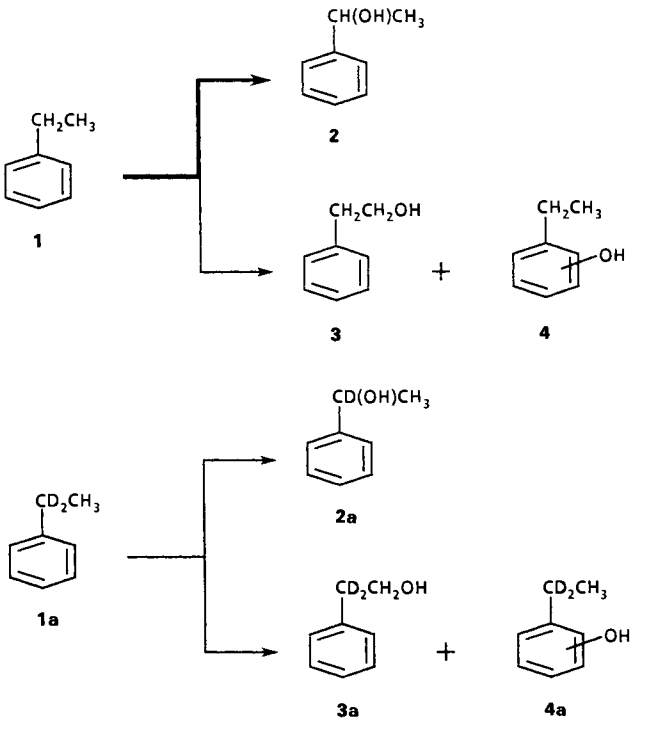
Introduction. – There is increasing evidence for the existence of isotopically sensitive branching ('metabolic switching') in enzymatic processes, that is, when the usual site of hydrogen abstraction is hindered by D substitution, thus reorienting the substrate into another juxtaposition to give rise to a reaction at a different site [1][1]). For example, the Cytochrome-P-450-mediated hydroxylation of ethylbenzene (*Scheme 1*) involves preferentially the α-position (**1** → **2**); oxidation of the Me group (**1** → **3**) or attack of the benzene ring (**1** → **4**) are of minor importance. In contrast, due to the presence of isotopes at the α-positions, the [α,α-D_2]isotopomer **1a** exhibits increased formation of **3a** and **4a** at the expense of **2a** [1d].

In this paper, we report for the first time that isotopically sensitive branching also pertains in the activation of C–H bonds by bare Fe^+ in the gas phase[2]). In particular, we will demonstrate that the extent to which a reactive conformation participates in the Fe^+-mediated dehydrogenation is determined by the configuration at the isotopically

[1]) For a detailed description of the kinetics that pertain to chemical and enzymatic systems of this kind, see [2a] and [2b], respectively.

[2]) For selected references for the activation of C–H bonds by bare transition-metal ions, see [3].

Scheme 1



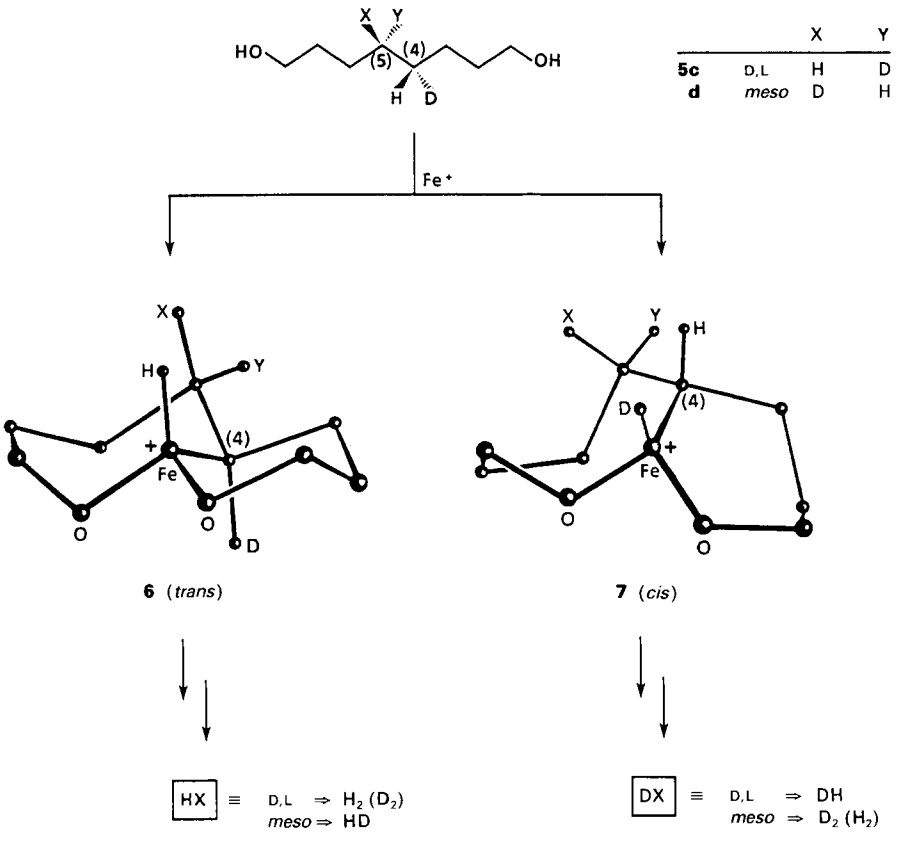
labeled centres of the substrate. Alcohols were chosen as a model, as previous studies [4] have indicated a high regioselectivity for ROH/transition-metal ion complexes. In fact, these results demonstrate that well-defined segments of the alkyl chain undergo oxidative addition to the 'anchored' metal ion. To exert some rigidity to the system and to get a handle on the stereochemical features of the process, we have decided to study regio- and stereospecifically labeled *diols* which, in view of previous experiences with other difunctional substrates [5], can be expected to form chelates with the bare transition-metal ion.

From first principle considerations, it follows that the oxidative addition of the 'anchored' metal ion to a C–H bond can proceed *via* either of two stereochemical paths. One commences with a staggered conformation of the central part C(4)/C(5) of the alkyl chain of **5** and leads to a *trans*-fused bicyclic intermediate **6**[3][4]). The second alternative,

[3]) We stress that, for the time being, neither experimental nor reliable, theoretical data on the actual structures of any of the species described in this and related studies [3–5] are available. While numerous conformers of **6** and **7** are conceivable, the fundamental difference of the two ring junctions and their bearing on the dehydrogenation are not invalidated by our present lack of more detailed structural information, provided no inversion of configuration at the metal centre occurs. To our knowledge, no data exist in favour of a rapid stereoinversion of a metal–H bond in transition-metal ion complexes. In addition, as will be demonstrated in the present study, this assumption is indeed not invalid.

[4]) For the sake of simplicity and clarity, in *Scheme 2* only two out of four possible modes of C–H(D) bond activations are depicted. Without affecting our conclusions, a *trans*-form **6** is also accessible by first activating the C–D bond of C(4). As a consequence, the D,L-isotopomer **5c** would then give rise to loss of D_2; for the *meso*-form **5d** elimination of HD is expected to occur. Similar arguments apply to the formation of **7**.

Scheme 2



		X	Y
5c	D,L	H	D
d	*meso*	D	H

possibly demanding more energy than the path leading to **6**, starts from an eclipsed-like conformation and results in a *cis*-fused bicyclic intermediate **7** (*Scheme 2*). β-H transfer from the *syn*-side (relative to the metal–H bond) of the larger ring[5]) gives rise to intermediates which serve as immediate precursors for the reductive elimination of molecular hydrogen (*Scheme 2*). If one ignores for the sake of simplicity[6]) *i*) the operation of kinetic isotope effects and *ii*) contributions from the methylene groups C(3) and C(6), chemical intuition leads one to predict that the Fe^+ complex of the *meso*-form **5d** should preferentially undergo loss of HD with the elimination of H_2 and D_2 being of minor importance. In distinct contrast, the Fe^+ complex of the D,L-isotopomer **5c** is predicted to favour the elimination of H_2 and D_2 as compared to HD loss. In addition and most importantly, if isotopically sensitive branching also plays a role in the present

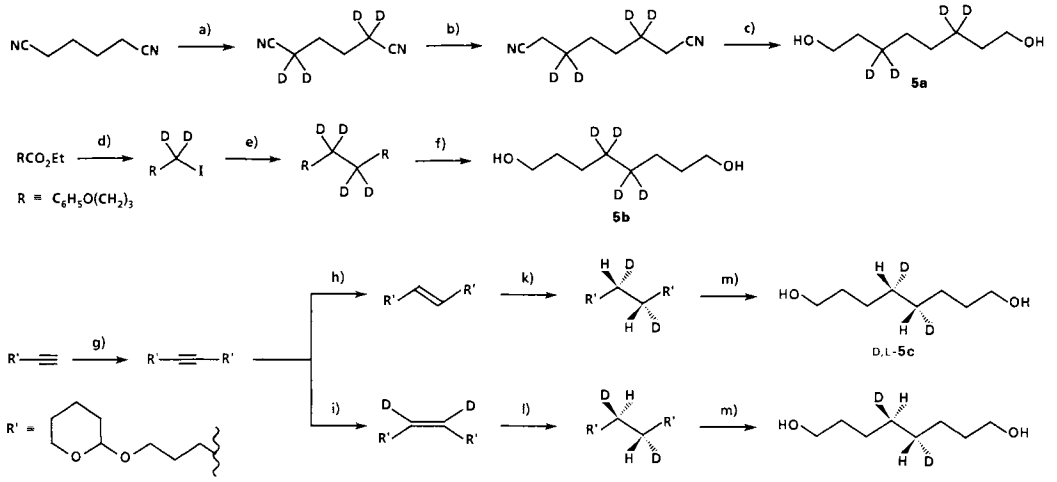
[5]) The preference of the larger ring to serve as a H-atom source in the β-H transfer is an immediate consequence of the fact that the propensity of a β-H transfer is quite sensitive to the dihedral angle of the HCCFe unit.

[6]) As will be shown, these assumptions are not warranted. In fact, the study of the isotopomers **5a–d** permits us to sort out these important data and to quantify the contributions of **6** and **7** as a function of the configuration at C(4)/C(5).

system, we predict different amounts of '*trans*'/'*cis*'-contributions to the metal-ion mediated dehydrogenation for the D,L- and *meso*-forms. More precisely, for the *meso*-form we expect a smaller and for the D,L-stereoisomer a larger '*trans*'/'*cis*'-ratio. As will be demonstrated in the following, these expectations are precisely born out experimentally. Further, the analysis of the isotopomers **5a–d** of octane-1,8-diol permits an estimate of the regioselectivity of the Fe^+-mediated dehydrogenation (*e.g.* activation of the C(3)/C(4) *vs.* the C(4)/C(5) segments) as well as a determination of the overall kinetic isotope effects associated with the reaction[7]).

Experimental. – The experimental setup has been described in [3m, q, t] [4]. Briefly, a 1:5 to 10 mixture of $Fe(CO)_5$ and octane-1,8-diol is bombarded with 100-eV electrons in the chemical ionization source (repeller voltage 0 V) of a modified *ZAB* mass spectrometer of BEBE configuration (B stands for magnetic and E for electric sector)[8]). Although the actual mechanism by which the complexes are generated is yet unknown, the pressure in the ion source is high enough to permit collisional cooling thus increasing the lifetime of the complex **5**-Fe^+ such that time-delayed decomposition reactions after *ca.* 1 μs take place (metastable-ion (MI) dissociations). To this end, organometallic complexes **5**-Fe^+ having 8-keV kinetic energy are mass-selected and focused with B(1)E(1) at a resolution sufficient to separate isobaric multiplets. Unimolecular reactions occurring in the field-free region between E(1) and B(2) were recorded by scanning B(2). In the present experiments, the fourth sector E(2) is not used. Spectra were recorded on-line and averaged by using signal-averaging techniques employing the *AMD Intectra* data system. In typical experiments, 50–150 spectra were recorded. The short-time reproducibility of the MI spectra is excellent, and the standard deviation of measurements repeated after months is better than ± 5%. All compounds were synthesized by standard laboratory procedures [7], as depicted in *Scheme 3*, purified by chromatographic means and fully characterized by NMR and MS.

Scheme 3. *Synthesis of the Octane-1,8-diol Isotopomers* **5a–d**



a) CH_3OD/CH_3ONa. b) 1. DCl/D_2O, 2. $LiAlH_4$, 3. HBr, 4. KCN/DMSO. c) 1. H_3O^+/H_2O, 2. $LiAlH_4$, 3. H_2O. d) 1. $LiAlD_4$, 2. H_2O, 3. TsCl/KOH, 4. LiI/CH_3COCH_3. e) Na/toluene. f) 1. Br_3B, 2. H_2O/Na_2CO_3/1,3-dimethylimidazolidin-2-one. g) 1. BuLi, 2. R'Br/HMPT. h) Na, NH_3, liq. [7a]. i) D_2/*Lindlar* catalyst. k) $KO_2CN{=}NCO_2K/CH_3OD/CD_3CO_2D$ CD_3CO_2D [7b]. l) $KO_2CN{=}NCO_2K/CH_3OH/CH_3CO_2H$ [7b]. m) $TsOH/CH_3OH$.

---

[7]) It goes without saying that the operation of stereochemical effects involving C(3)/C(4) is also conceivable; however, the study of **5a–d** does not permit any further conclusion concerning the stereochemical details of dehydrogenation.

[8]) Actually, our four-sector tandem mass spectrometer consists of two double-focussing units: MS-I is the original *ZAB-2F* part and MS-II is an *AMD 604* mass spectrometer. For a detailed description, see [6].

Results and Discussion. – In the *Table*, the data are given for the unimolecular loss of molecular hydrogen from the Fe^+ complexes of **5** and its isotopomers **5a–d**. To account for the kinetic isotope effect, the data are normalized to the intensity of the non-decomposing precursor-ion complexes **5**-Fe^+–**5d**-Fe^+, respectively. Additional unimolecular dissociations of **5**-Fe^+, which are not further discussed in the present paper, are due to the eliminations of H_2O (27% relative to the loss of H_2 (100%)), C_2H_4 (4%), C_3H_6 (1%), and C_3H_6/H_2O (2%).

Table. *Unimolecular Dehydrogenation of Fe^+ Complexes of Octane-1,8-diol* (**5**) *and Its Isotopomers* **5a–d**[a])

Precursor	H_2	HD	D_2	Σ $H_{2-x}D_x$
5	1.90			1.90
5a	1.53	0.22		1.75
5b	< 0.01	0.26	0.43	0.69
5c[b])	1.04	0.23	0.18	1.45
5d	0.46	0.72	0.06	1.24

[a]) To account for kinetic isotope effects, the signal intensities for losses of H_2, HD, and D_2 are divided by the intensities of the respective precursor signals.

[b]) **5c** corresponds to the D,L-form.

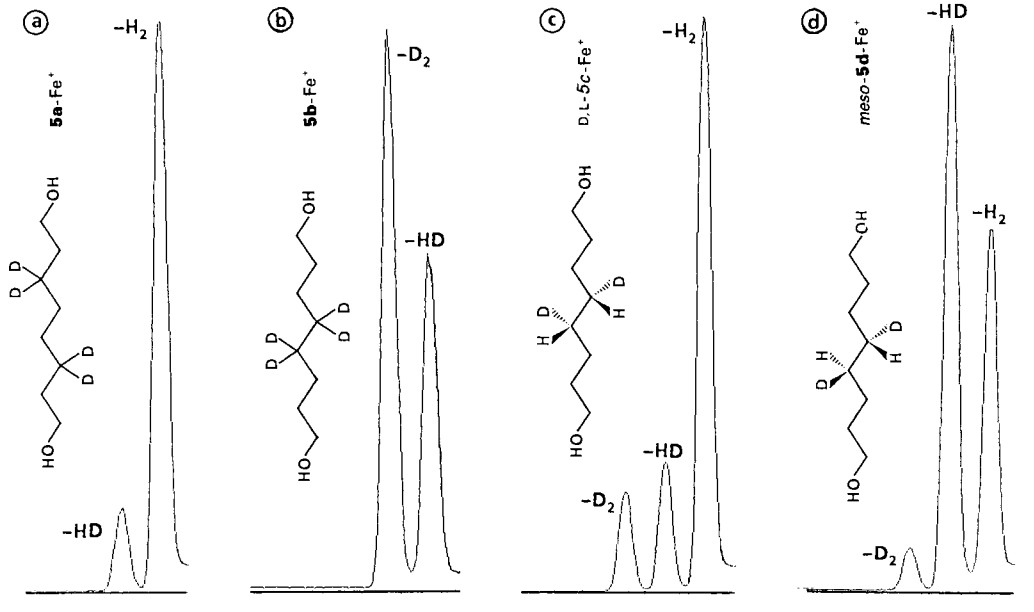


Figure. *Metastable-ion (MI) mass spectra of the Fe^+ complexes of octane-1,8-diol isotopomers* **5a–d**

In the *Figure*, the part of the MI spectra, relevant to the dehydrogenation, is given. This *Figure* already allows to make the following comments: *i*) The comparison of the spectra ⓐ and ⓑ demonstrates that most of the molecular hydrogen originates from the segment C(4)/C(5) with minor contributions from positions C(3)/C(4) or C(5)/C(6). Due to the symmetry of the molecule, the latter positions are equivalent. The absence of

signals for loss of H_2 from **5b**-Fe^+ (*Fig.*, ⓑ) rules out contributions of other sites of the alkyl chain. Further, this absence also suggests that in the reaction scheme, oxidative addition of the metal ion to a C–H(D) bond → β-H (D) transfer → reductive elimination of molecular hydrogen, reversible steps are not likely to play a role. Similarly, mechanistic concepts based on 1,1-eliminations can be ruled out. Rather, the reaction can be described in terms of an irreversible, 1,2-elimination of molecular hydrogen.

ii) The MI mass spectra ⓒ and ⓓ indicate that kinetic isotope effects are operative; this also follows from the data of **5a–d** given in the last column of the *Table*.

iii) The distributions of H_2, HD, and D_2 in the MI mass spectra of the Fe^+ complexes of the D,L-form **5c** and the *meso*-stereoisomer **5d** are very distinct. These observations clearly demonstrate two points: *1*) The stereochemical feature of the isotopically labeled positions C(4)/C(5) is of crucial importance for the Fe^+-mediated dehydrogenation. This finding necessitates the intermediacy of relatively rigid intermediates, as for example chelates. *2*) In the course of this reaction, stereo-equilibration is highly unlikely to occur.

Next, we will use the data given in the *Table* for a more quantitative analysis of the points raised in the previous section as well as in the *Introduction*.

The overall kinetic isotope effect k_{H_2}/k_{HD} for dehydrogenation involving the C(3)/C(4) positions can be estimated from the data of **5** and **5a**. The contribution of this segment is, to a first approximation, given by the difference 1.90–1.53 = 0.37; this number, divided by the normalized intensity of the actually observed loss of HD from **5a**-Fe^+ (0.22) provides the kinetic isotope effect $k_{H_2}/k_{HD} = 1.68$ associated with dehydrogenation of the C(3)/C(4) segment.

This isotope effect together with elementary statistical considerations permits to correct the MI spectra of **5c** and **5d** for the contribution of H_2 and HD from the C(3)/C(4) positions. If this is properly done[9]), one obtains 'corrected' data for the losses of H_2, HD, and D_2. This data reflect only the contribution from the C(4)/C(5) positions of octane-1,8-diol and are pertinent for the analysis according to *Scheme 2*. The discussion of the 'side reaction' involving C(3)/C(4) will not further pursued **5c**: H_2 (0.86), HD (0.12), D_2 (0.18); **5d**: H_2 (0.28), HD (0.61), D_2 (0.06).

The kinetic isotope effect k_{H_2}/k_{D_2} for the reaction proceeding *via* the *trans*-fused intermediate **6** is obtained directly from **5c**, with $k_{H_2}/k_{D_2} = 0.86/0.18 = 4.77$; for the *cis*-fused intermediate **7** the corresponding figure is available from the data of **5d** (0.28/0.06) and amounts to $k_{H_2}/k_{D_2} = 4.66$. Obviously, in distinct contrast to the isotope distribution (to be discussed in the next section) the kinetic isotope effects associated with dehydrogenation of the C(4)/C(5) segment are to a first approximation not very sensitive to the stereochemical details of the reaction centre.

A striking difference is, however, noted for the relative contribution of **6** and **7** to the overall C(4)/C(5) dehydrogenation of the two stereoisomers **5c** and **5d**. For the D,L-form **5c**, we estimate from the ratio $(H_2 + D_2)/HD$ that 89% of the dehydrogenation proceeds *via* **6** and only 11% *via* **7**, thus confirming our conjecture that the former intermediate is more easily accessible than the latter. For the *meso*-form **5d**, however, the numbers are quite different with only 65% involving **6** and 35% proceeding *via* **7** (estimated from the ratio $HD/(H_2 + D_2)$). We suppose that this result is, as predicted in the *Introduction*, an immediate manifestation of an isotopically sensitive branching: for the *meso*-form **5d**,

[9]) For a numerical analysis as well as a discussion of many conceivable models, not further outlined here, see [8].

any conceivable *trans*-fused intermediate will invariably lead to the generation of HD. Thus, due to the isotope effect the system 'bypasses' **6** and explores to a larger extent the alternative route proceeding *via* the *cis*-fused isomer **7**. The opposite situation holds true for the D,L-labeled isotopomer **5c**. Here, the *trans*-fused intermediate has the option to undergo either loss of H_2 and D_2 (favouring the former by a factor of 4.77; see above). Consequently, the need to an isotopically enforced switch to populate the intermediate **7** is much less pronounced.

In conclusion, the analysis of the data lends full support to our conjecture that 'metabolic switching' well-known to be operative in enzymatic hydrogen abstractions, has its counterpart in the Fe^+-mediated activation of C–H bonds of aliphatic alcohols in the gas phase. In the present system, the isotope-induced branching is reflected in different amounts of the *trans- vs. cis*-fused bicyclic intermediates as a function of the configuration of the isotopically labeled methylene groups C(4)/C(5) of **5c** and **5d**.

We would not be too surprised if, in the future, similar findings were reported for other systems thus underlining the point that isotopically sensitive branching is, indeed, of quite general importance [1] [2]. Actually, preliminary studies of the Fe^+ complexes of several α,ω-dinitriles [8] [9] tend to support the results described in the present paper for the gas-phase chemistry of octane-1,8-diol Fe^+ complexes[10]).

The generous support of our work by the following institutions is appreciated: *Deutsche Forschungsgemeinschaft, Volkswagen-Stiftung, Fonds der Chemischen Industrie, Graduiertenkolleg Chemie*, and *Gesellschaft von Freunden der Technischen Universität Berlin.*

REFERENCES

[1] a) G.T. Miwa, J.S. Walsh, A.Y.H. Lu, *J. Biol. Chem.* **1984,** *259,* 3000; b) N. Harada, G.T. Miwa, J.S. Walsh, A.Y.H. Lu, *ibid.* **1984,** *259,* 3005; c) K.S. Eble, J.H. Dawson, *ibid.* **1984,** *259,* 14389; d) R.E. White, J.P. Miller, L.V. Favreau, A. Bhattacharyya, *J. Am. Chem. Soc.* **1986,** *108,* 6024; e) J.P. Jones, K.R. Korzekwa, A.E. Rettie, W.F. Trager, *ibid.* **1986,** *108,* 7074, and further ref. cit. therein; f) F.P. Guengerich, L.A. Peterson, R.H. Böcker, *J. Biol. Chem.* **1988,** *263,* 8176.

[2] a) L. Melander, Ed., 'Reaction Rates of Isotopic Molecules', Wiley, New York, 1980, p.293; b) D.B. Northrop, *Biochemistry* **1975,** *14,* 2644.

[3] a) J. Müller, *Angew. Chem. Int. Ed.* **1972,** *11,* 653; b) J. Müller, 'The Organic Chemistry of Iron', Academic Press, New York, 1978, Vol. 1, p. 145; c) J.L. Beauchamp, A.E. Stevens, R.R. Corderman, *Pure Appl. Chem.* **1979,** *51,* 967; d) I.K. Gregor, M. Guilhaus, *Mass Spectrom. Rev.* **1984,** *3,* 39; e) B.S. Freiser, *Talanta* **1985,** *32,* 697; f) J. Allison, *Progr. Inorg. Chem.* **1986,** *34,* 627; g) P.B. Armentrout, 'Structure/Reactivity and Thermochemistry of Ions', Eds. P. Ausloos and S.G. Lias, D. Reidel, Dordrecht, 1987, No. 193, p.97; h) D.P. Ridge, *ibid.* p.165; i) R.R. Squires, *Chem. Rev.* **1987,** *87,* 623; j) J.L. Beauchamp, 'High Energy Processes in Organometallic Processes', Ed. K.E. Suslick, ACS Symposium Ser. 333, Washington, DC,1987; k) J. Allison, A. Mavridis, J.F. Harrison, *Polyhedron* **1988,** *7,* 1559; l) S.W. Buckner, B.S. Freiser, *Polyhedron* **1988,** *7,* 1583; m) G. Czekay, T. Drewello, K. Eller, C.B. Lebrilla, T. Prüsse, C. Schulze, N. Steinrück, D. Sülzle, T. Weiske, H. Schwarz, 'Organometallics in Organic Synthesis 2', Eds. H. Werner and G. Erker, Springer Verlag, Heidelberg, 1989, p.203; n) 'Gas Phase Inorganic Chemistry', Ed. D.H. Russell, Plenum Press, New York, 1989; o) P.B. Armentrout, R. Georgiadis, *Polyhedron* **1988,** *7,* 1573; p) H. Schwarz, *Acc. Chem. Res.* **1989,** *22,* 282; q) K. Eller, H. Schwarz, *Chimia* **1989,** *43,* 371; r) P.B. Armentrout, J.L. Beauchamp, *Acc. Chem. Res.* **1989,** *22,* 315; s) B.S. Freiser, *Chemtracts-Anal. Phys. Chem.* **1989,** *1,* 65; t) K. Eller, S. Karrass, H. Schwarz, *Ber. Bunsenges. Phys. Chem.* **1990,** *94,* 1201; u) K. Eller, H. Schwarz, *Chem. Rev.*, in press.

[10]) Recently, it was demonstrated that D isotopic perturbation also determines the strereochemical outcome of transition-metal-complex-mediated chain propagation in solution [10].

[4] a) T. Prüsse, H. Schwarz, *Organometallics* **1989,** *8,* 2856; b) T. Prüsse, J. Allison, H. Schwarz, *Int. J. Mass Spectrom. Ion Processes*, in press.

[5] a) A. Tsarbopoulos, J. Allison, *Organometallics* **1984,** *3,* 86; b) T. Prüsse, T. Drewello, C.B. Lebrilla, H. Schwarz, *J. Am. Chem. Soc.* **1989,** *111,* 2857; c) N. Steinrück, O. Dange, D. Stöckigt, H. Schwarz, *Angew. Chem. Int. Ed.* **1990,** *29,* 402; d) O. Dange, N. Steinrück, D. Stöckigt, H. Schwarz, *Chem. Ber.* **1990,** *123,* 1583; e) A. Hässelbarth, T. Prüsse, H. Schwarz, *ibid.* **1990,** *123,* 209; f) T. Prüsse, G. Czekay, H. Schwarz, *ibid.* **1991,** *124,* 141; g) T. Prüsse, H. Schwarz, in preparation.

[6] a) R. Srinivas, D. Sülzle, W. Koch, C.H. DePuy, H. Schwarz, *J. Am. Chem. Soc.*, in press; b) R. Srinivas, D. Sülzle, T. Weiske, H. Schwarz, *Int. J. Mass Spectrom. Ion Processes*, in press.

[7] a) M. Schwarz, R.M. Waters, *Synthesis* **1972,** 567; b) W.C. Baird, Jr., B. Franzus, J.H. Surridge, *J. Am. Chem. Soc.* **1967,** *89,* 410.

[8] T. Prüsse, Ph.D. Thesis, Technische Universität Berlin, in preparation.

[9] T. Prüsse, H. Schwarz, unpublished results.

[10] a) H. Krauledat, H.H. Brintzinger, *Angew. Chem.* **1990,** *102,* 1459; b) W.E. Piers, J.E. Bercaw, *J. Am. Chem. Soc.* **1990,** *112,* 9406.