83. *exo/endo*-Selectivity in the Reaction of 'Bare' FeO⁺ with Bicyclo[2.2.1]heptane (Norbornane)

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'Bare' FeO⁺ reacts in the gas phase with norbornane with collision efficiency, and the most prominent cationic products correspond to [FeC₅H₆]⁺ (32%), [FeC₇H₈]⁺ (19%), [FeC₃H₆O]⁺ (19%), and [FeC₆H₆]⁺ (14%), which are structurally characterized by ligand exchange as well as collision-induced dissociation experiments. Circumstantial evidence is provided which indicates that the complexes [FeC₅H₆]⁺, [FeC₇H₈]⁺, and [FeC₆H₆]⁺ originate from an Fe(norbornene)⁺ intermediate which itself is formed by elimination of H₂O from the [FeO(norbornane)]⁺ encounter complex. Although the reactions are preceded and/or accompanied by partial H/D exchange, the isotope distribution in the product ions clearly points to a preferential *endo*-attack of bare FeO⁺, with an *endo/exo*-ratio of *ca.* 10.3 and kinetic isotope effects k_H/k_D for the *endo*-abstraction of 2.4 and of 7.7 for approaching an *exo*-C–H bond. The preferred *endo*-approach of bicyclo[2.2.1]heptane by 'bare' FeO⁺ is in distinct contrast to the P-450-mediated or the iron(III)porphyrin-catalyzed hydroxylation of this substrate which favor reactions at the *exo*-face.

Selective O-atom transfer from molecular oxygen to unactivated organic substrates such as saturated and/or unsaturated hydrocarbons is of fundamental importance in organic chemistry, biochemistry, and chemical industry [1]. In biological systems, oxidative transformations are mediated by the iron-centered cytochrome P-450 [2] and related enzyme systems. P-450 is known to mediate hydroxylation of, for example, fatty acids, arenes, as well as the oxidative metabolization of xenobiotic compounds. These enzymes have received considerable interest, since there exist no adequate 'synthetic analogs' in preparative organic chemistry. In condensed-phase studies, addressing the question of the stereochemistry of the hydroxylation of norbornane (**1**) by reconstituted P-450 [3] as well as by highly halogenated Feᴵᴵᴵ-porphyrins [4], the experimental findings point to the absence of carbocationic skeletal rearrangements, and the loss of stereochemistry together with large primary kinetic isotope effects (KIEs) provide strong evidence for a radical cage rebound mechanism (see *Scheme 1*) [2] [3] [5]. Abstraction of both *exo*- and *endo*-H-atoms from C(2) *via* a free-radical process was also observed, and the investigation of all-*exo*-(2,3,5,6-²H₄)norbornane (**4**) demonstrated a substantial loss of stereospecificity. However, the P-450 and the Feᴵᴵᴵ-porphyrins have in common a large *exo/endo*-preference [4].

*Scheme 1*

1　　O₂ / P-450　　→　　[HO—P-450] cage　　- P-450 →　　**2** OH　　+　　**3** OH
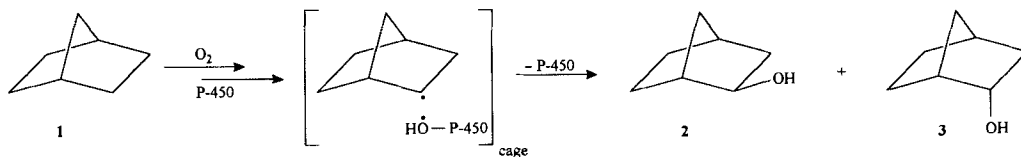
Gas-phase studies are particularly suited for the elucidation of mechanistic aspects, since they are not hampered by disturbing factors such as aggregation phenomena, solvent or 'gegenion' effects prevailing in the liquid phase. Recently, we have investigated C—H bond activation of benzene [6], toluene [7], ethane [8], and methane [9] by 'bare' FeO^+ in the gas phase[1]). An intriguing aspect of the C—H bond activation mediated by metal oxides concerns the face selectivity of the reaction, and bicyclo[2.2.1]heptane (1; norbornane) is an ideal substrate due to the rigidity of the molecule. Here, we report the reactions of FeO^+ with 1, and it will be demonstrated that – in distinct contrast to the P-450 and the Fe^{III}-porphyrin-mediated C—H bond activation – attack of an *endo-*C—H bond constitutes the intrinsically favored reaction mode.

Experimental. – The experiments were performed using a *Spectrospin CMS-47X* mass spectrometer, equipped with an external ion source. The apparatus and its operation have been described in detail in [11]. Briefly, the Fe^+ cations are formed *via* laser desorption/ionization [12] by focusing the beam of a Nd:YAG laser (*Spectron* systems, fundamental frequency $\lambda = 1064$ nm) onto a stainless steel target which was affixed in the external ion source [13]. The ions are extracted from the source and transferred into the analyzer cell by a system of electrostatic potentials and lenses. The ion source, the transfer system, and the ICR cell are differentially pumped by three turbomolecular pumps (*Balzers TP 330* for the source and the cell and *Balzers TPU 50* in the middle of the transfer system). After deceleration, the Fe^+ ions were trapped in the field of a superconducting magnet (*Oxford Instruments*), which has a maximum field strength of 7.05 Tesla. The isolation of the metal's most abundant isotope ($^{56}Fe^+$) and all

Scheme 2
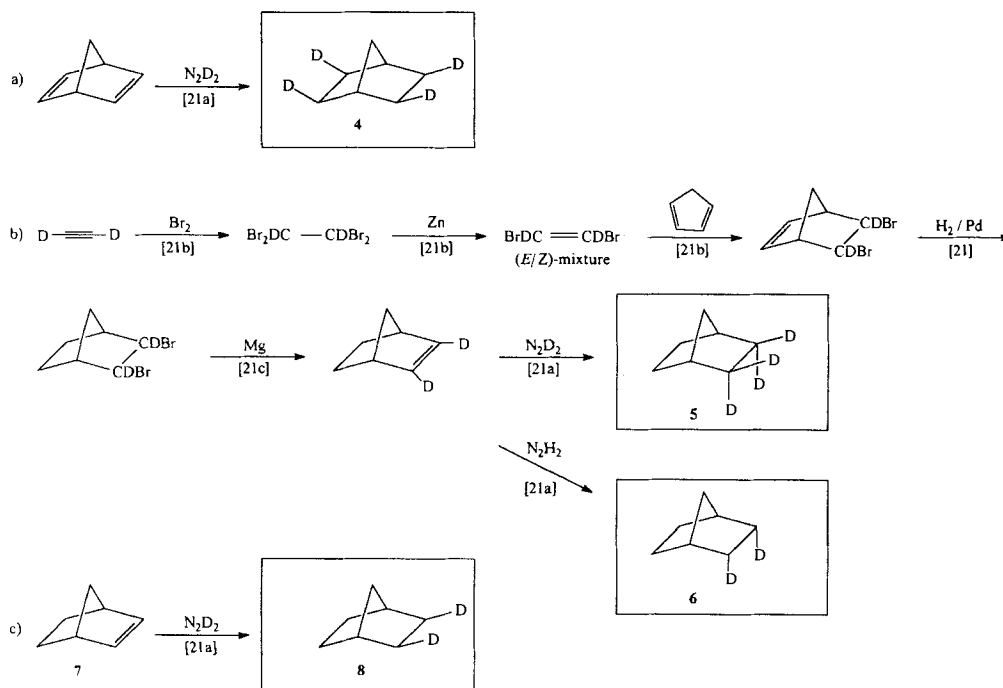
[1]) For earlier work on reactions of FeO^+ with various hydrocarbons, see [10a]. For a comprehensive review on the gas-phase reactions of bare transition-metal-oxide cations, see [10b].

subsequent isolations were performed by using FERETS [14], a computer-controlled ion-ejection protocol which combines frequency sweeps and single frequency pulses to optimize the ion isolation. FeO^+ was produced by reacting Fe^+ with pulsed-in N_2O [15]. For collisional cooling of excited states, possibly formed by the generation process, Ar was present as a buffer gas, which was also used as a collision gas in collision induced dissociation experiments (CID) [16] at a static pressure of *ca.* 10^{-7} mbar. High-resolution and double-resonance experiments were performed as described in [11a] [17]. The pressure of the org. substrates were measured with an (uncalibrated) ionization gauge (*Balzers IMG 070*) and corrected for the reactant gas efficiency [18]. For ligand-displacement experiments [19], the reagent gases were either introduced through pulses [20] or leak valves, depending on the vapor pressure of the respective compounds. All functions of the instrument were controlled by a *Bruker Aspect 3000* minicomputer. The labeled compounds were synthesized and purified according to well established procedures [21], and fully characterized by NMR and MS. A schematic description of the syntheses of the labeled norbornanes **4, 5, 6,** and **8** is given in *Scheme 2.*

Results and Discussion. – The products of the reaction of FeO^+ with norbornane (**1**) are summarized in *Scheme 3.* A comparison of the experimental rate constant of the overall reaction ($k_r = 1.4 \cdot 10^{-9}$ cm^3 molecule^{-1} s^{-1}) with the rate constant calculated according to the *Langevin* theory [22] ($k_L = 1.3 \cdot 10^{-9}$ cm^3 molecule^{-1} s^{-1}) shows that the reaction occurs with collision frequency. The somewhat greater value of the experimental rate constant is most probably due to the uncertainties associated with the measurement of the norbornane pressure [18]. The major cationic products of the reaction have the elemental compositions $[Fe(C_5H_6)]^+$ (32%), $[Fe(C_7H_8)]^+$ (19%), $[Fe(C_3H_6O)]^+$ (19%), and $[Fe(C_6H_6)]^+$ (14%), and various experiments were conducted aimed at structurally characterizing these Fe^+ complexes.

Scheme 3
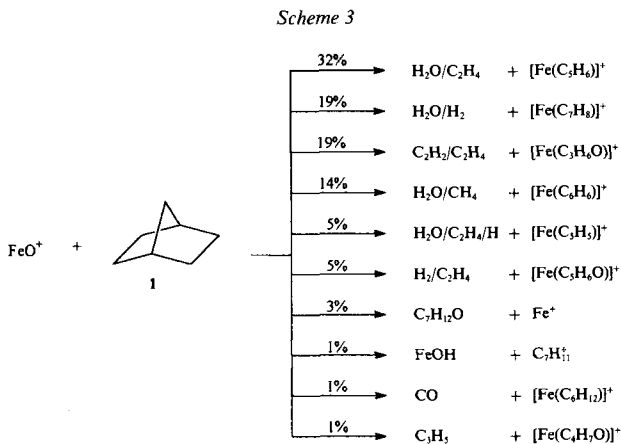
Based on the well-known ion/molecule reactions [23] with benzene resulting in the specific formation of $[Fe(C_{11}H_{11})]^+$ as well as the observation of six H/D exchanges in the presence of C_2D_4 [24], we assign for $[Fe(C_5H_6)]^+$ the structure of an [Fe(cyclopentadiene)]$^+$ complex. Similarly, $[Fe(C_6H_6)]^+$ is suggested to correspond to an [Fe(benzene)]$^+$ complex, as the ion undergoes thermoneutral ligand exchange with C_6D_6 or looses the entire C_6H_6 ligand upon collisional activation with Ar. For $[Fe(C_7H_8)]^+$, the most plausible structure would correspond to an [Fe(toluene)]$^+$ complex as supported by ligand exchange with C_6D_6 or CID experiments. For the $[Fe(C_3H_6O)]^+$ product, whose genesis and experimental

exploration of the potential energy surface of $[FeC_3H_6O]^+$ isomers form the subject of an independent study [25], ligand exchange and CID experiments suggest an $[Fe(C_3H_5)(OH)]^+$ complex which is formed via combined losses of C_2H_2/C_2H_4 from FeO$^+$-1.

With regard to the three major Fe$^+$-hydrocarbon product ions mentioned above, thermochemical considerations [26] and labeling experiments (to be discussed further below) indicate that all three ionic products are formed via an Fe(norbornene)$^+$ intermediate which itself is the outcome of H_2O elimination from the encounter complex FeO$^+$-1. This assumption is underlined by looking at the product distribution obtained when 'bare' Fe$^+$ is reacted with norbornene (7). From the data in Table 1, it follows that the encounter complex Fe$^+$-7 does indeed dissociate to $[Fe(C_5H_6)]^+$, $[Fe(C_6H_6)]^+$, and $[Fe(C_7H_8)]^+$ via losses of C_2H_4, CH_4, and H_2, respectively. From the data reported in Table 1, it is also evident that in the reaction of norbornane (1) with FeO$^+$ the oxygenated products, i.e., the Fe$^+$ complexes of exo- and endo-2-norbornols (Fe$^+$-2 and Fe$^+$-3), are not likely to play a decisive role. This is clearly demonstrated by a comparison of the propensity to form $C_7H_{11}^+$ (via loss of FeOH): while this signal forms the base peak in the ICR spectra of Fe$^+$-2 and Fe$^+$-3, with 52 and 45% product ion intensities, respectively; in the reaction of FeO$^+$ with 1 this signal is very weak indeed (1%).

Table 1. *Product Ions Formed in the Reaction of Fe$^+$ with Norbornane-Related Systems*

Product ion[a]	Fe$^+$-7	Fe$^+$-2	Fe$^+$-3
$[Fe(C_5H_6)]^+$	83	18	23
$[Fe(C_7H_8)]^+$	6	7	10
$[Fe(C_3H_6O)]^+$	–	7	3
$[Fe(C_6H_6)]^+$	11	8	10
$[Fe(C_5H_5)]^+$	–	–	1
$[Fe(C_5H_6O)]^+$	–	5	6
$C_7H_{11}^+$	–	52	45
$[Fe(OH)]^+$	–	1	–
$[Fe(C_3H_4O)]^+$	–	1	–
$[Fe(C_5H_8O)]^+$	–	1	2

[a]) The intensities are given in Σ(products) = 100%.

Although, in a strict sense, not absolutely conclusive, the study of the reactions of FeO$^+$ with the isotopomeric norbornanes 4, 5, 6, and 8 is quite revealing with regard to the central problem of exo/endo-face selectivity mentioned above. An inspection of the labeling data (*Table 2*) for the three processes giving rise to [Fe(cyclopentadiene)]$^+$, [Fe(toluene)]$^+$, and [Fe(benzene)]$^+$ via the Fe(norbornene)$^+$ intermediate Fe$^+$-7 points to three important aspects:

i) The reactions are not 'clean' in the sense that H/D exchange processes proceding and/or accompanying the combined losses of H_2O and hydrocarbons (or molecular hydrogen) can be ruled out. In fact, the presence of odd-numbers of D-atoms clearly points to the operation of these processes.

ii) Complete positional loss of H/D-atoms, however, can be ruled out. If this were the case, the isotope distribution should be the same (or at least similar to each other) in the

Table 2. *Isotope Distributions of Product Ions Formed in the Reaction of FeO$^+$ with Labeled Norbornanes*[a])

Product ions	FeO$^+$-4	FeO$^+$-5	FeO$^+$-6	FeO$^+$-8
$[Fe(C_5H_6)]^+$	3	47	55	49
$[Fe(C_5H_5D)]^+$	20	7	34	18
$[Fe(C_5H_4D_2)]^+$	72	17	11	33
$[Fe(C_5H_3D_3)]^+$	5	27	–	–
$[Fe(C_5H_2D_4)]^+$	< 1	2	–	–
$[Fe(C_7H_8)]^+$	–	–	21	9
$[Fe(C_7H_7D)]^+$	10	–	45	33
$[Fe(C_7H_6D_2)]^+$	22	45	34	58
$[Fe(C_7H_5D_3)]^+$	36	43	–	–
$[Fe(C_7H_4D_4)]^+$	32	12	–	–
$[Fe(C_6H_6)]^+$	16	–	17	38
$[Fe(C_6H_5D)]^+$	16	18	37	40
$[Fe(C_6H_4D_2)]^+$	36	49	46	22
$[Fe(C_6H_3D_3)]^+$	25	11	–	–
$[Fe(C_6H_2D_4)]^+$	7	22	–	–

[a])　The intensities are given in Σ(products) = 100% for each reaction channel. The relative intensities of the isotopomeric ions $[Fe(C_5H_{5-x}D_x)]^+$ and $[Fe(C_5H_{6-x}D_x)]^+$ were determined under high-resolution conditions in order to resolve isobaric ions, *e.g.* $[Fe(C_5H_4D)]^+$ and $[Fe(C_5H_6)]^+$.

spectra of the pairs FeO$^+$-4/FeO$^+$-5, and FeO$^+$-6/FeO$^+$-8, respectively. This is not observed.

iii) A closer inspection of the data in *Table 2* reveals some interesting pattern which, in spite of the partial H/D scrambling, will guide us in our attempt to provide an at least semi-quantitative analysis. For example, in the formation of [Fe(cyclopentadiene)]$^+$ *via* a combined loss of H_2O/C_2H_4 – presumably *via* the Fe(norbornene)$^+$ complex followed by a *retro-Diels-Alder*-reaction[2]) – we note the following: in the spectrum of the all-*exo*-(2,3,5,6-$^2H_4$)norbornane (**4**), the major product ion (72%) corresponds to the formation of $[Fe(C_5H_4D_2)]^+$, while the completely unlabeled product $[Fe(C_5H_6)]^+$ is generated with much smaller abundance (3%). Similarly, while in the spectrum of FeO$^+$-**5** the $[Fe(C_5H_6)]^+$ signal dominates (47%), there is also a strong signal (17%) for the D_2-containing product; an analogous D_0/D_2 pattern is observed when FeO$^+$ is reacted with *exo,exo*-(2,3-$^2H_2$)norbornane (**8**; *i.e.*, 49% *vs.* 33%). In fact, the isotope distribution for the formation of $[Fe(C_5H_{6-x}D_x)]^+$ ($x = 0, 2$) from the isotopologues **4**, **5**, and **8** can be used to derive, in a first approximation, both the relative probability for an *endo-* *vs.* *exo*-attack en route to the formation of the *endo/exo*-[Fe(norbornene)]$^+$ complexes Fe$^+$-**7**. To this end, we assume that H_2O loss from the initial insertion products follows a *syn-*1,2-elimination (*Scheme 4*). Further, we ignore any exchange and/or scrambling processes which, anyhow, might also take place prior to the expulsion of C_2H_4, CH_4, or H_2 from Fe$^+$-**7**. A simple algebraic system using the D_0/D_2 intensity ratios for **4**, **5**, and **8** provides us with the following results: *1*) Attack of an *endo*-C–H bond of norbornane is by a factor of 10.3 favored over a reaction commencing at the *exo*-surface. *2*) The kinetic isotope effects (k_H/k_D) are as follows: $KIE_{endo} = 2.4$ and $KIE_{exo} = 7.7$. To evaluate the

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[2])　For further examples of metal-ion-mediated *retro-Diels-Alder* reactions of similar systems, see [27].

Scheme 4
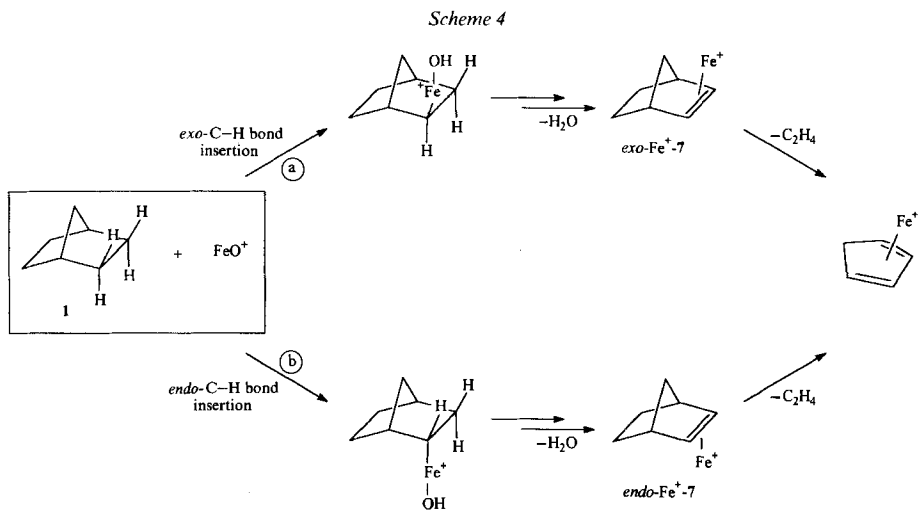
validity of this model and its remarkable result – which is, as far as the site selectivity is concerned, distinctly different from the P-450 and the Fe^{III}-porphyrin-mediated activation of norbornane [3] [4] – we have used these figures to predict the D_0/D_2 ratio in the formation of $[Fe(C_5H_{6-x}D_x)]^+$ ($x = 0, 2$) from **6**; the predicted value amounts to 5.5 which compares surprisingly well with the experimental result (5.0). In a qualitative sense, the data for the formations of $[Fe(C_6H_{6-x}D_x)]^+$ and $[Fe(C_7H_{8-x}D_x)]^+$ also indicate a preferential attack of the *endo*-face of norbornane by FeO^+.

Although we are not yet in a position to quantitatively describe all aspects of the reactions of 'bare' FeO^+ with norbornane, the results discussed demonstrate that, under strictly bimolecular gas-phase conditions at a molecular level, it is the *endo*-face of this bicyclic hydrocarbon which is intrinsically more reactive than the *exo*-side.

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