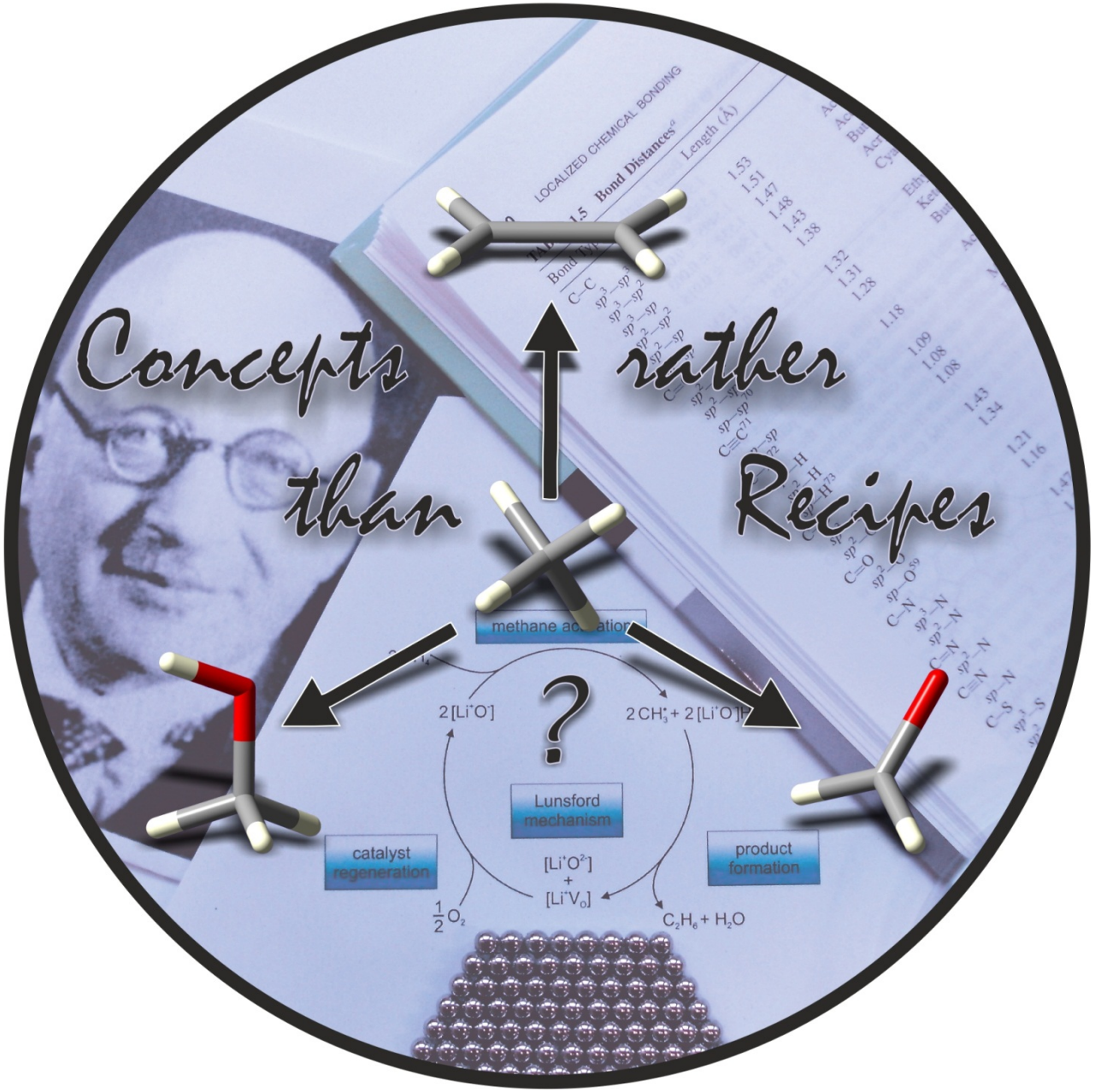
DU SCHWARZ
ICH WEISS
Zeichnung: Brösel

CHEMISTRY

with

METHANE

Helmut Schwarz, TU Berlin


Concepts rather than Recipes
LOCALIZED CHEMICAL BONDING
Bond Distances
Length (Å)
methane activation
2 [Li⁺O⁻]
2 CH₃• + 2 [Li⁺O⁻]H
?
Lunsford mechanism
[Li⁺O²⁻] + [Li⁺V_O]
½ O₂
C₂H₆ + H₂O
catalyst regeneration
product formation

Grand challenges to direct (selective, low-temperature) conversions of methane

$$CH_4 + 0.5\,O_2 \longrightarrow CH_3OH$$

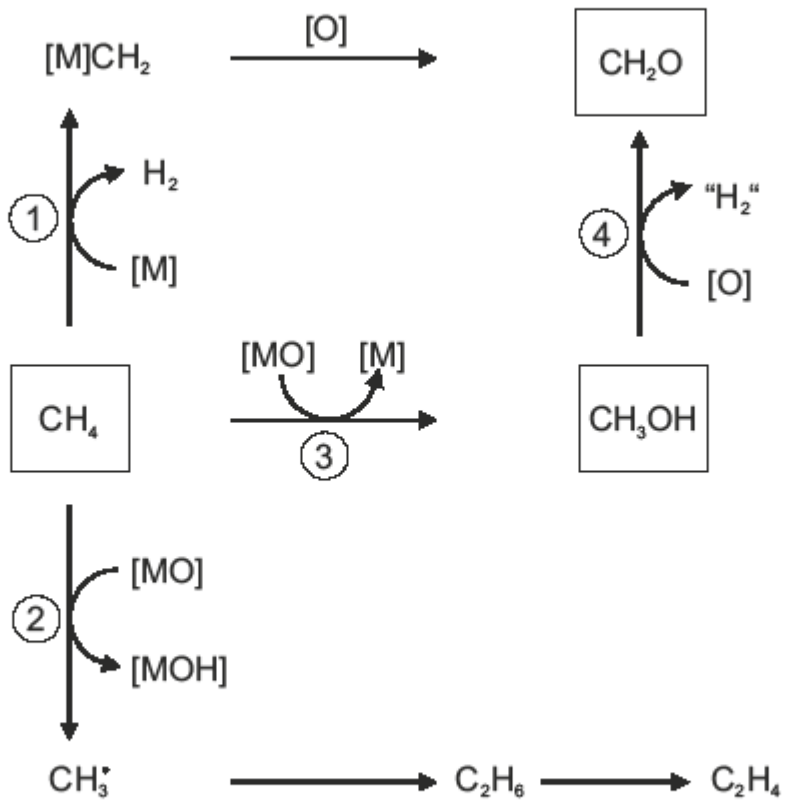
$$CH_4 + CO_2 \longrightarrow CH_3CO_2H$$

$$CH_4 + 3\,O_2 \longrightarrow H_2O_2 + CO_2$$

$$1.5\,CH_4 + 1.5\,O_2 + N_2 \longrightarrow 2\,NH_3 + 1.5\,CO_2$$

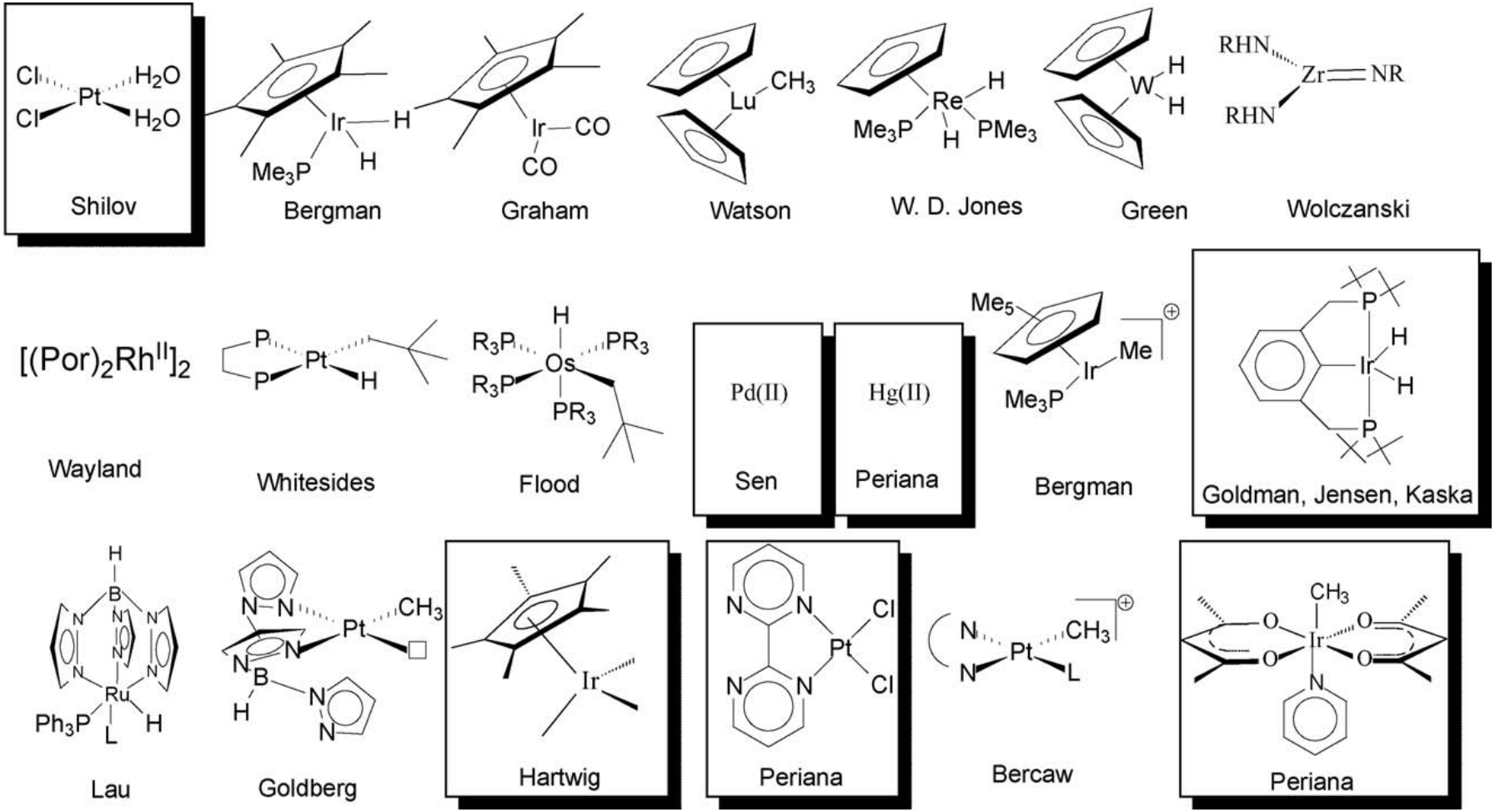
CH_4

BDE (C–H)	=	104.8 kcal/mol
$\Delta E_{LUMO-HOMO}$	≈	13 eV
IE (CH_4)	=	12.5 eV
EA (CH_4)	<	0 eV
PA (CH_4)	=	4.4 eV
pK_a (CH_4)	=	48



Scheme 1

Methane activation by metal complexes in solution



taken from: B. L. Conley et al. *J. Mol. Catal. A: Chemical* **2006**, *251*, 8

$$M^{+1-10} + A-B \longrightarrow M\begin{matrix} A \\ B \end{matrix} \rightrightarrows$$

Gas-phase experiments with 'bare' <u>metal</u> atoms

- No interference by counter ions, solvents, aggregates, ...

- - Intrinsic properties, e.g. electronic structure role, are accessible,

  Mechanistic features can be uncovered at a molecular level,

  ....

Experimental / Computational Methods

- FT-ICR
- SIFT

→ rate constants

- CIB

→ thermochemistry

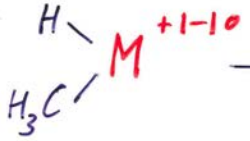
- DFT
- ab initio

→ electronic structure(s)

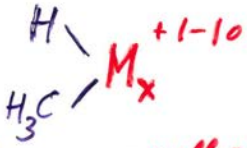
→ Potential energy landscapes

Intrinsic reactivity profiles

Activation of CH_4 by 'Bare' Transition Metal Ions

① $CH_4 + M^{+1-10} \not\longrightarrow$  $\longrightarrow$ products

Oxidative addition is endothermic for most ground-state transition metals M^{+1-10}

② $CH_4 + M_x^{+1-10} \not\longrightarrow$ 

↳ clusters (homo- as well as heteronuclear)

③ $CH_4 + M^{+1-10} \longrightarrow M^{+1-10}(CH_2) + H_2$

$\Delta H_r \leq 0$ only for M^{+1-10}

BDE: (kcal/mol)
Na^+-CH_2: 76
Pd^+-CH_2: 68

$BDE(M-CH_2) \geq 111$ kcal/mol

Stoichiometric Dehrydogenation of Methane by Third-row Transition-metal Cations

$$CH_4 + M^+ \xrightarrow[-H_2]{} M(CH_2)^+$$

M^+ ↕ Ta, W, Os, Ir, Pt

Irikura, Beauchamp

• Wesendrup

Armentrout

Bondybey; Maître

"[Relativistic effects] are therefore of no importance in the consideration of atomic and molecular structure and ordinary chemical reactions."

P. A. M. Dirac, 1929

$\sqrt{3}$

J. Chem. Phys.

Relativistic effects in the cationic platinum carbene $PtCH_2^+$

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Institut für Organische Chemie der Technischen Universität Berlin,

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Kenneth G. Dyall

Thermosciences Institute, NASA Ames Research Center, Mail Stop 230-3,

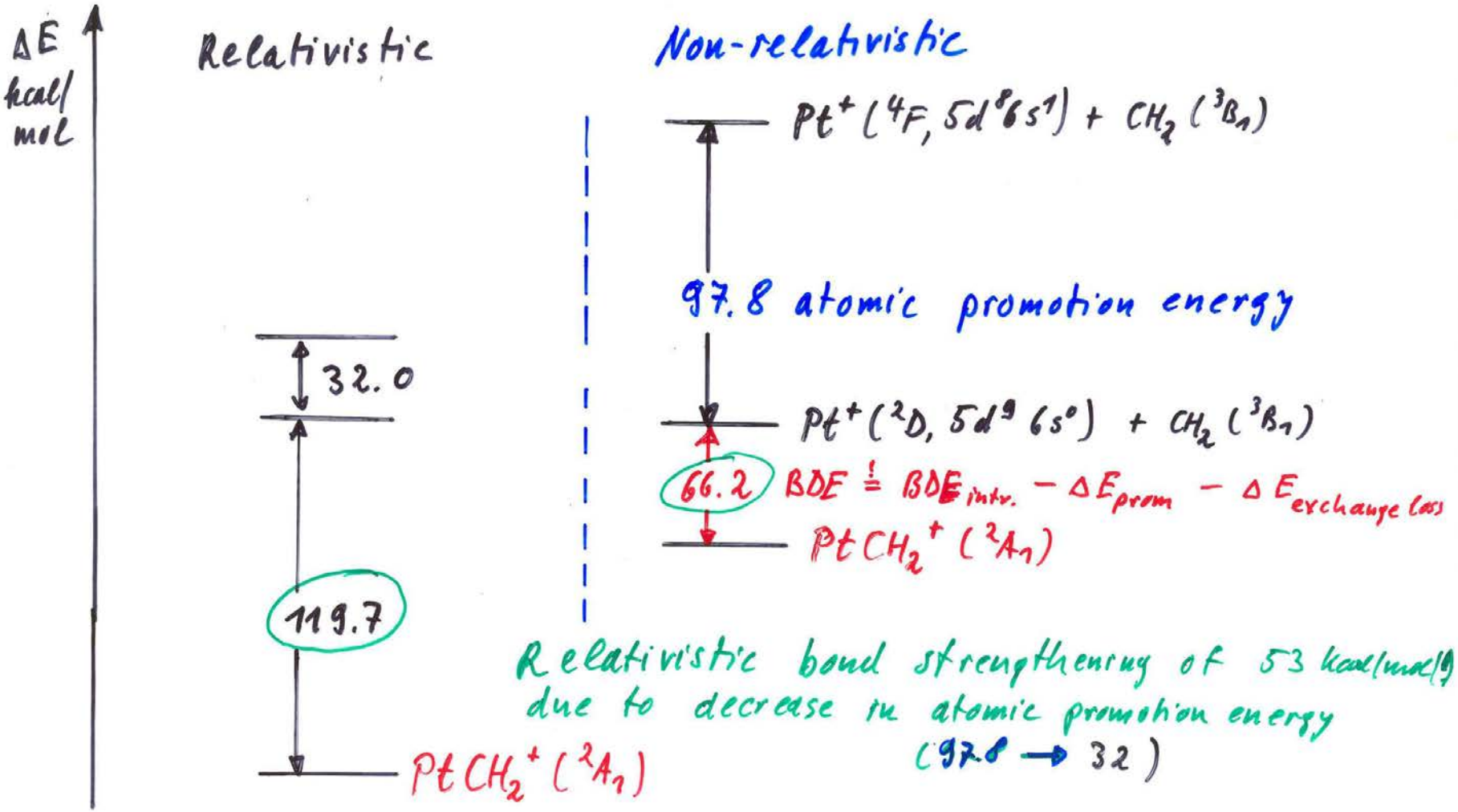
Moffet Field, CA 94035-1000, USA.

Abstract: Fully relativistic four-component Dirac-Fock Coulomb calculations in conjunction with a second-order perturbational estimate for the correlation energy have been performed in benchmark calculations on geometric and electronic structures as well as the binding energy of the cationic platinum carbene complex $PtCH_2^+$. The relativistic stabilization of this species amounts to as much as 50 kcal/mol and the combination of relativistic and correlation effects shorten the Pt-C bond length by nearly 1 bohr, changing the bond order from one to two. The relative importance of spin-free and spin-dependent relativistic effects on the geometry, the electronic structure and the binding energy is evaluated by comparison to the Douglas-Kroll method. Relativistic effective core potentials are shown to describe the spin-free effects reliably. The best theoretical estimate for the bond dissociation energy underestimates the experimental value by 13% due to truncation errors in the one- and n-particle space treatments. The mixed Hartree-Fock/density-functional method Becke3-Lee-Yang-Parr performs surprisingly well with respect to the structure and binding energy of the target molecule.

$BDE(Pt^+ - CH_2) = 11\cancel{2}$ - kcal/mol

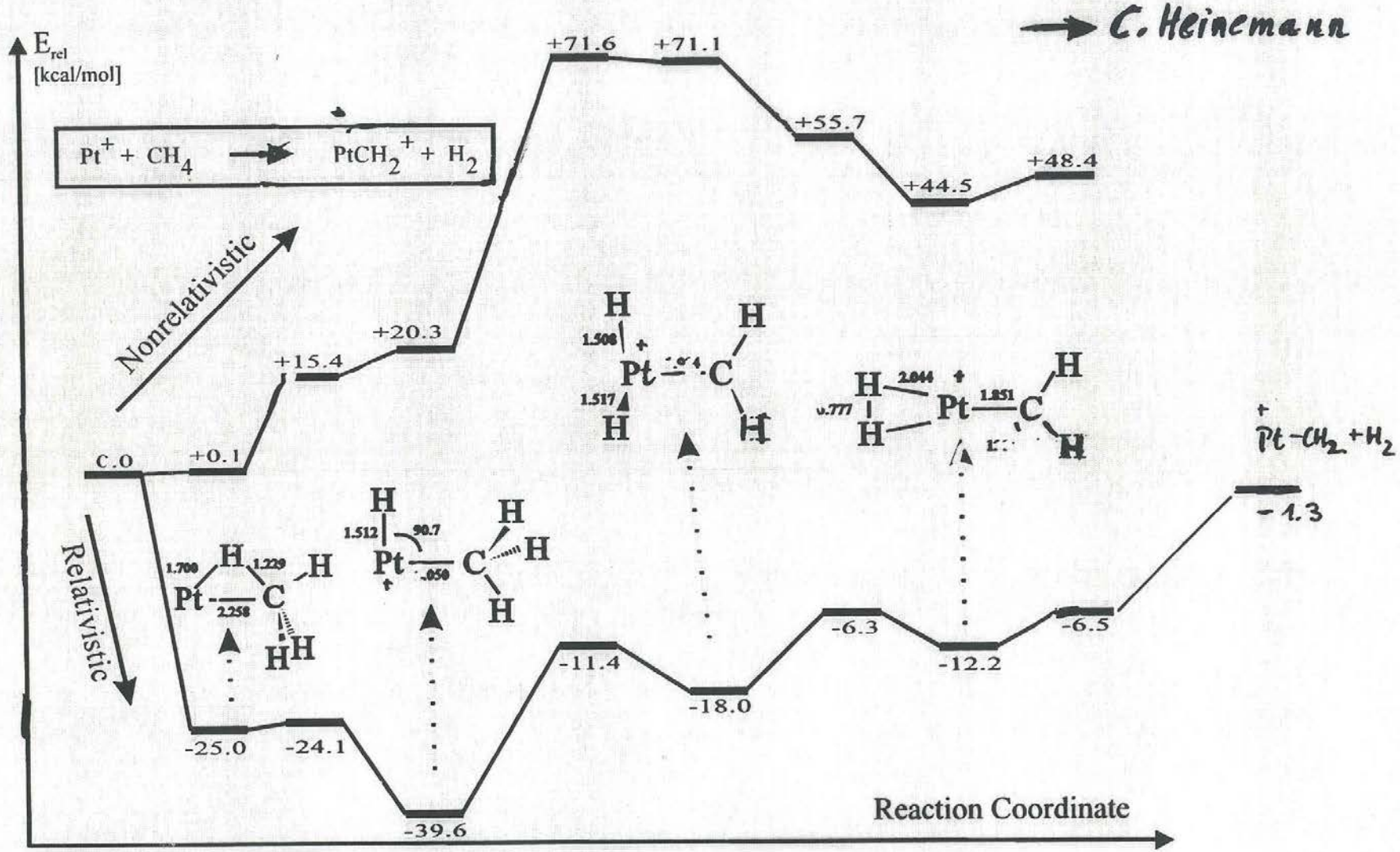
114

How Does Relativity Affect Bond Energies?



Relativistic bond strengthening of 53 kcal/mol(!) due to decrease in atomic promotion energy (97.8 → 32)

Relativity and the Potential Energy Surface for Methane Activation



Method: Nonrelativistic and scalar relativistic
(Baerends, Ziegler 1989) density functional calculations
Program system ADF

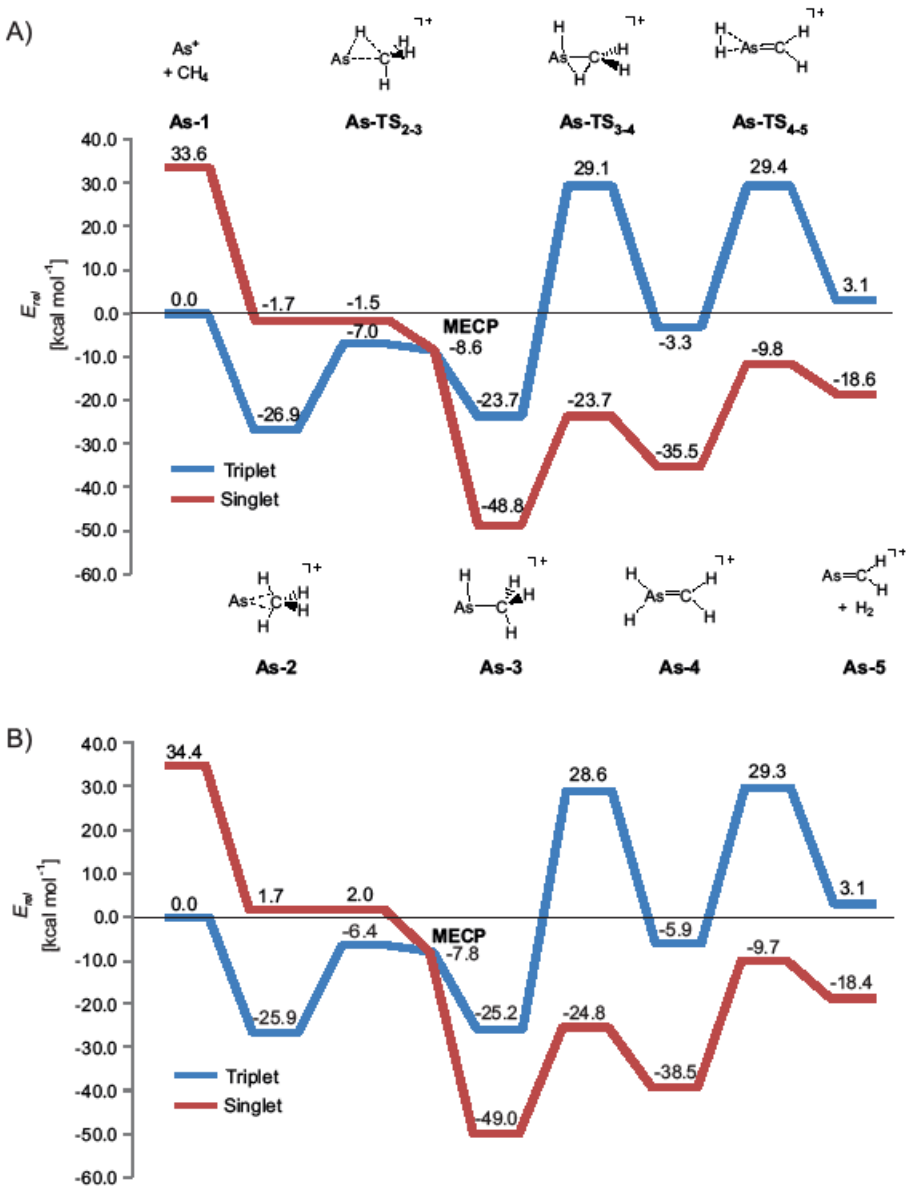

A)
As+ + CH4
As-1
As-TS2-3
As-TS3-4
As-TS4-5
33.6
29.1
29.4
0.0
-1.7
-1.5
-7.0
MECP
-8.6
-3.3
3.1
-9.8
-18.6
-26.9
-23.7
-23.7
-35.5
-48.8
Triplet
Singlet
As-2
As-3
As-4
As-5
+ H2
Erel [kcal mol-1]
B)
34.4
28.6
29.3
0.0
1.7
2.0
-6.4
MECP
-7.8
-5.9
3.1
-9.7
-18.4
-25.9
-25.2
-24.8
-38.5
-49.0
Triplet
Singlet
Erel [kcal mol-1]

Fig. 1

Role of ligands and of (formal) oxidation states for 3d metal-ion complexes

$$M(L_n)^+$$

in C-H bond activation of methane?

1) $M^+ + CH_4 \xrightarrow{\#} M^+(H)(CH_3)$

M = Fe, Co, Ni, V, Cr, Mn, Cu ...

Freiser, 1983
Beauchamp, 1984
Schwarz, 1986

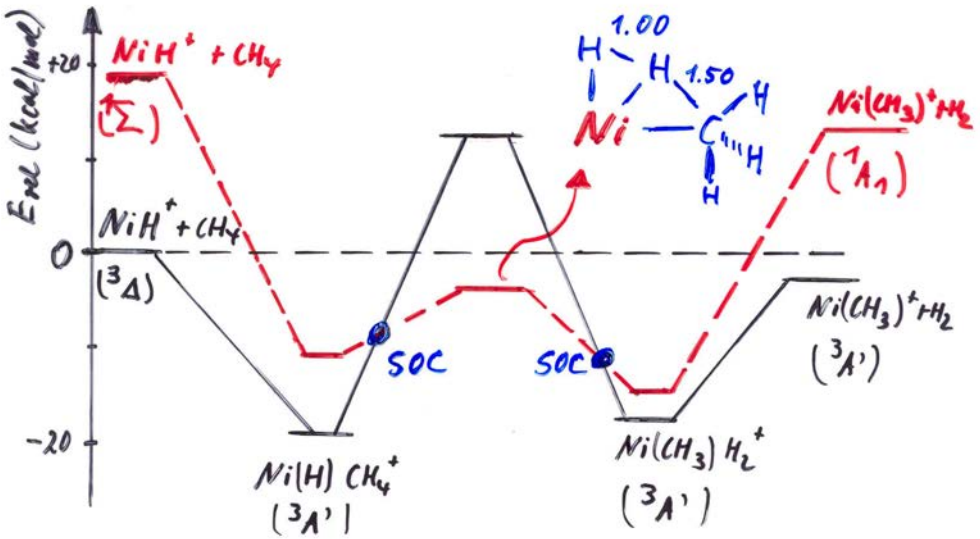
2) But:

$NiH^+ + CH_4 \xrightarrow{80\,K\,(!)} Ni(CH_3)^+ + H_2$

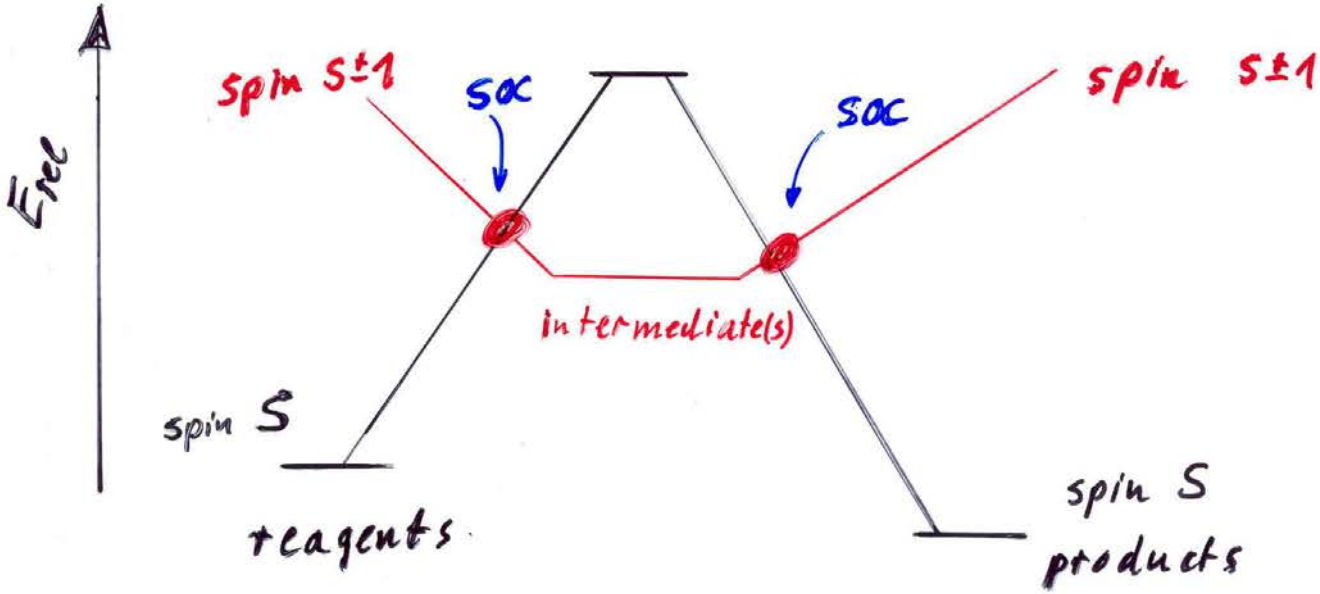
$NiD^+ + CH_4 \rightarrow$ 20% $NiH^+ + CH_3D$; 80% $Ni(CH_3)^+ + HD$

Freiser, 1983
Bowers, 2004
Schlangen/Schwarz, 2006

3)



Spin change as a reaction acceleration(!) phenomenon



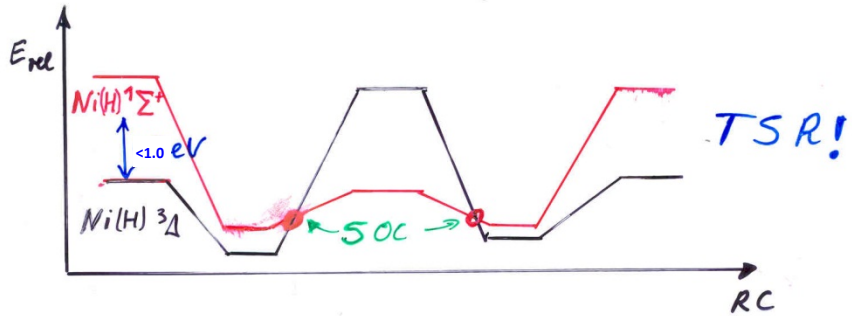
See, also: a) R. Poli, J. N. Harvey
Chem. Soc. Rev. 2003, 32, 1–8
b) R. Poli, J. Organomet. Chem. 2004, 689, 4291–

"The same and NOT the same ....."

R. Hoffmann, 1995

$$M(H)^+ + CH_4 \longrightarrow M(CH_3)^+ + H_2$$

•



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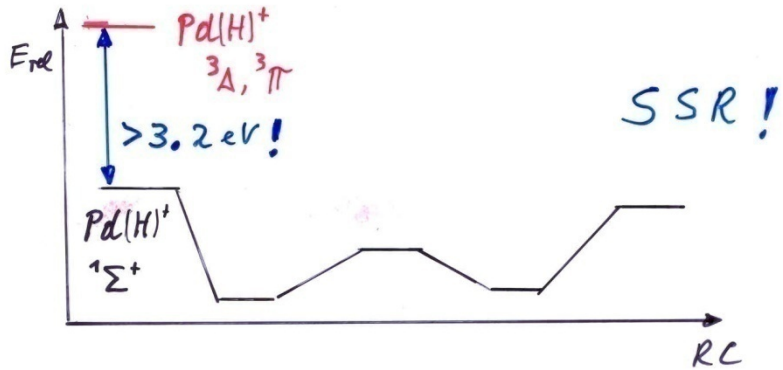

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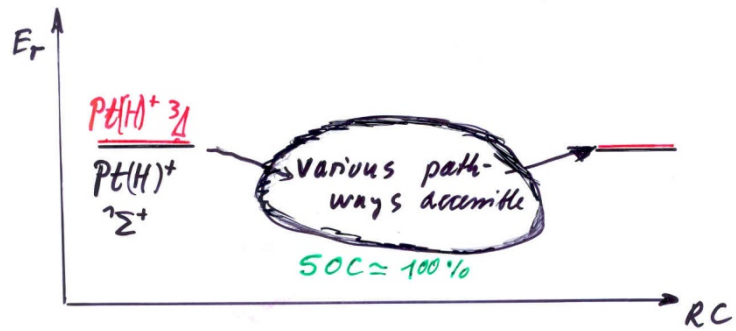
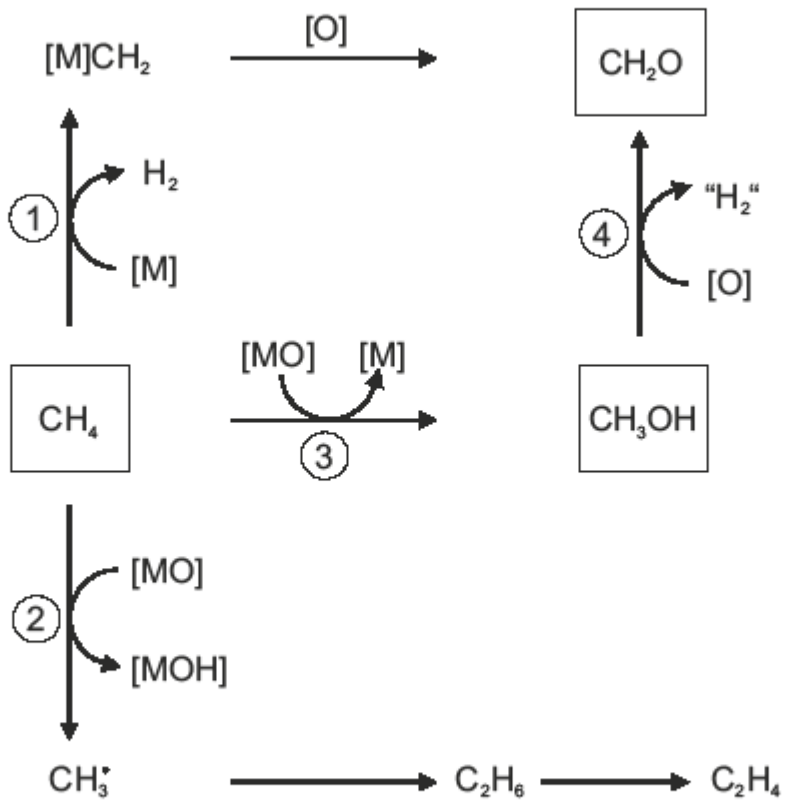




Scheme 1

"Dem Anwenden muß
das Erkennen voraus-
gehen."

M. Planck, 1919

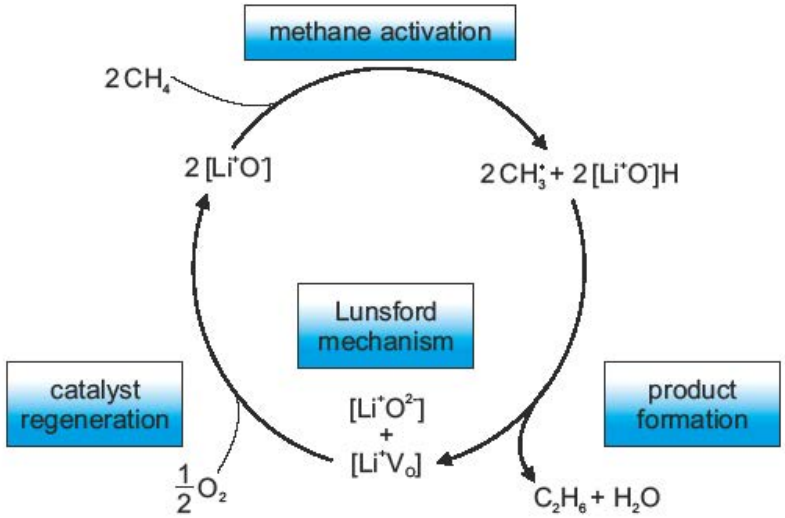
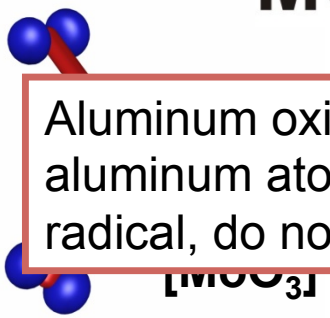

methane activation
2 CH4
2 [Li+O-]
2 CH3• + 2 [Li+O-]H
Lunsford mechanism
catalyst regeneration
product formation
[Li+O2-]
+
[Li+VO]
1/2 O2
C2H6 + H2O

Fig. 3

Oxygen centered radicals

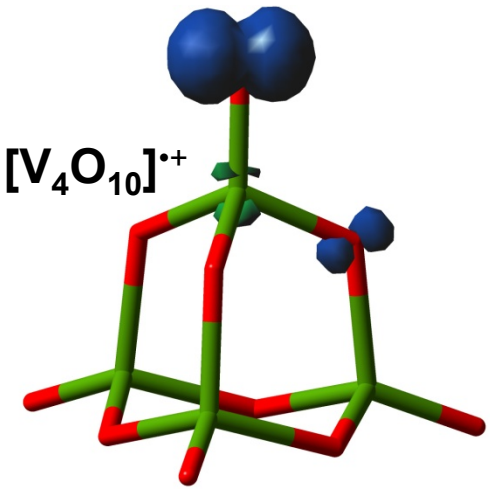
$$MO^{\bullet} + CH_4 \longrightarrow MOH + CH_3^{\bullet}$$

Aluminum oxide cluster cations with an *odd* number of aluminum atoms, thus lacking an oxygen-centered radical, do not react with methane.

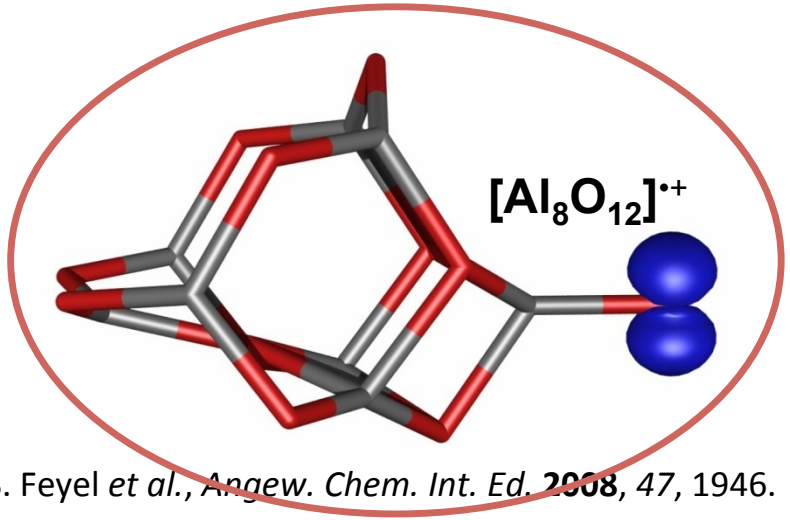


I. Kretzschmar *et al.*, *J. Phys Chem A.* **1997**, *101*, 6252.

D. Schröder *et al.*, *Angew. Chem. Int. Ed.* **2006**, *45*, 5705.



S. Feyel *et al.*, *Angew. Chem. Int. Ed.* **2006**, *45*, 4681.

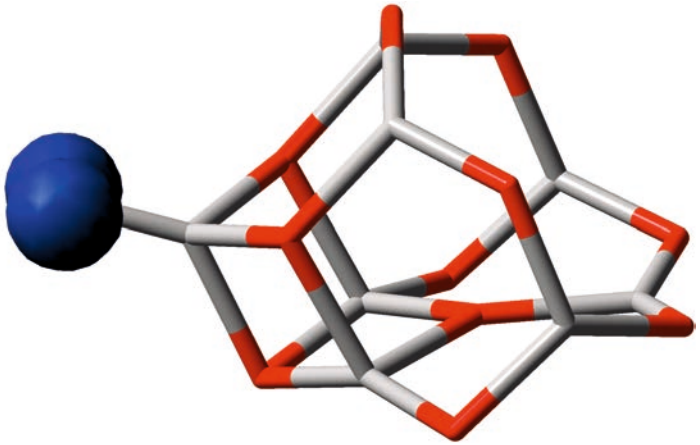


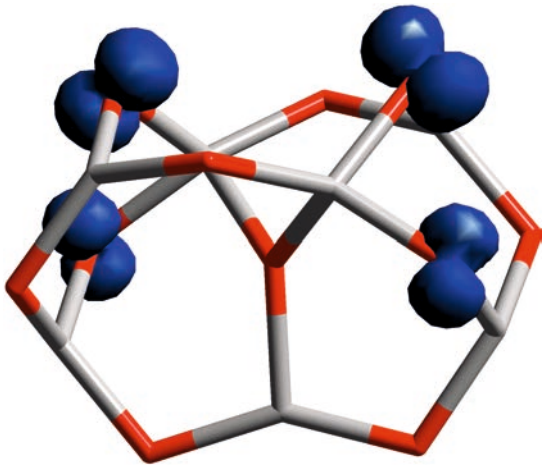
S. Feyel *et al.*, *Angew. Chem. Int. Ed.* **2008**, *47*, 1946.

Spin does count!

$$[Al_8O_{12}]^{\bullet+} + CH_4 \longrightarrow [Al_8O_{11}(OH)]^{+} + CH_3^{\bullet}$$

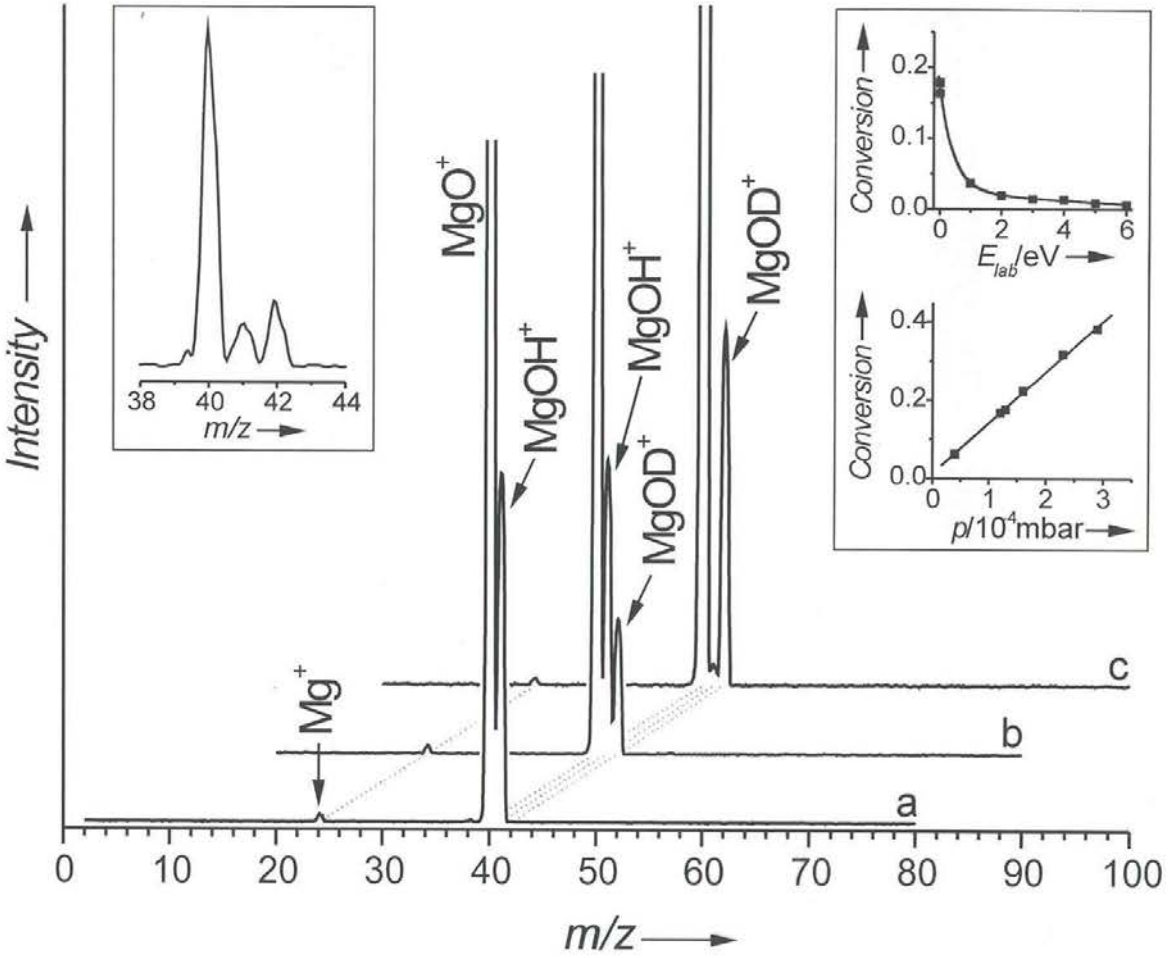
$$[Al_7O_{11}]^{+} + CH_4 \not\longrightarrow [Al_7O_{10}(OH)]^{\bullet+} + CH_3^{\bullet}$$





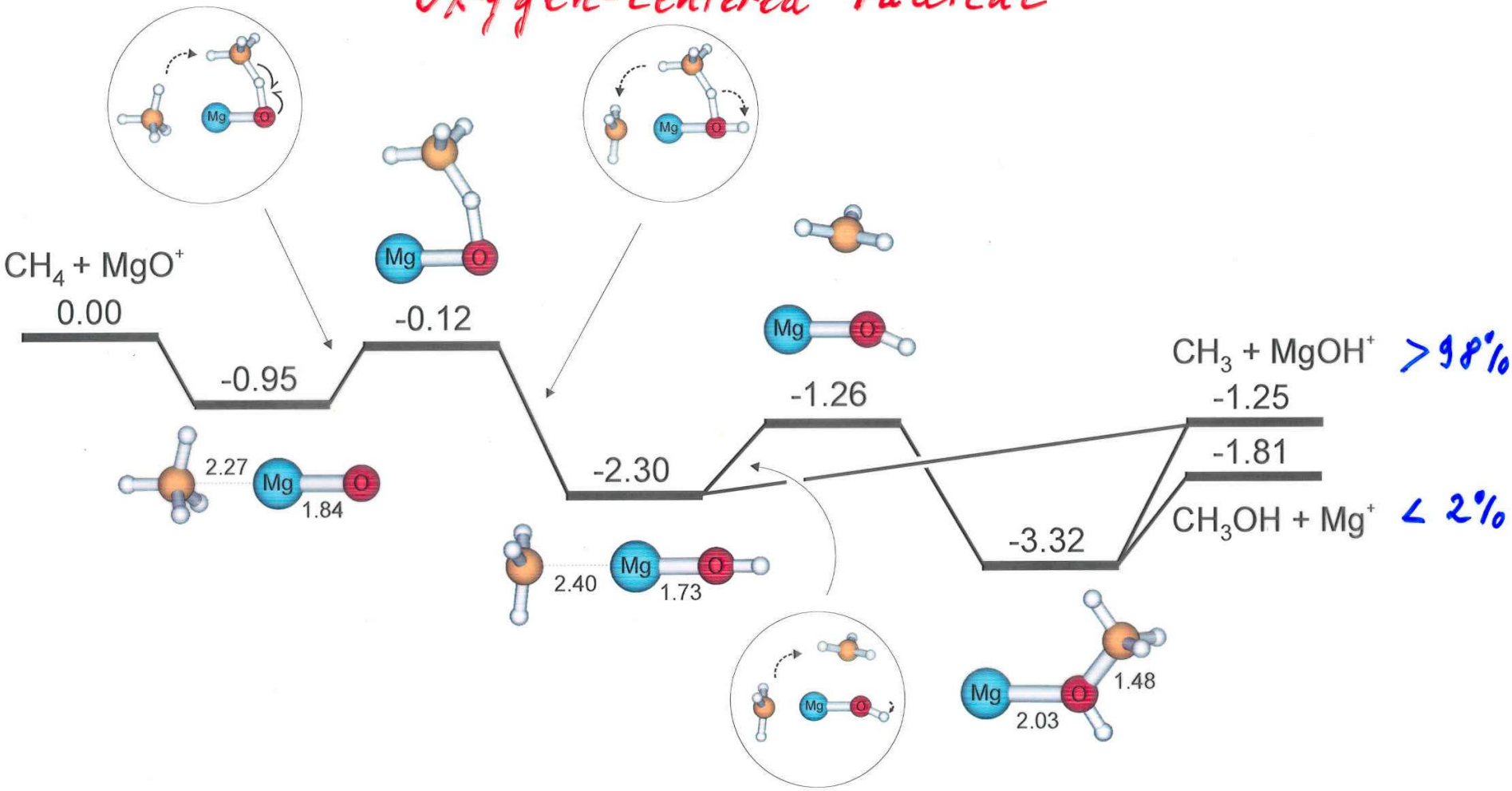
Beyer, Sauer, Schwarz, *et al.*, *Angew. Chem. Int. Ed.* **2008**, *47*, 1946.

$MgO^{+\cdot} + CH_4 \xrightarrow{\phi = 0.40} Mg(OH)^+ + CH_3^{\cdot}$; KIE $(CH_2D_2) = 2.1 \pm 0.1$



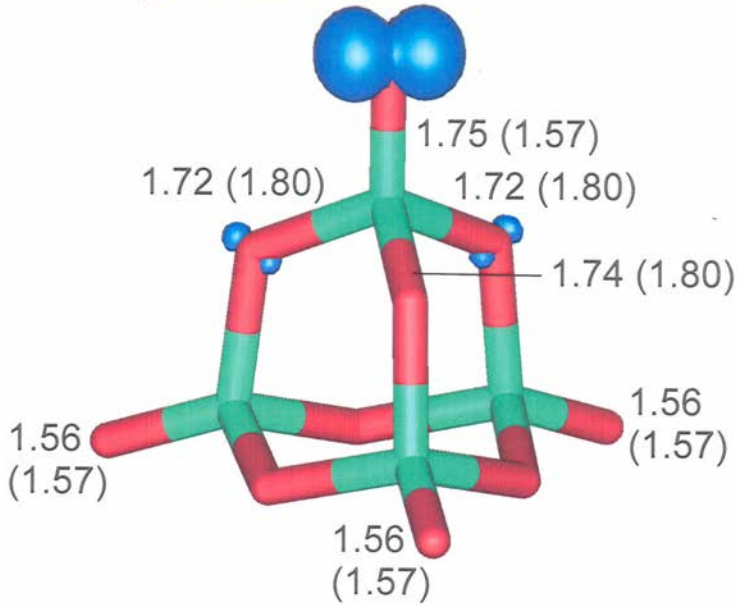
D. Schröder, J. Roithová
Angew. Chem. 2006

Metal-assisted C-H bond activation by an oxygen-centered radical



MP2/6-311+G(2d,2p)

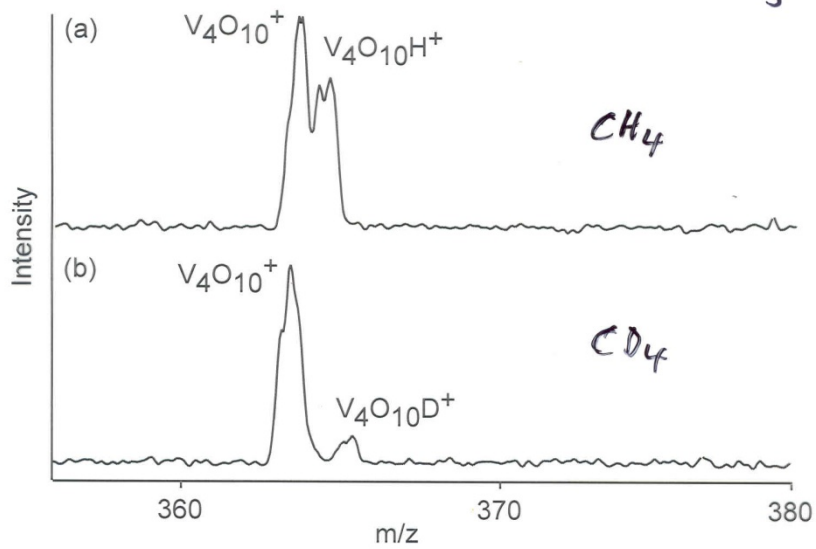
$V_4O_{10}^{+\bullet}$



Structure of the most stable isomer of $V_4O_{10}^+$ with spin density (expressed as blue areas). V-O distances for $V_4O_{10}^+$ and V_4O_{10} (in parenthesis) are given in Ångström.

S. Feyel et al.
Angew. Chem. Int. Ed.
2006

$$ESI \Rightarrow V_4O_{10}^{+\cdot} + CH_4\,(CD_4) \xrightarrow{\phi = 0.6} CH_3^{\cdot}\ (CD_3^{\cdot})$$



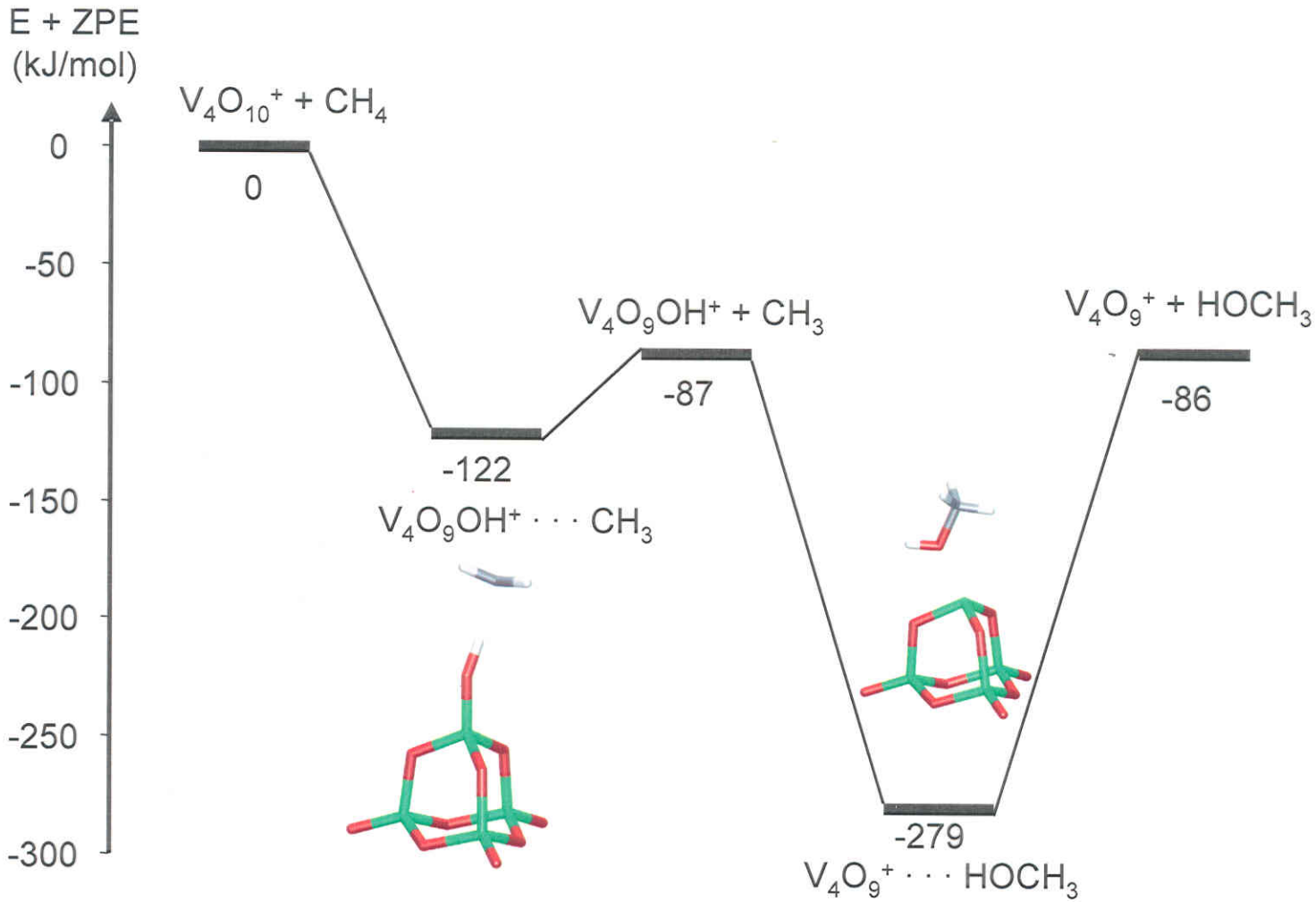
Reaction of mass-selected $V_4O_{10}^+$ with (a) CH_4 and (b) CD_4.

$$V_4O_{10}^{+\cdot} + CH_2D_2 \rightarrow CHD_2^{\cdot} + CH_2D^{\cdot} \qquad \frac{k_H}{k_D} = 1.35$$

Note:

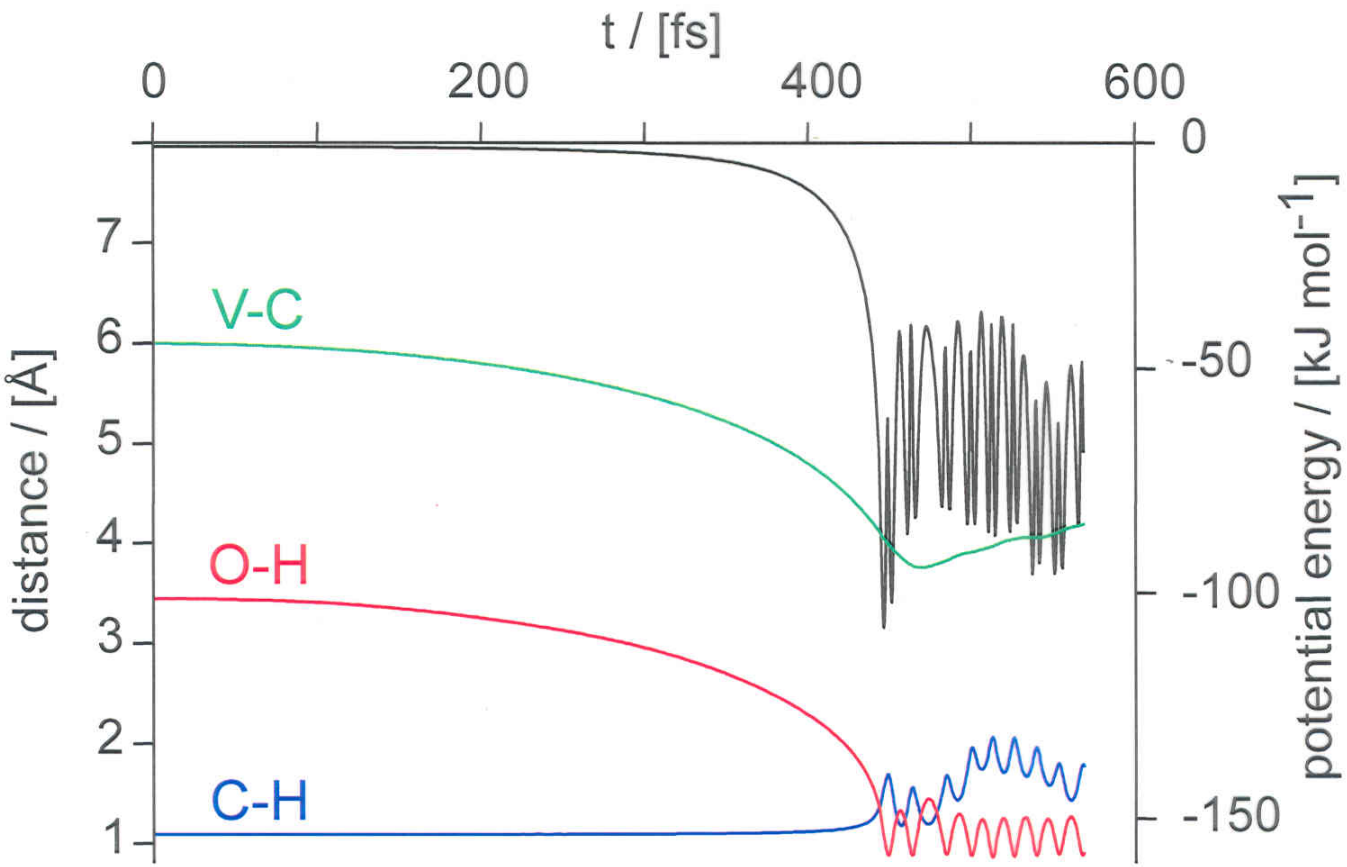
$$HO^{\cdot} + CH_2D_2 \rightarrow CHD_2^{\cdot} + CH_2D^{\cdot} \qquad \frac{k_H}{k_D} = 1.30$$

Sauerssig et al. 2001



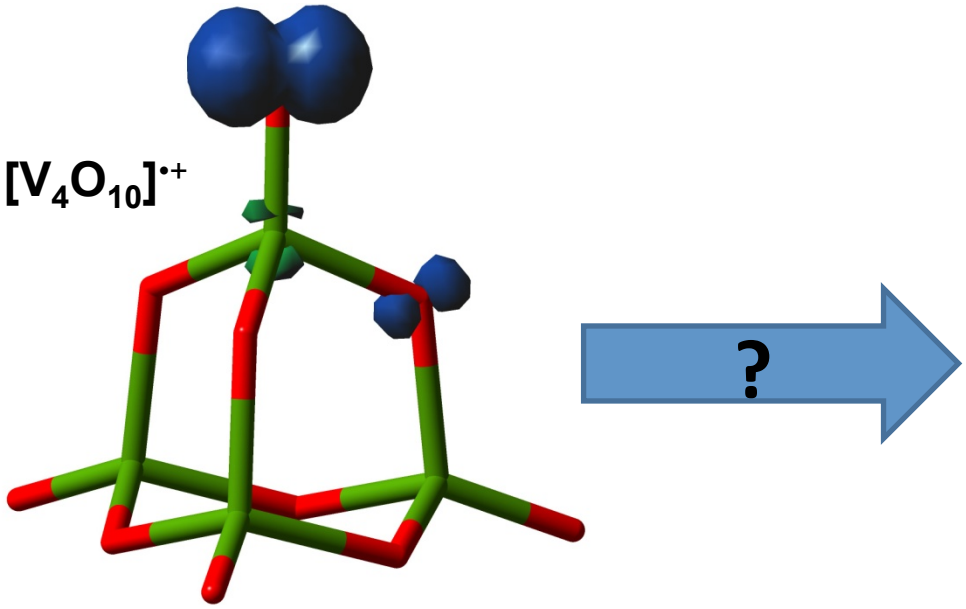
Energy diagram for the reaction of $V_4O_{10}^+$ and methane. The values are relative to the entrance channel, corrected for zero-point energy and given in kJ mol^{-1}.

B3LYP // TZVP

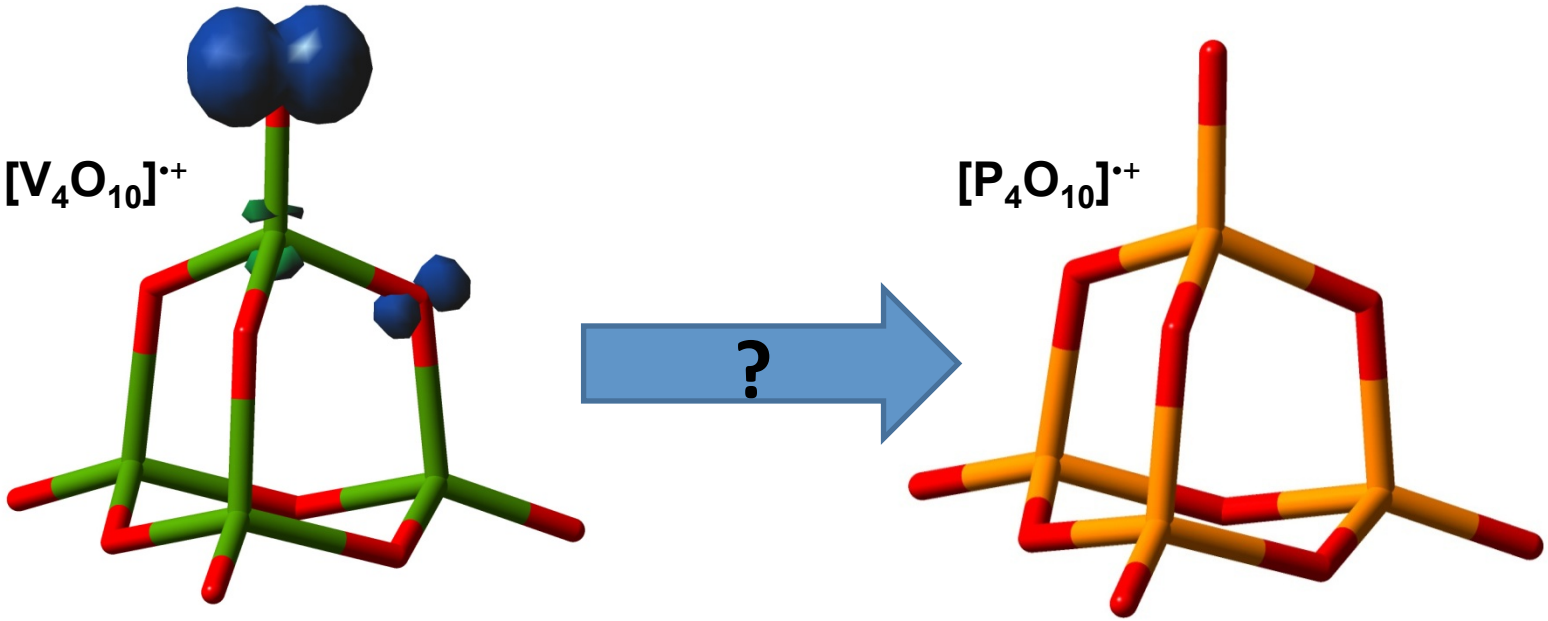


Evolution of the potential energy and bond distances of a MD simulation of $V_4O_{10}^+$ with methane versus time. The energy is shown in black, the distances of C-H in blue, O-H in red and V-C in green. The fluctuations after 450 fs are due to vibrational motions, mainly of the O-H group.

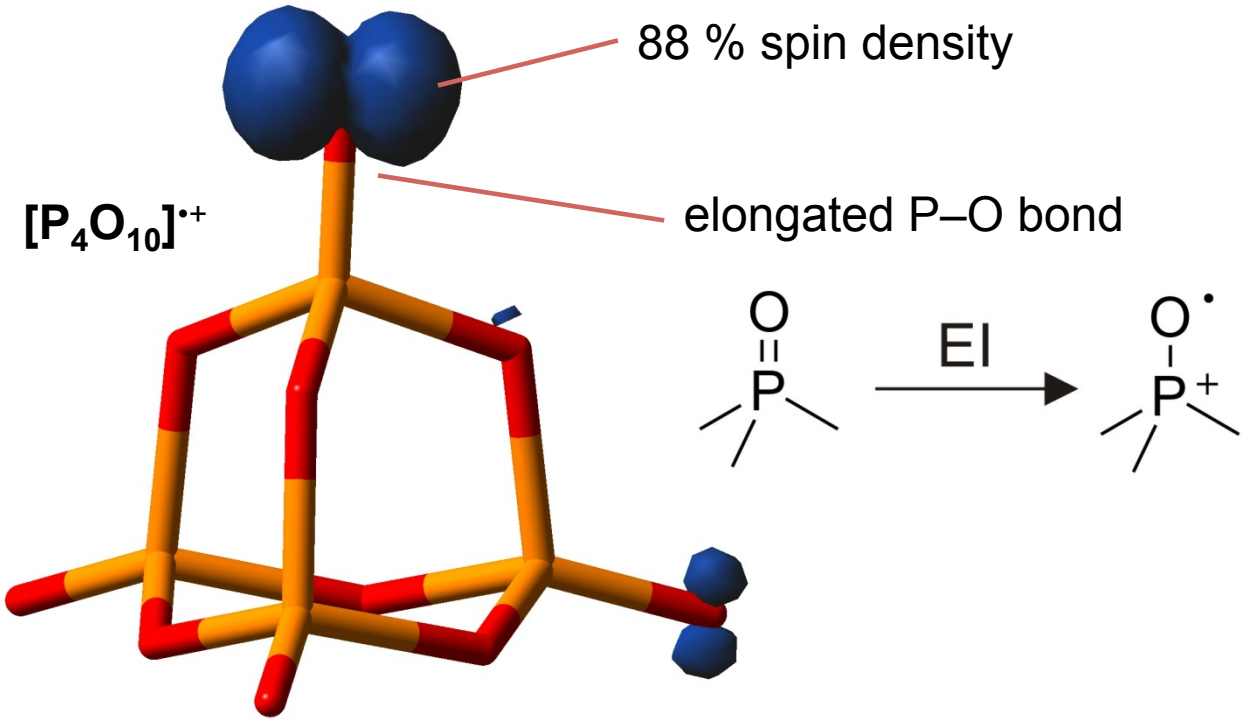
Metallic vs. Non-metallic



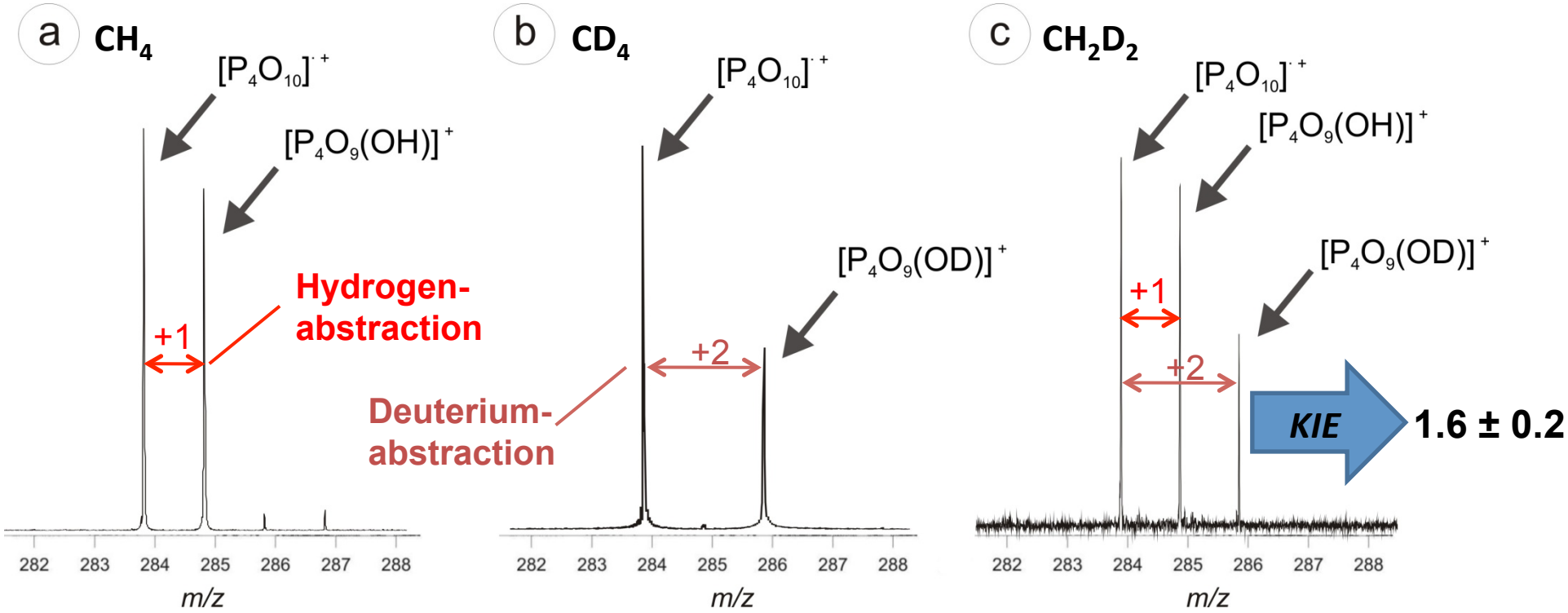
Metallic vs. Non-metallic



Metallic vs. Non-metallic

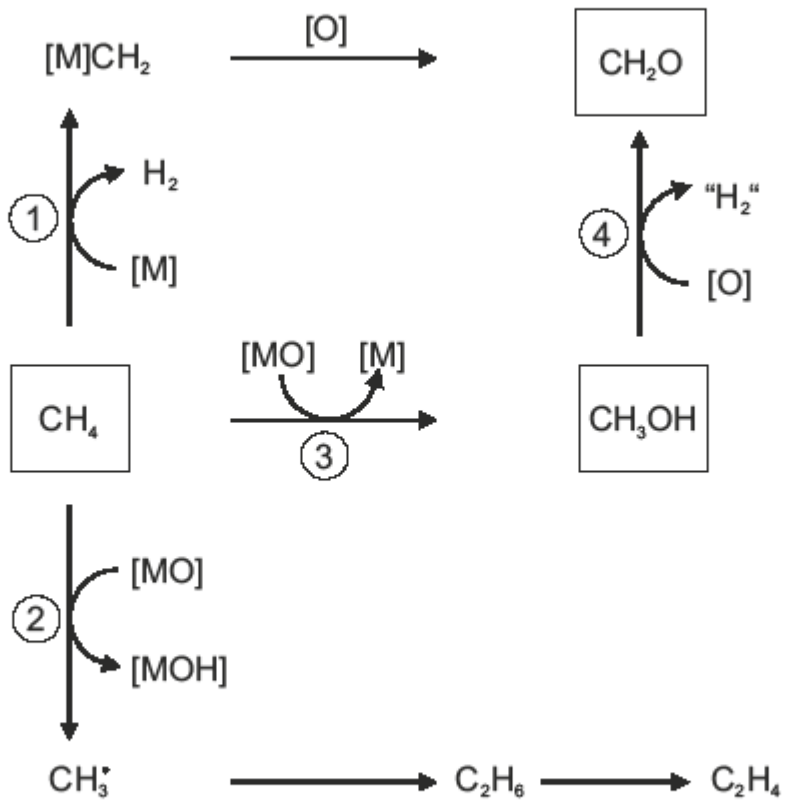


The reaction of $[P_4O_{10}]^{\bullet+}$ with CH_4



$$[P_4O_{10}]^{\bullet+} + CH_4 \longrightarrow [P_4O_9(OH)]^+ + CH_3^{\bullet}$$

N. Dietl, M. Engeser, H. Schwarz, *Angew. Chem. Int. Ed.* **2009**, *48*, 4861



Scheme 1

The reaction looks so simple on paper:

$$\boxed{CH_4 + \tfrac{1}{2} O_2 \rightarrow CH_3OH}$$

Chem. Eng. News

Ten challenges for catalysis

Many unsolved problems face the catalysis research community, says James F. Roth, retired corporate chief scientist at Air Products & Chemicals. He has selected 10 challenges that typify the present needs of industrial catalysis:

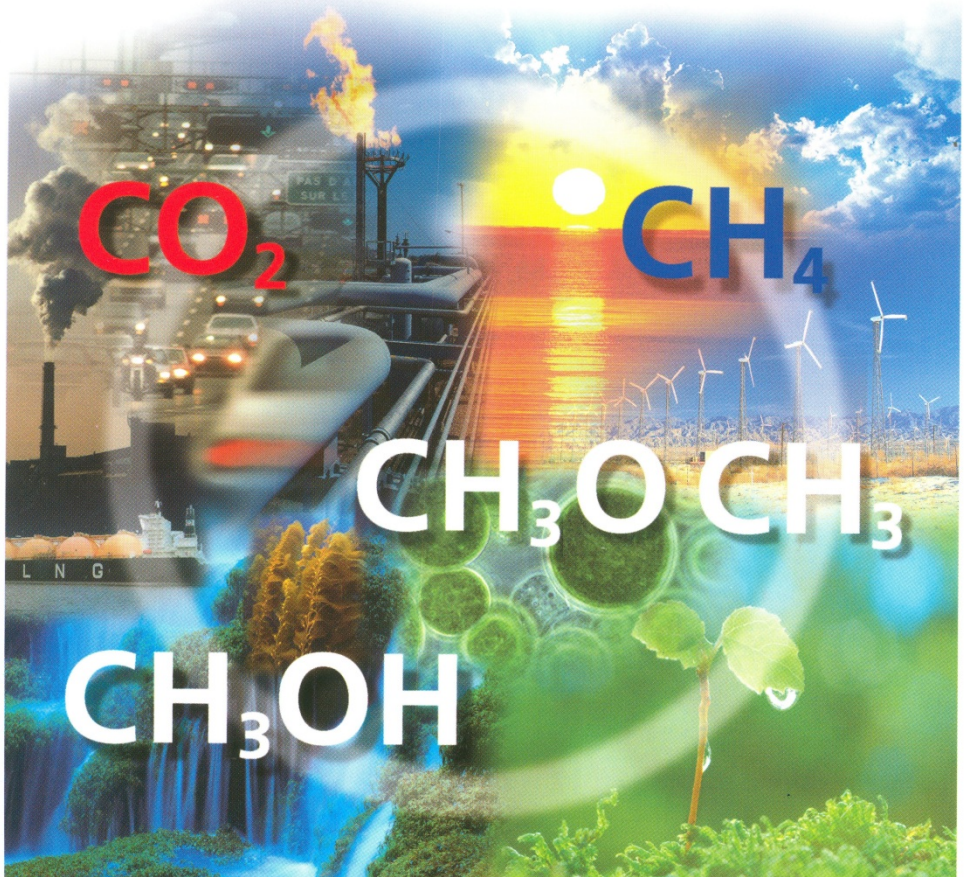
- A new catalyst for low-temperature oxidation of sulfur dioxide to sulfur trioxide in the manufacture of sulfuric acid. Sulfuric acid is the largest volume chemical made in the U.S., and the production process has had only incremental improvements througout many years. What is needed is not another incremental improvement but a substantially different way of making the acid.
- An oxidation catalyst for selective oxidation of methane to methanol. There is no such catalyst at present. Most of the research in this area focuses on high-temperature oxidation catalysts. A low-temperature, liquid-phase catalyst would be very desirable.
- A new catalyst for the facile decomposition of nitrogen oxides to molecular nitrogen and oxygen in the presence of water and carbon dioxide. This would be a great advance in environmental protection.
- A high-conversion, high-selectivity catalyst for production of ethylene, propylene, and styrene from their respective alkanes. Ethylene is the industry's most important feedstock, with about 40% of all organic chemicals production based on it. The usual method is isothermal cracking, which generates many byproducts and is both capital- and energy-intensive.
- A selective catalyst for oxidative coupling of methanol to ethylene. This would shift the feedstock base from ethylene to methanol.
- A selective catalyst for producing phenol by direct oxidation of benzene using molecular oxygen rather than the present cumene-based process.
- Catalysts for the selective, direct synthesis of hydrogen peroxide from hydrogen and oxygen under mild conditions.
- Low-temperature selective oxidation catalysts for the epoxidation of ethylene by molecular oxygen.
- Synthesis of aromatic amines via the direct interaction of aromatics with ammonia.
- Anti-Markovnikov addition of water or ammonia to olefins to directly synthesize primary alcohols or amines.

George A. Olah, Alain Goeppert, and G.K. Surya Prakash

WILEY-VCH

Beyond Oil and Gas: The Methanol Economy

Second Updated and Enlarged Edition



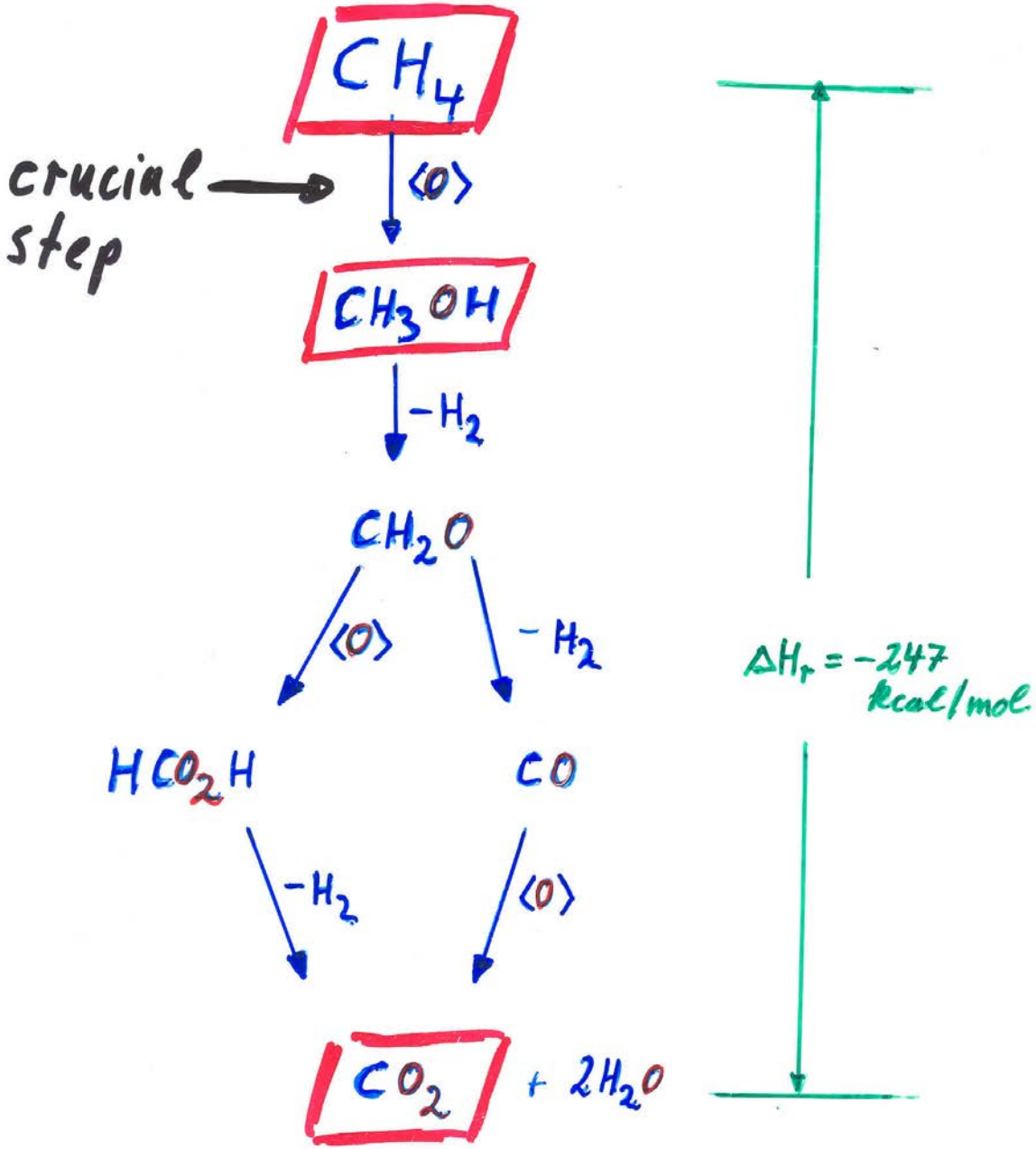
Four problems:

(i) Stoichiometry

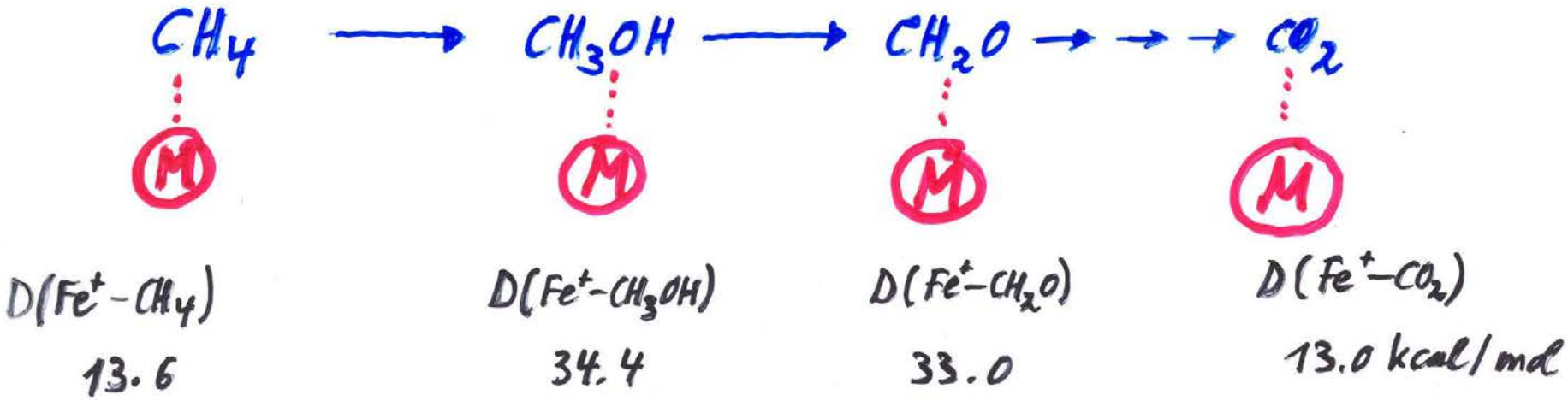
(ii) Kinetic control
(overoxidation)

(iii) selectivity

(IV) Spin problematic
(Wigner's rules)


CH_4
crucial step
⟨O⟩
CH_3OH
$-H_2$
CH_2O
⟨O⟩
$-H_2$
HCO_2H
CO
$-H_2$
⟨O⟩
CO_2
$+ 2H_2O$
$\Delta H_r = -247$ kcal/mol

The problem of over-oxidation



Polar products co-ordinate to the active sites of a catalyst (M) better than the substrate hydrocarbons.

$$RH + O_2 \longrightarrow ROOH$$

The thermochemistry-spin dilemma

		$\Delta_r H$ [kcal/mol]	Wigner's rule violated
$^1CH_4 + {}^3O_2 \longrightarrow$	$^1CH_3OOH$	-14	
$\longrightarrow$	$^3CH_3OOH$	$+28$	obeyed
$^1CH_4 + {}^3O_2 \longrightarrow$	$^2CH_3^{\cdot} + {}^2HOO^{\cdot}$	$+55$	obeyed
$^2CH_3^{\cdot} + {}^2HOO^{\cdot} \longrightarrow$	$^1CH_3OOH$	-69	obeyed

$$CH_4 + O_2 + NADH + H^+ \xrightarrow[pH \approx 7;\ 1\,atm]{RT,} CH_3OH + H_2O + NAD^+$$

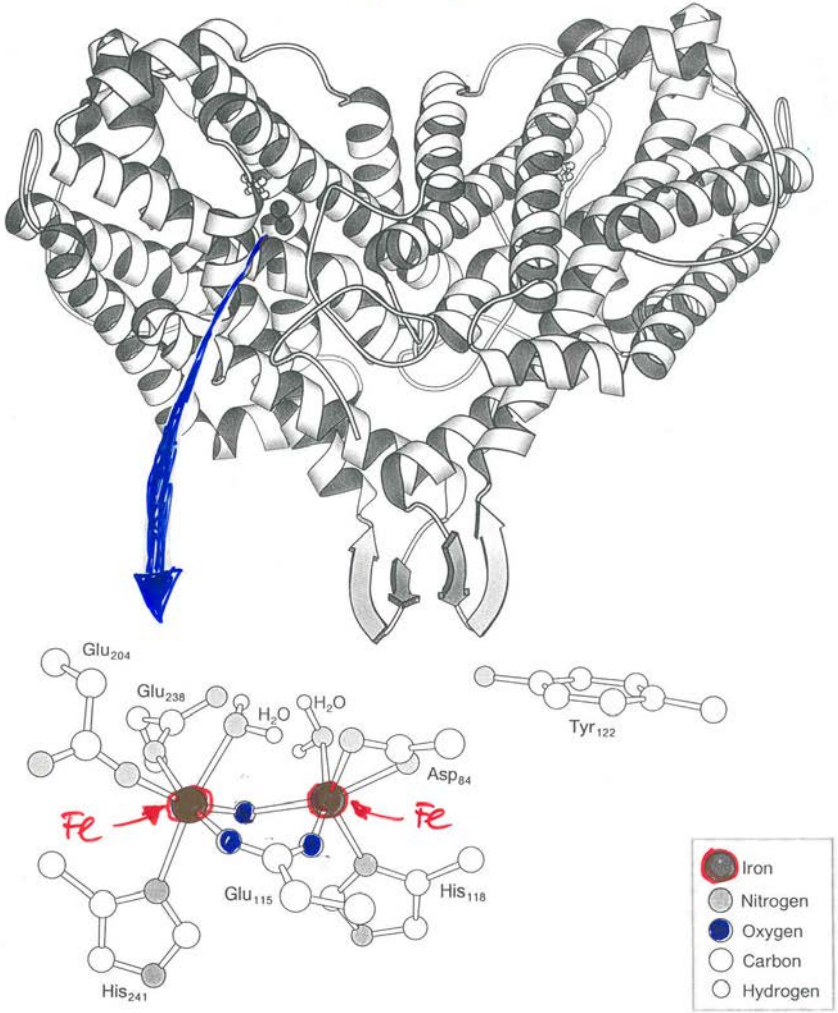
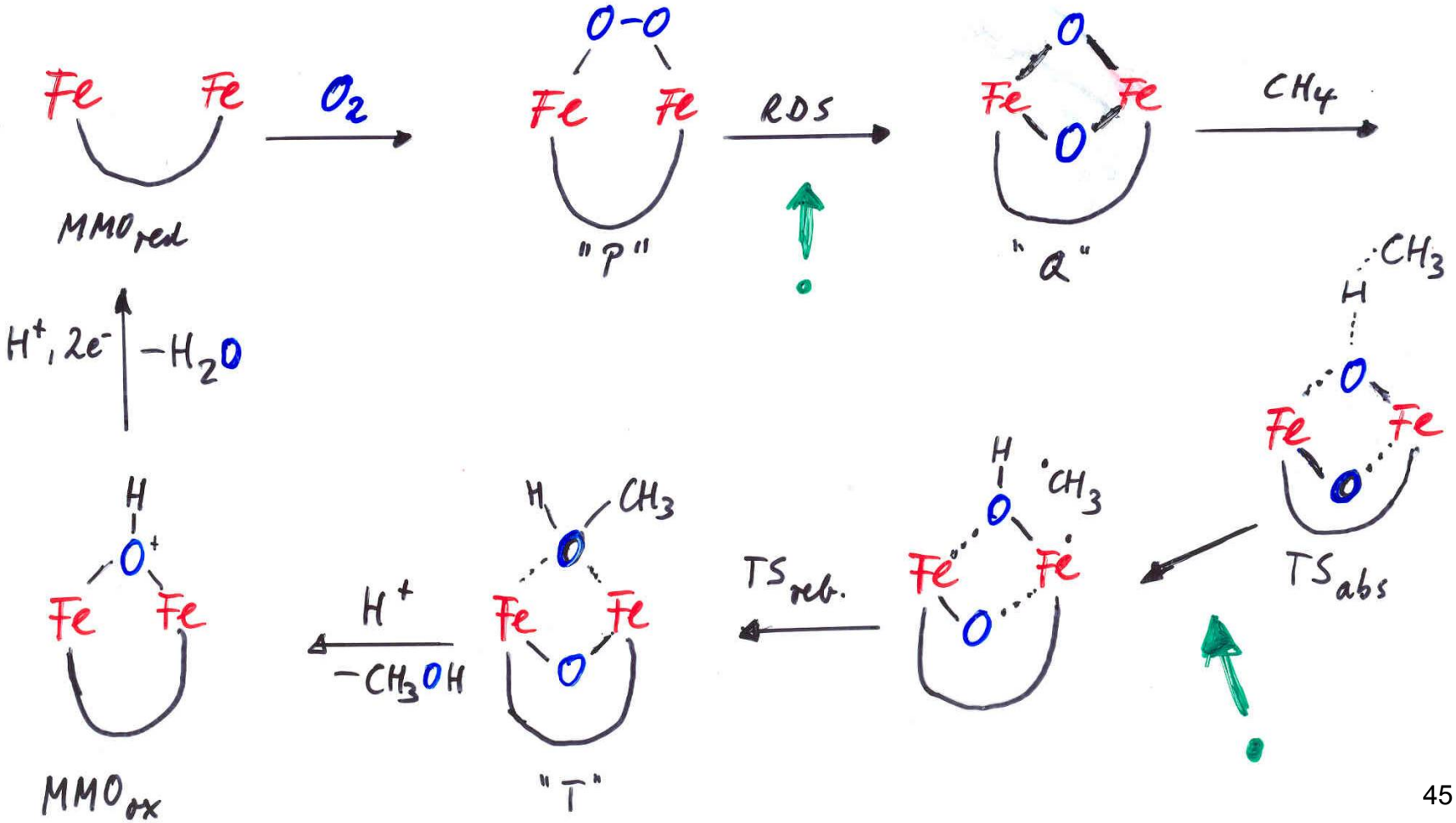


Figure 11.15
Structure of the R2 protein of bacterial ribonucleotide reductase displaying the dinuclear iron center and nearby tyrosyl radical.

taken from: S.J. Lippard, J.M. Berg
"Principles of Bioinorganic Chemistry"

Schematic Representation of the Key Intermediates of Methane Activation with MMO



Oxygenation of C-H Bonds

enzymes

homogeneous catalysts

surfaces

$$[M-O] \xrightarrow{R-H} R-O-H + [M]$$

"reaction centre"

role of electronic structure of M-O ?

What role plays the

electronic structure

of

M–O ?

- Uncovering intrinsic features

Stoichiometric Gas-phase Oxidation of Methane by MO^+

$$MO^+ + CH_4 \rightarrow \begin{cases} MOH^+ + CH_3^{\cdot} \\ MCH_2^+ + H_2O \\ M^+ + CH_3OH \end{cases}$$

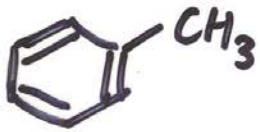
MO^+	ground state	ϕ [%]	% $CH_3^{\cdot}$	% H_2O	% CH_3OH
MnO^+	$^5\Pi$	40	$\boxed{100}$		$<<1$
FeO^+	$^6\Sigma^+$	20	57	<1	42
CoO^+	$^5\Delta$	<1			$\boxed{100}$
NiO^+	$^4\Sigma^-$	20			$\boxed{100}$
PtO^+	$^4\Sigma^-$	100		$\boxed{75}$	25

Oxygenation of Hydrocarbons by MO^+

- CH_4

  J. Am. Chem. Soc. 1994, 9565
  Angew. Chem. Int. Ed. Engl. 1995, 1973

  Helv. Chim. Acta 1992, 1281
  J. Am. Chem. Soc. 1994, 1096
  J. Am. Chem. Soc. 1999, 147



  Helv. Chim. Acta 1992, 1792

-

  Helv. Chim. Acta 1995, 1013
  Helv. Chim. Acta 1999, 1784

The most 'simple' case

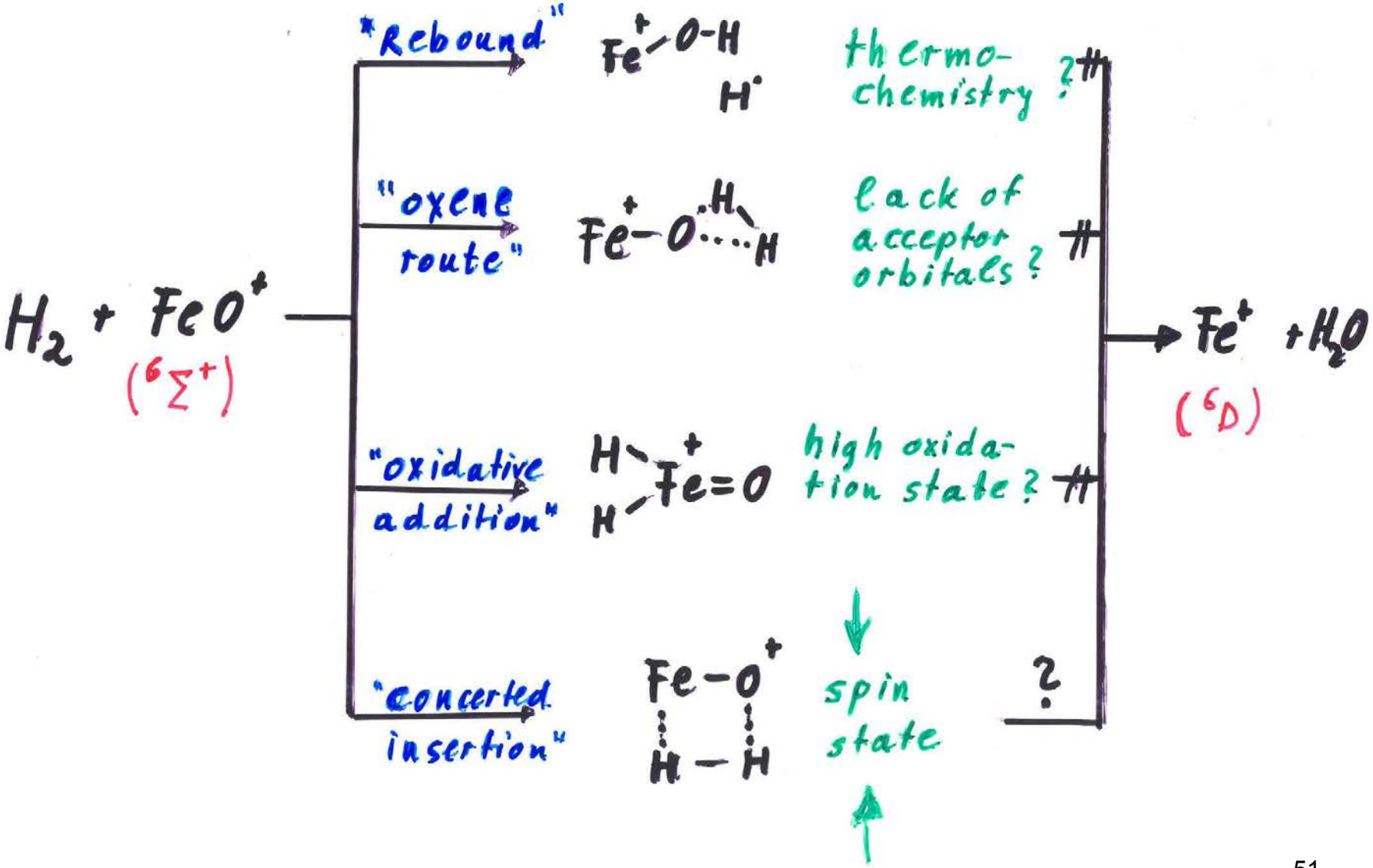
$$FeO^+ + H_2 \longrightarrow Fe^+ + H_2O$$

Int. J. Mass Spectrom.
1997, 161, 175

Features:

- exothermic ($\Delta H_r = -36$ kcal/mol) and spin-allowed
- Yet, rate efficiency $< 1\%$!
- Inverse energy dependence
  $T\ (E_k) \uparrow$ rate constant $\downarrow$
- Nature of barrier ?
- Kinetic isotope effects (H_2, HD, D_2) are negligible

Conceivable Mechanistic Variants



$FeO^+ + H_2 \rightarrow Fe^+ + H_2O$

J. Phys. Chem. A **1998,** *102,* 3835−3846

Theoretical Investigation of Two-State-Reactivity Pathways of H−H Activation by FeO^+: Addition−Elimination, "Rebound", and Oxene-Insertion Mechanisms

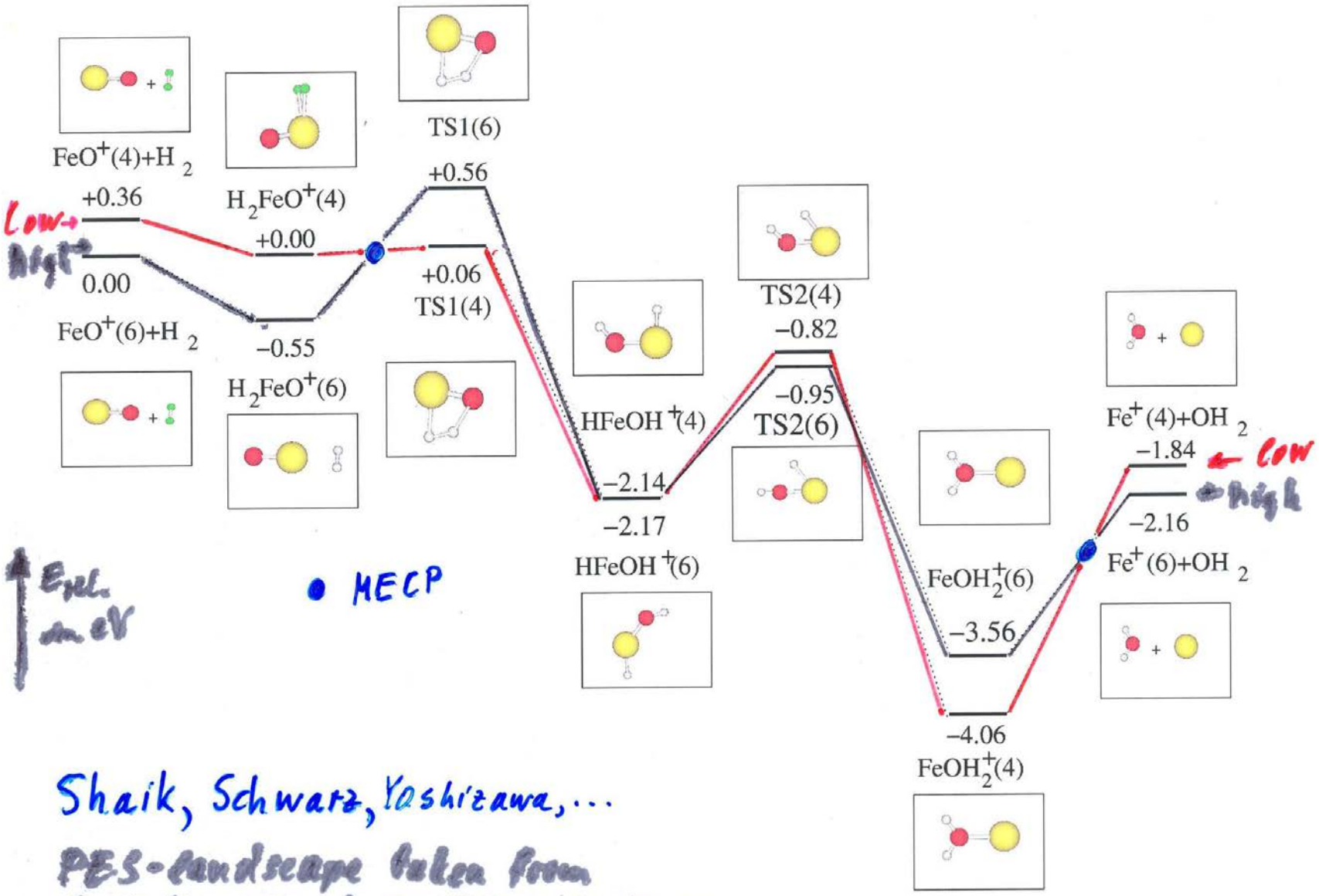
Michael Filatov and Sason Shaik*

Department of Organic Chemistry and the Lise Meitner-Minerva Centre for Computational Quantum Chemistry, The Hebrew University, 91904 Jerusalem, Israel

Received: January 28, 1998

Density functional calculations using the B3LYP, BP86, and FT97 functionals with an extended basis set are employed to investigate the mechanisms of H_2 oxidation by FeO^+. Three mechanisms are considered, addition−elimination, "rebound", and oxene-insertion. The oxene-insertion is characterized by high barriers and only second-order saddle points. The addition−elimination and "rebound" mechanisms are competitive and both exhibit two-state-reactivity (TSR) with a crossing between sextet and quartet states. TSR provides a low-energy path for bond activation and is predicted to be the dominant pathway at room temperature. Both TSR mechanisms are concerted: the addition−elimination mechanism involves 2+2 addition in the bond activation step, while the rebound mechanism is effectively concerted involving the H-abstraction followed by a barrierless "rebound" of the H-radical. At elevated temperature (above a threshold of $^3/_2RT = 0.5$ eV), the stepwise "rebound" mechanism starts to dominate and produces $FeOH^+ + H^\bullet$ via a single-state-reactivity (SSR) on the sextet surface. Kinetic isotope effect calculations have been performed, and their comparison with the experimental data[10] seems to be characteristic of TSR. Thus, the measured isotope effects probe the extent of H···H (D···D) cleavage in a mechanism whereby bond activation and spin-inversion occur in a concerted manner. Some predictions have been made regarding the factors that affect the mechanistic competition.

→ Also, see: A. Fiedler et al. JACS 116, 10734



Shaik, Schwarz, Yoshizawa, ...

PES-landscape taken from J.M. Ugalde et al. I.J.M.S. 2005, 240, 33

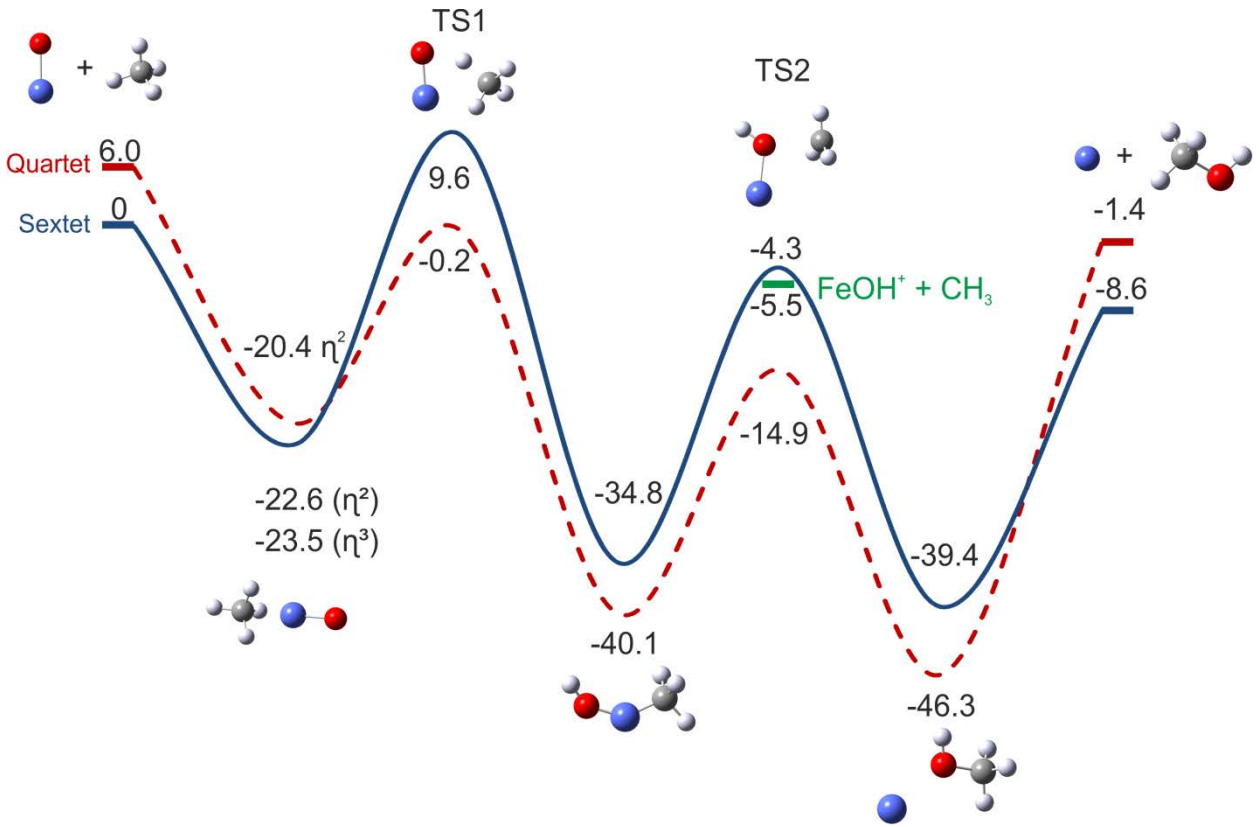
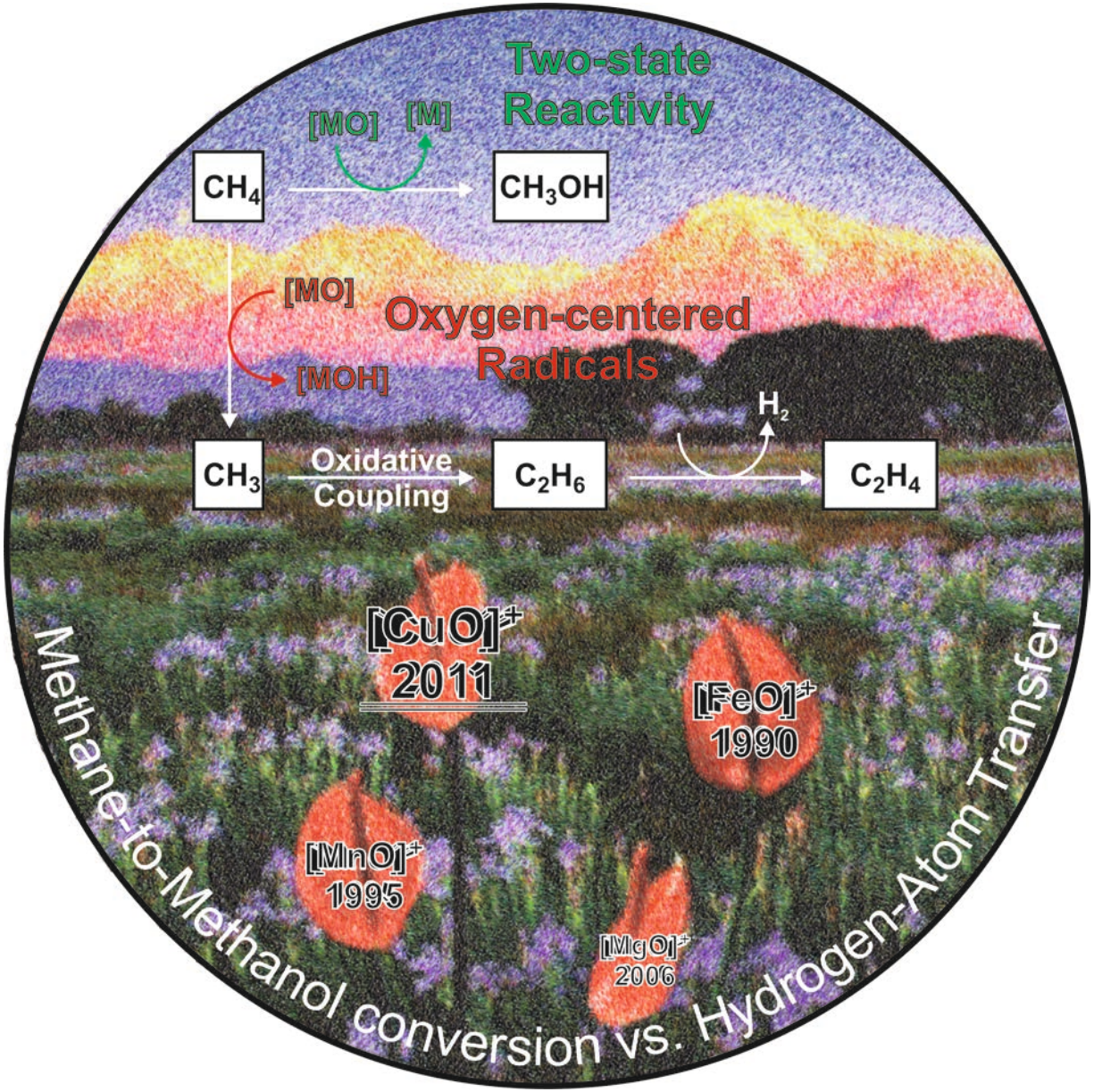
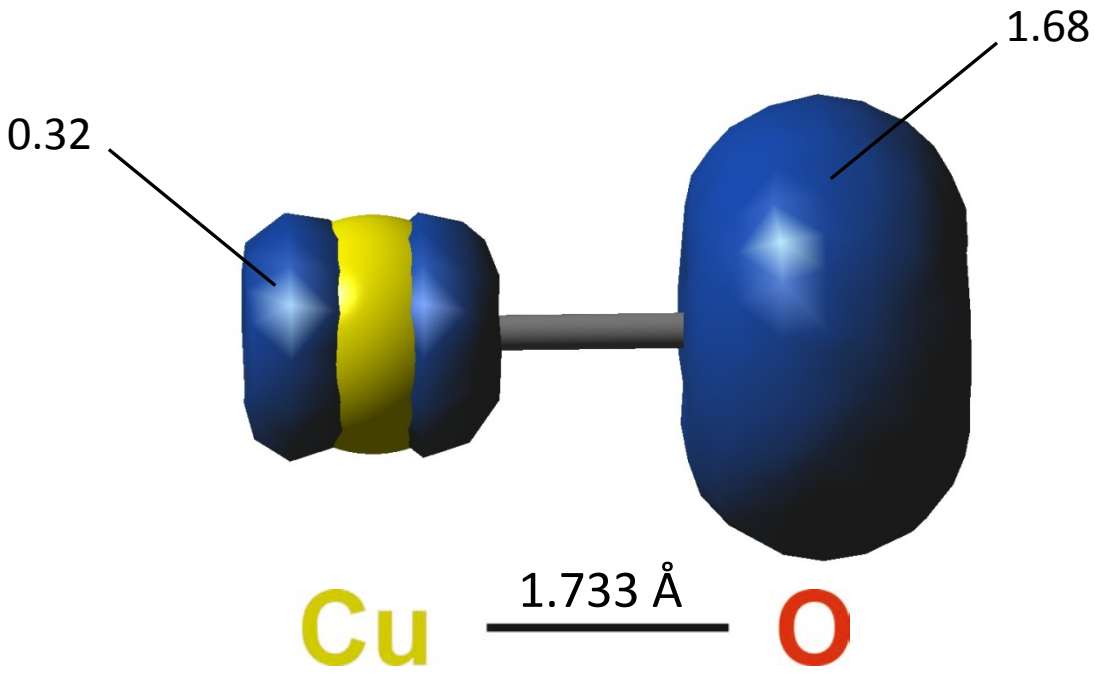


Figure 7.
Schematic potential energy surface for the reaction $FeO^+ + CH_4 \rightarrow Fe^+ + CH_3OH$. Relative energies (kcal mol^{-1}) are calculated at the CBS-QB3 level of theory (adapted from ref. [34e]).


Two-state Reactivity
[MO]
[M]
CH_4
CH_3OH
[MO]
[MOH]
Oxygen-centered Radicals
H_2
CH_3
Oxidative Coupling
C_2H_6
C_2H_4
$[CuO]^+$
2011
$[FeO]^+$
1990
$[MnO]^+$
1995
$[MgO]^+$
2006
Methane-to-Methanol conversion vs. Hydrogen-Atom Transfer

Spin distribution in triplet $[CuO]^+$ ($^3\Sigma^-$)



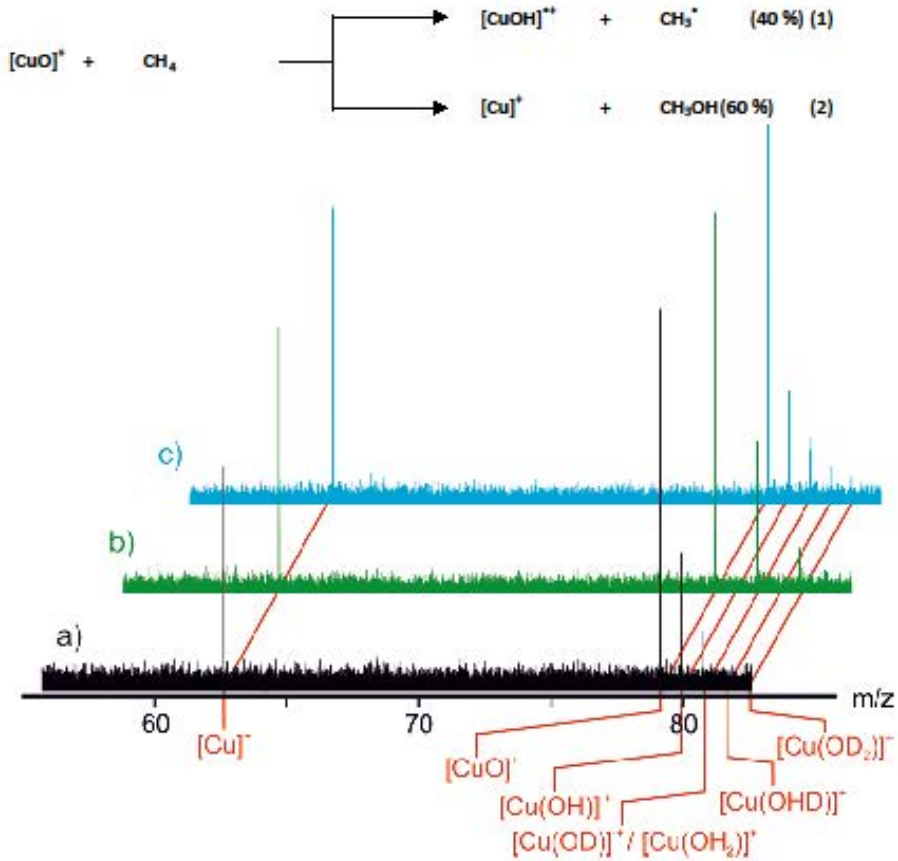
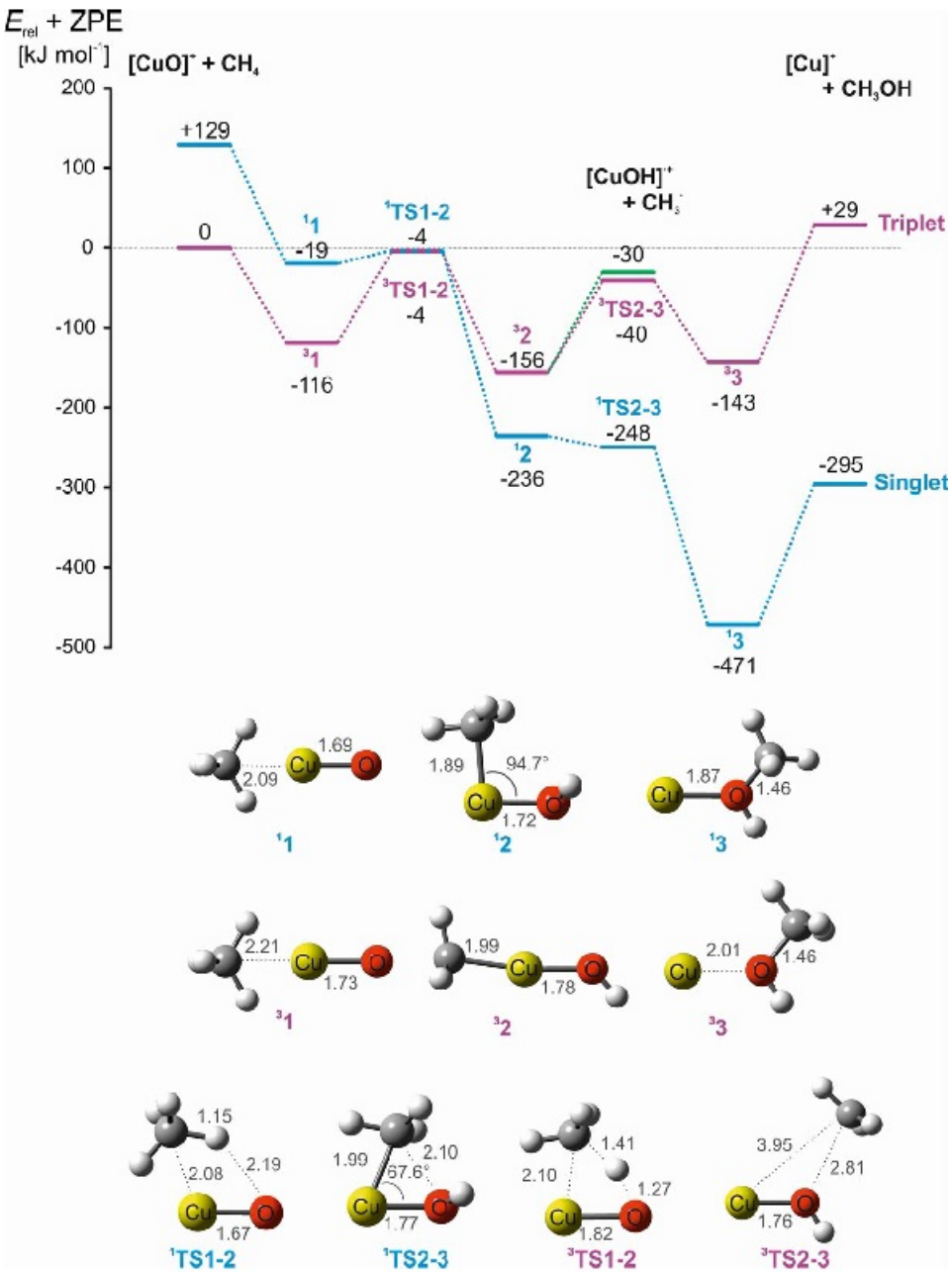


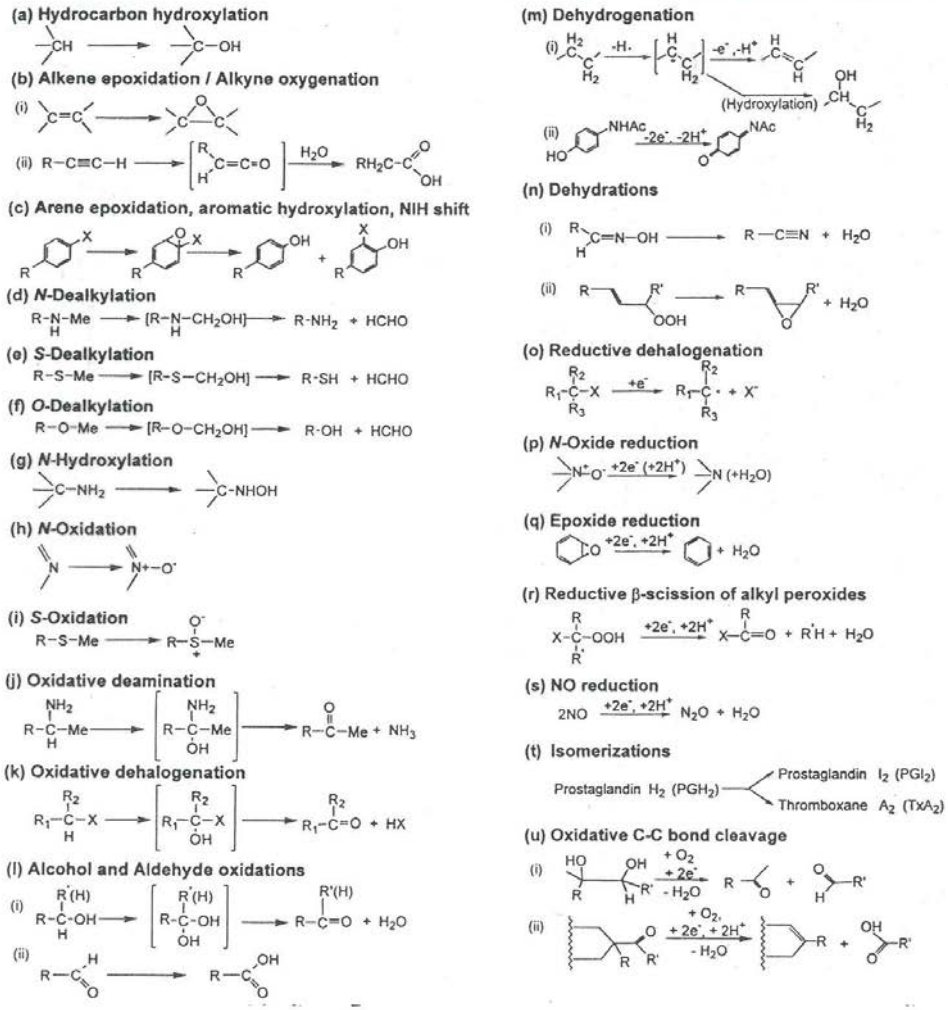
Figure 1. Mass spectra showing the reactivity of mass-selected $[CuO]^+$ with methane at $1.5 \cdot 10^{-8}$ mbar: a) CH_4, b) CD_4, and c) CH_2D_2.


E_{rel} + ZPE
[kJ mol^{-1}]
[CuO]$^{+}$ + CH$_4$
[Cu]$^{+}$ + CH$_3$OH
[CuOH]$^{+}$ + CH$_3^{\cdot}$
200
100
0
-100
-200
-300
-400
-500
+129
0
^{1}1
-19
^{1}TS1-2
-4
^{3}TS1-2
-4
^{3}1
-116
^{3}2
-156
^{1}2
-236
-30
^{3}TS2-3
-40
^{1}TS2-3
-248
^{3}3
-143
^{1}3
-471
+29
Triplet
-295
Singlet
2.09
1.69
1.89
94.7°
1.72
1.87
1.46
2.21
1.73
1.99
1.78
2.01
1.46
1.15
2.08
2.19
1.67
1.99
2.10
67.6°
1.77
2.10
1.41
1.27
1.82
3.95
2.81
1.76
^{1}TS1-2
^{1}TS2-3
^{3}TS1-2
^{3}TS2-3

Cytochrome P-450 Catalyzed Reactions

Dawson et al.:

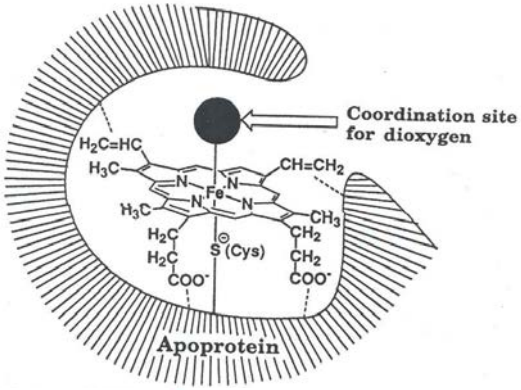
Chemical Reviews, 1996, Vol. 96, No. 7 2845



Es ist der Valenzwechsel einer Eisenverbindung, auf dem die katalytische Oxydation in der lebendigen Substanz beruht.

Otto Warburg, *Le Prix Nobel* (1931)

$$R\text{-}H + 0.5\,O_2 \xrightarrow{P\text{-}450} R\text{-}O\text{-}H$$



Details ??

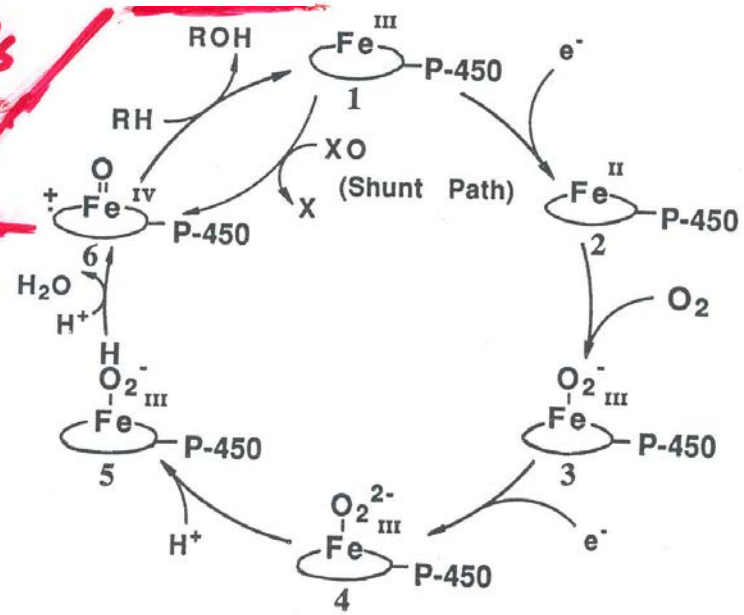
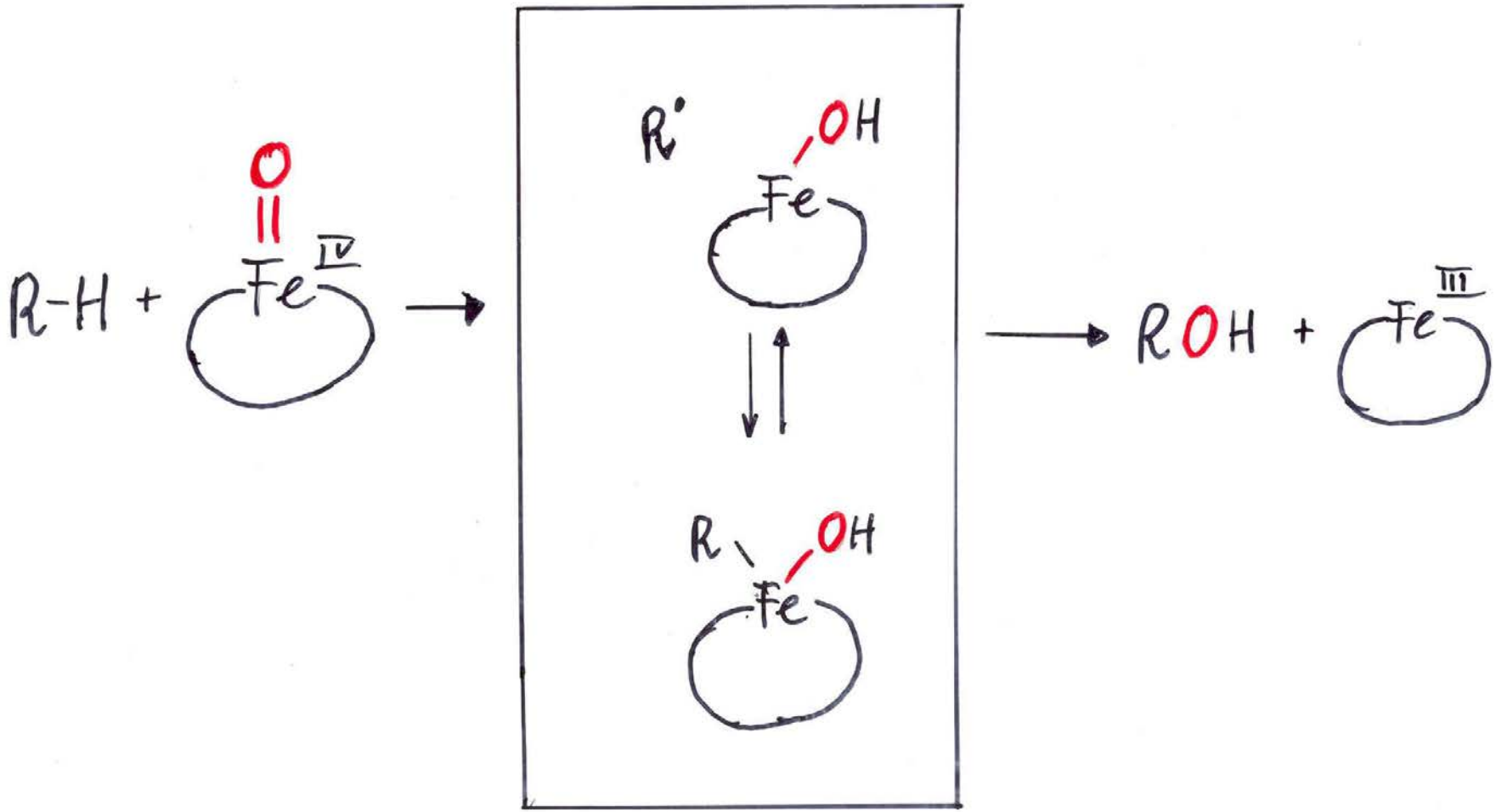


Fig. 2. Structure of active site (top) and proposed reaction mechanism for cytochrome P-450.

I. Schlichting et al., Science, 2000, 287, 1615


R-H +
O
Fe IV
R•
OH
Fe
R
OH
Fe
ROH +
Fe III

radical intermediates (Frey)
rearrangement products, (Groves)
kinetic isotope effects (Dinnocenzo)

support

radical lifetimes
(Newcomb)

questions

rebound mechanism

The cytochrome P-450 dilemma of C-H bond hydroxylation:

"Radicals are both present and absent, and the rebound mechanism is both right and wrong"

S. Shaik, H. Schwarz, et al.

Curr. Opinion Chem. Biol.

Chem. Eur. J.
1998, 4, 193

Electronic Structure Makes a Difference: Cytochrome P-450 Mediated Hydroxylations of Hydrocarbons as a Two-State Reactivity Paradigm

Sason Shaik, Michael Filatov, Detlef Schröder, and Helmut Schwarz*

Dedicated to George A. Olah on the occasion of his 70th birthday.

Keywords: alkane hydroxylation • bond activation • metal oxides• spin state control

Abstract: This paper describes a reactivity paradigm called two-state-reactivity (TSR) in C-H bond activation by metal oxenoid cations (*e. g.*, FeO^+). The paradigm is applied to the hydroxylation of alkanes by the active species of the enzyme cytochrome P-450, and a mechanistic scheme is proposed based on the competition between TSR pathways to single-state-reactivity (SSR) pathways. Generally, the oxide cations of the late transition metals (MO^+) possess the same bonding patterns as the O_2 molecule; having a high-spin ground state, and an adjacent low-spin excited state. The adjacency of the spin states together with the poor bonding capability of the high spin state and the good bonding capability of the low spin state, leads to a spin crossover along the reaction coordinate and opens a low-energy TSR path for hydroxylation. The competing pathway is SSR, where the reaction starts, occurs and ends on the same spin state. The TSR/SSR competition is modulated by the probability of spin crossover. Generally, TSR leads to concerted pathways which conserve stereochemical information while SSR results in stepwise mechanisms which scramble this information. The TSR/SSR competition is used to shed some light on recent results which are at odds with the consensus mechanism of P-450 hydroxylation. The fundamental features of the paradigm are outlined and the theoretical-experimental challenges for its articulation are spelled out.

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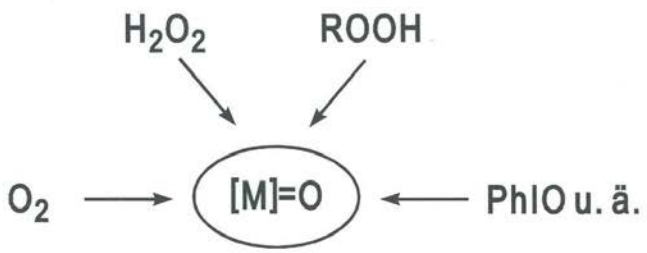
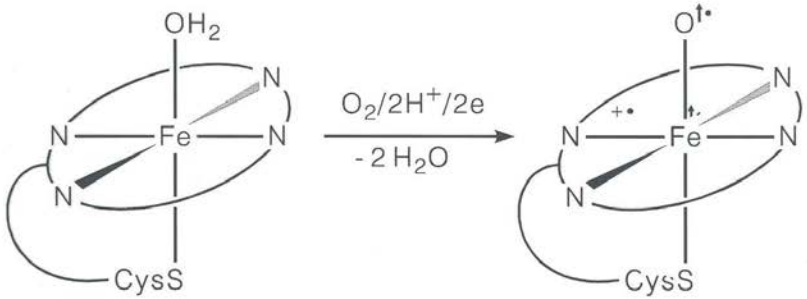
H. Schwarz, D. Schröder, Institut für Organische Chemie, Technische Universität Berlin, Straße des 17. Juni 135, D-10623 Berlin (Germany), Tel.: ++49-30-314-23483, Telefax: ++49-30-314-21102, e-mail: schw0531@www.chem.tu-berlin.de.

Übergangsmetalloxenoide

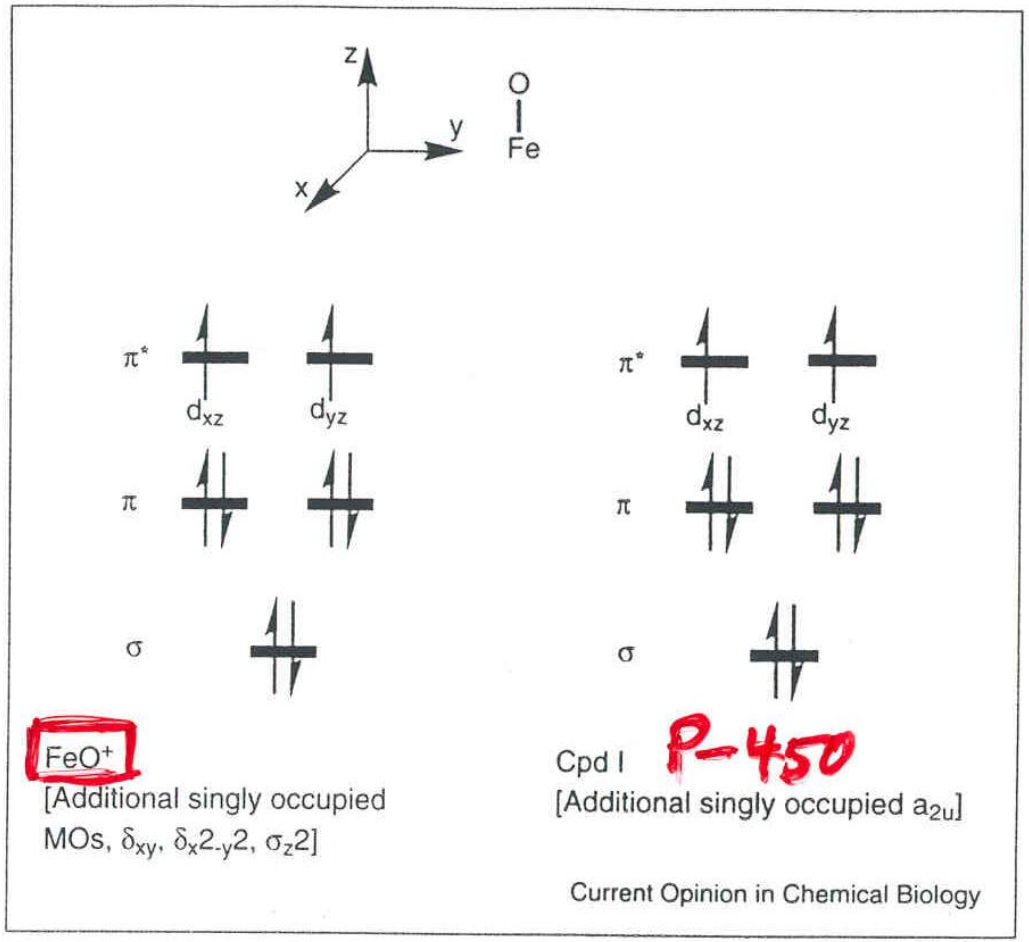


- Metall-Oxenoide als O-Atom Donoren
- Breite Substratpalette

- Beispiel: Cytochrom P-450



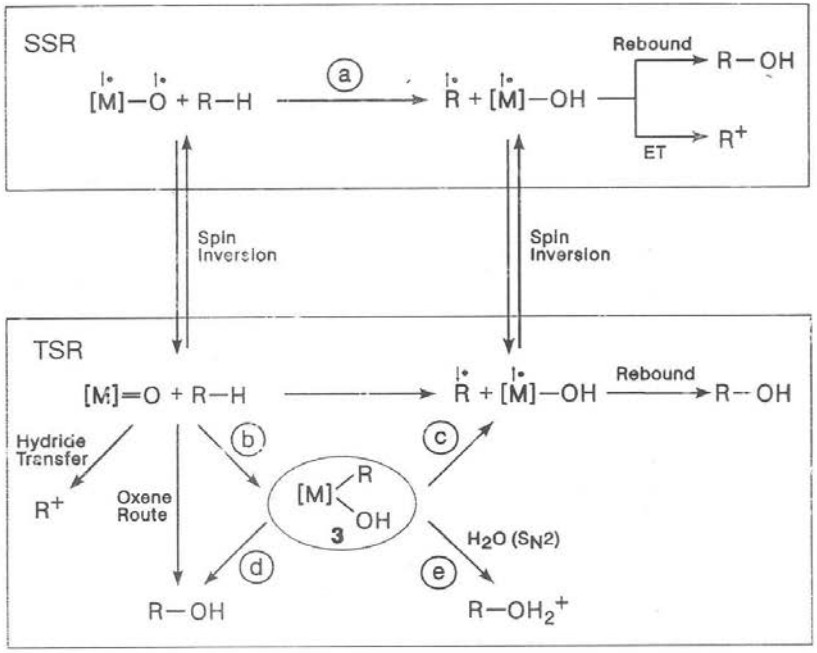
$[FeO]^+$



Bonding block orbitals of the ferryl (FeO) moieties of FeO^+ and Cpd I. The π and π* orbitals are made from appropriate combinations of the $3d_{xz,yz}(Fe)-2p_{x,y}(O)$ atomic orbitals. The σ orbital is made from the bonding combination of a $3d_{z^2}-4p_z-4s(Fe)$ hybrid and a $2p_z-2s(O)$ hybrid. Singly occupied nonbonding orbitals of FeO^+ and the porphyrin-based orbital of Cpd I, which are not shown, are indicated in brackets below the orbital diagrams.

TSR bei Cytochrom P-450

Konkurrenz von SSR- und TSR-Routen bei Cytochrom P-450



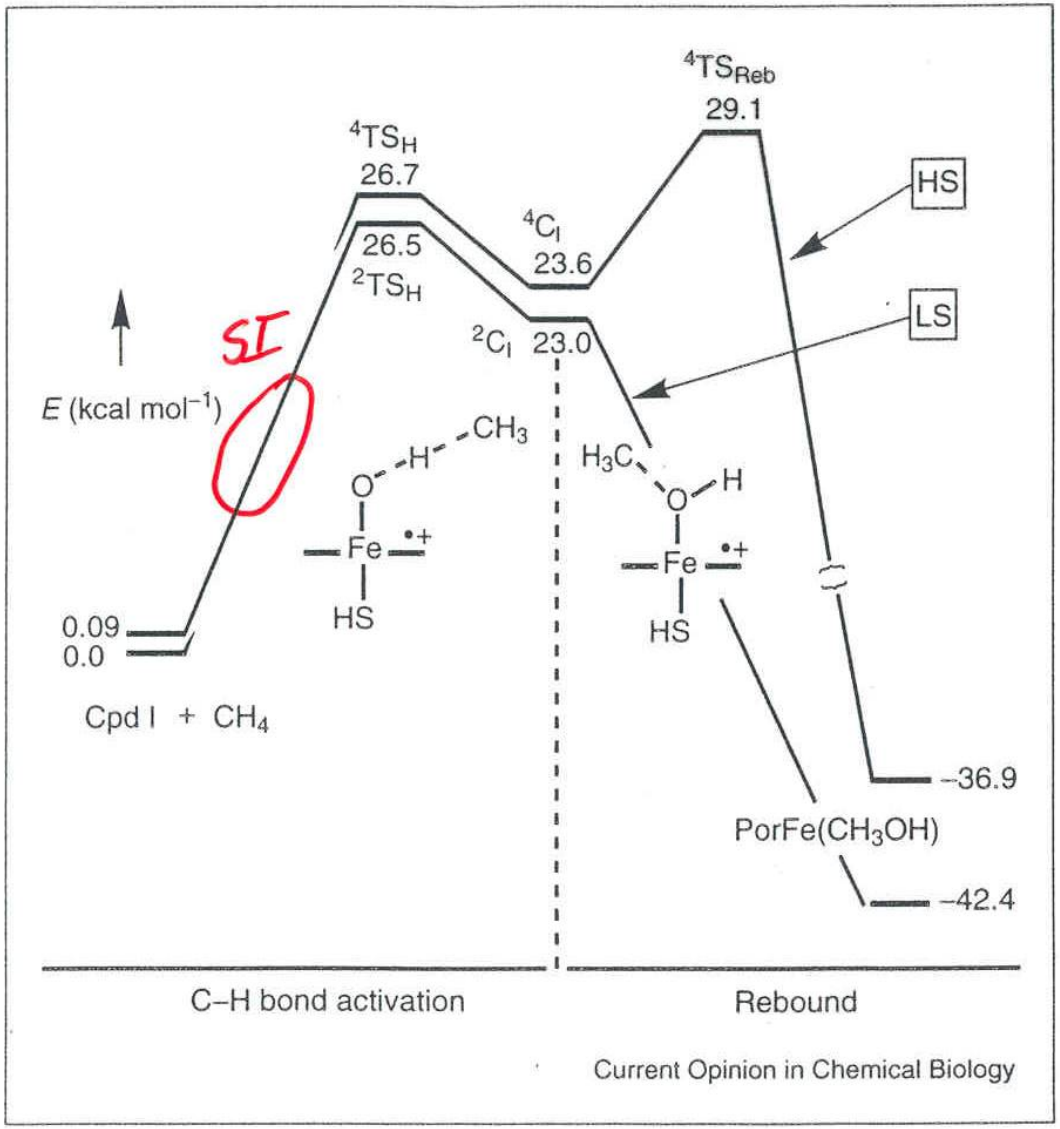
SSR: Nur radikalische Reaktion

TSR: Auch konzertierte Pfade

☞ Spin-Inversion wirkt als mechanistischer Distributor

Rolle von ax. S-Liganden

Natur der R-H-Bindung



Calculated reaction profiles and barriers (in kcal mol^{-1}) for CH_4 hydroxylation by Cpd I [20••,44•]. The rebound phase is shown starting from the cluster in its rebound position.

J|A|C|S ARTICLES

2004, 126, 4017

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Quantum Mechanical/Molecular Mechanical Investigation of the Mechanism of C−H Hydroxylation of Camphor by Cytochrome $P450_{cam}$: Theory Supports a Two-State Rebound Mechanism

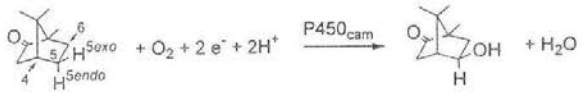
Jan C. Schöneboom,† Shimrit Cohen,‡ Hai Lin,† Sason Shaik,*,‡ and Walter Thiel*,†

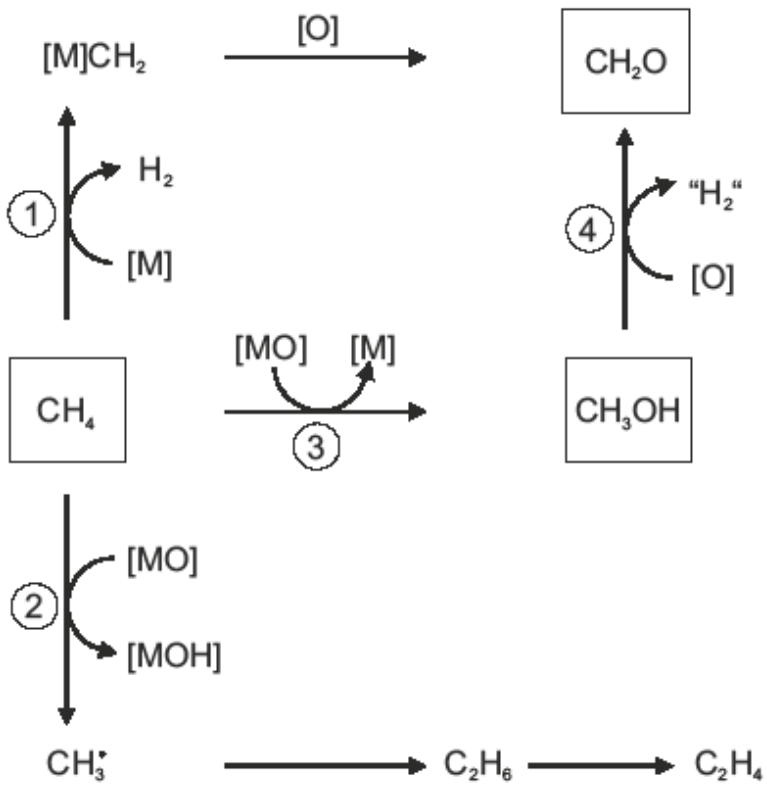
Contribution from the Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim an der Ruhr, Germany, and the Department of Organic Chemistry and the Lise Meitner Center for Computational Quantum Chemistry, The Hebrew University, 91904 Jerusalem, Israel

Received November 28, 2003; E-mail: (W.T.) thiel@mpi-muelheim.mpg.de; (S.S.) sason@yfaat.ch.huji.ac.il

Abstract: The stereospecific cytochrome P450-catalyzed hydroxylation of the $C^5-H^{(5-exo)}$ bond in camphor has been studied theoretically by a combined quantum mechanical/molecular mechanical (QM/MM) approach. Density functional theory is employed to treat the electronic structure of the active site (40−100 atoms), while the protein and solvent environment (ca. 24 000 atoms) is described by the CHARMM force field. The calculated energy profile of the hydrogen-abstraction oxygen-rebound mechanism indicates that the reaction takes place in two spin states (doublet and quartet), as has been suggested earlier on the basis of calculations on simpler models ("two-state reactivity"). While the reaction on the doublet potential energy surface is nonsynchronous, yet effectively concerted, the quartet pathway is truly stepwise, including formation of a distinct intermediate substrate radical and a hydroxo−iron complex. Comparative calculations in the gas phase demonstrate the effect of the protein environment on the geometry and relative stability of intermediates (in terms of spin states and redox electromers) through steric constraints and electronic polarization.

Scheme 1





Scheme 1

"It remains a source of frustration to know so much about the reactions of transition-metal ions with hydrocarbons and yet have so many questions remain unanswered."

P. B. Armentrout & J. L. Beauchamp, 1989

15

Ein Baguette ist mehr
als die Summe seiner Krümel

"There is no science
without fancy,
and no art without
facts..."

Vladimir Nabokov

DANK

Mein Werk ist das eines
Kollektivwesens, und es
trägt den Namen Goethe

1832 — der 82jährige
J. W. v. G.

THANKS ARE DUE TO:

Akkök, S.; Aliaga-Alcalde, N.; Allison, J.; Allspach, T.; Altau, G.; Altenbach, J. J.; Amer, I.; Anders, E.; Andrade, J. G.; Andrews, L.; Anklam, E.; Annen, U.; Apeloig, Y.; Arad, D.; Armélin , M.; Armentrout, P. B.; F. Arnold; Aschi, M.; Asmis, K. R.; Asmus K. D.; Ast, T.; Audier, H.-E.; Azran, Z.; Baer, T.; Baik, M.-H.; Bally, T.; Baranov, V. I.; Bärsch, S.; Beaudet, S.; Beck, A.; Becker, G.; Becker, H.-J.; Beckhaus, H. D.; Bender, B. R.; Bentley, T. W.; Berendsen, G. E.; Berger, R.; Beye, N.; Beyer, M. K.; Biali, S. E.; Blanksby, S.; Blech, S. K.; Blender, J. M.; Blisse, A.; Blomberg, M. R. A.; Blum, J.; Blum, O.; Blum, W.; Bobrich, M.; Boche, G.; Bohlmann, F.; Böhme, D. K.; Böhme, T.; Boldyrev, A.; Boyd, J. P.; Borchers, F.; Borisenko, K. B.; Bornowski, H.; Bowen, R. D.; Bowie, J. H.; Božović, A.; Brancks, N.; Brehm, M.; Brönstrup, M.; Broschag, M.; Brown, R.; Buchman, O.; Budzikiewicz, H.; Burgers, P. C.; Butschke, B.; Callahan, J. H.; Campbell, Cao, Y.; E. E. 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