VB Workshop, Paris
July 17-21st, 2012

The Valence Bond Way in Chemistry

Sason Shaik, The Hebrew University

- In 1977, when I started using VB theory to understand chemical reactivity, the VB landscape was barren, and there were very few groups which were still practicing this “ancient” art in Chemistry.
- At those times, it was inconceivable to think about a sizable meeting dedicated to VB theory. So, in many ways, this workshop is a historical event. As such, I wish to express my warmest thanks to the local organizing committee who has made this meeting possible (Benoit, Etienne, Francois). Benoit Braida conceived the idea to organize such a meeting, initiated the funding proposal to SECAM, and baby-sat the organization. For him and his colleagues Chapeau!

The Computational Paradise

Computational chemistry has at its disposal wonderful tools:

- **CCSD(T), CASPT2, Gn (n=3,…), Wn (n=1-4), etc. Can compute with accuracy of sub-kcal/mol.**
- **DFT, DFT/MM can probe all transition metal chemistry and enzymes with accuracy of ± 3 kcal/mol.**

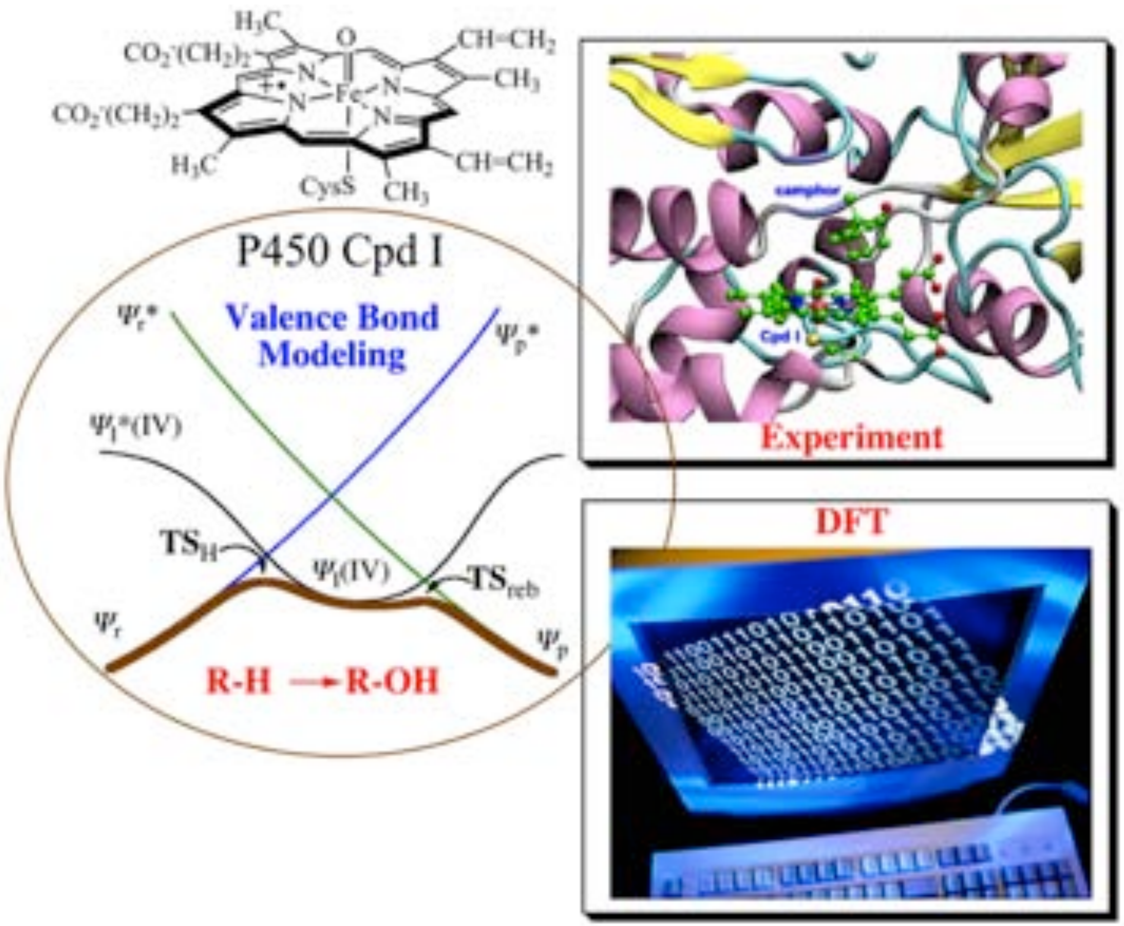
••• The sky is the limit, chemistry has entered paradise!

- **But even in Paradise, understanding and insight are essential. Or, as put so beautifully by Eugene Wigner: “*I am very glad the computer understands this. But I would like to understand it too*”**
- **Charles Coulson put it very provocatively in his famous “nightmare speech”: “*Give us insight not numbers*”**

My talk in this workshop consists of two main stories, and a few shorter ones, which try to follow Coulson’s dictum

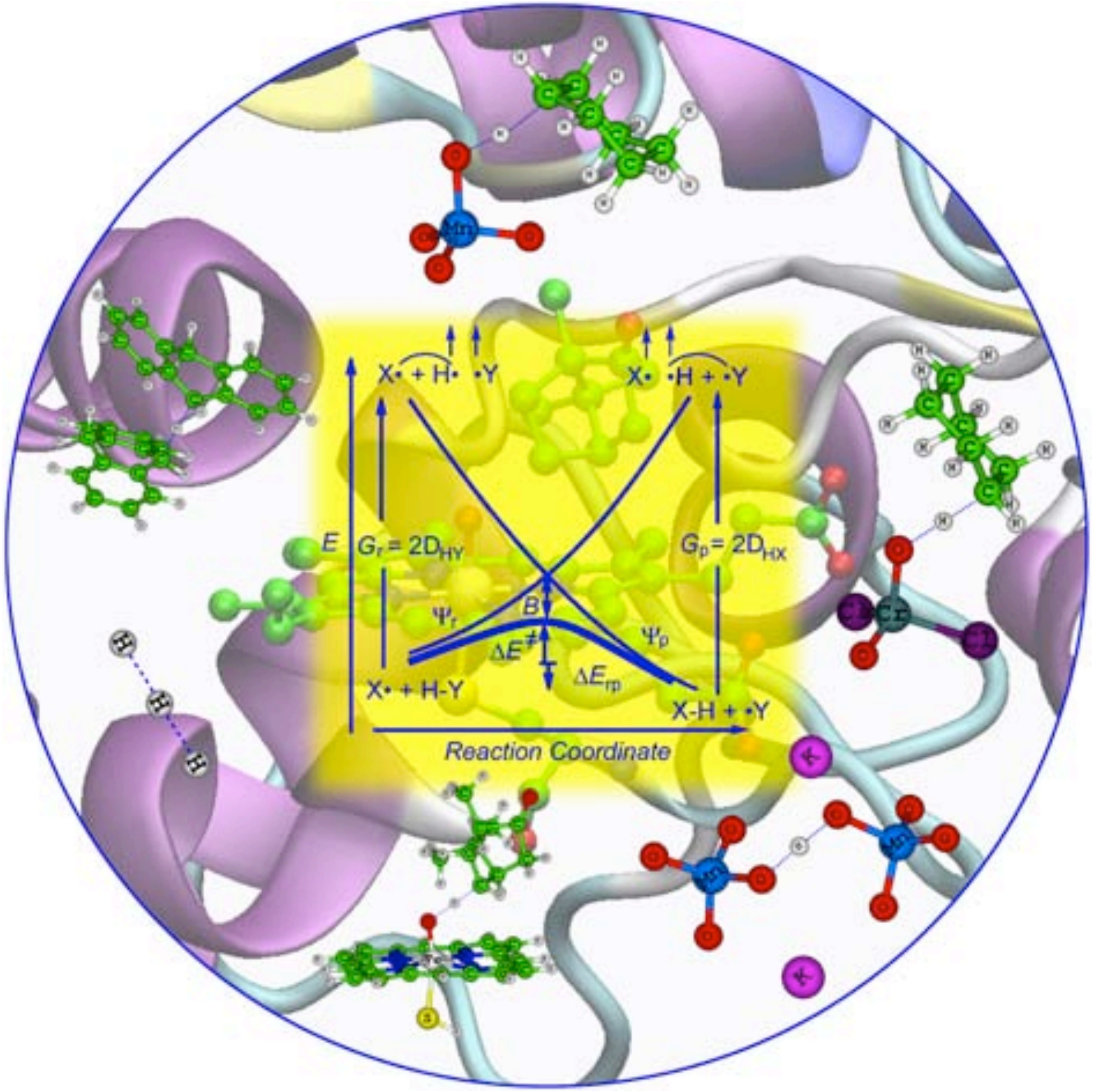
- The first main story will focus on the enzyme cytochrome P450, and its key oxidative reactions.

- In telling this story, I shall try to show that VB modeling is a perfect interface between experiment & computations:



- It creates order, predicts mechanisms, and enables to estimate barriers from raw data

- In the second main story, I shall attempt to demonstrate how the VB model creates unity for one of the most fundamental oxidative reactions in nature, the hydrogen atom transfer reaction; going from H + H_2 all the way to P450 hydroxylation…



Short Stories

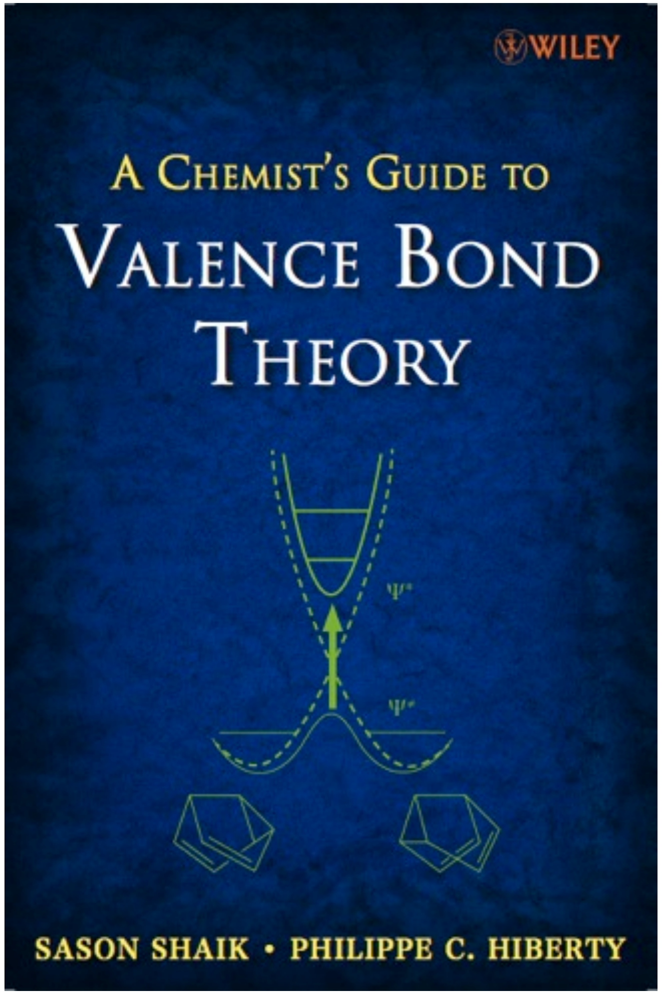
- Highlights of intermediate states
- Thinking about photochemical reactions
- VB reading of complex wave functions

However, before I can tell any of these stories, it is necessary to introduce some basic elements of VB Theory.

- **To this end, I will refer frequently to the recent textbook Philippe and I have written on VB theory.**

- **In addition to textual material, the book contains problem sets and answers for each chapter.**

- **There are three inspection copies, which are available to the participants of the Workshop.**

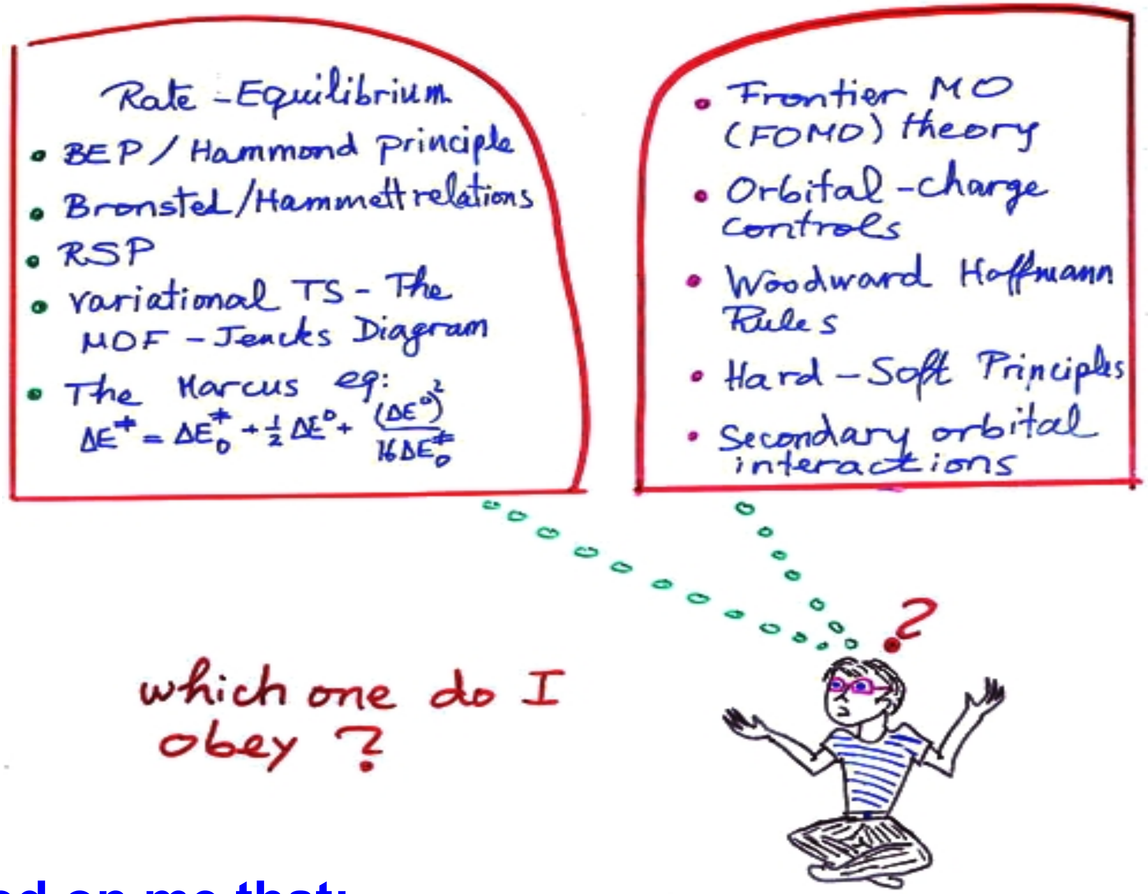


WILEY

A CHEMIST'S GUIDE TO
VALENCE BOND
THEORY

SASON SHAIK • PHILIPPE C. HIBERTY

How Has the Long VB Odyssey Begun for Me?



At some point it dawned on me that:

To Understand Chemical Reactivity one Must First Understand the Mechanism of Barrier Formation. This will Generate the Factors Governing Reactivity and will enable a unified understanding of reactivity. But…

- But, as a devout fan of MO theory I was concerned because with the exception of “forbidden reactions” MO theory gave no clue as to the mechanism of barrier formation.

- After scratching my head I started to decompose MO and MO-CI wave functions into wave functions based on fragment orbitals.

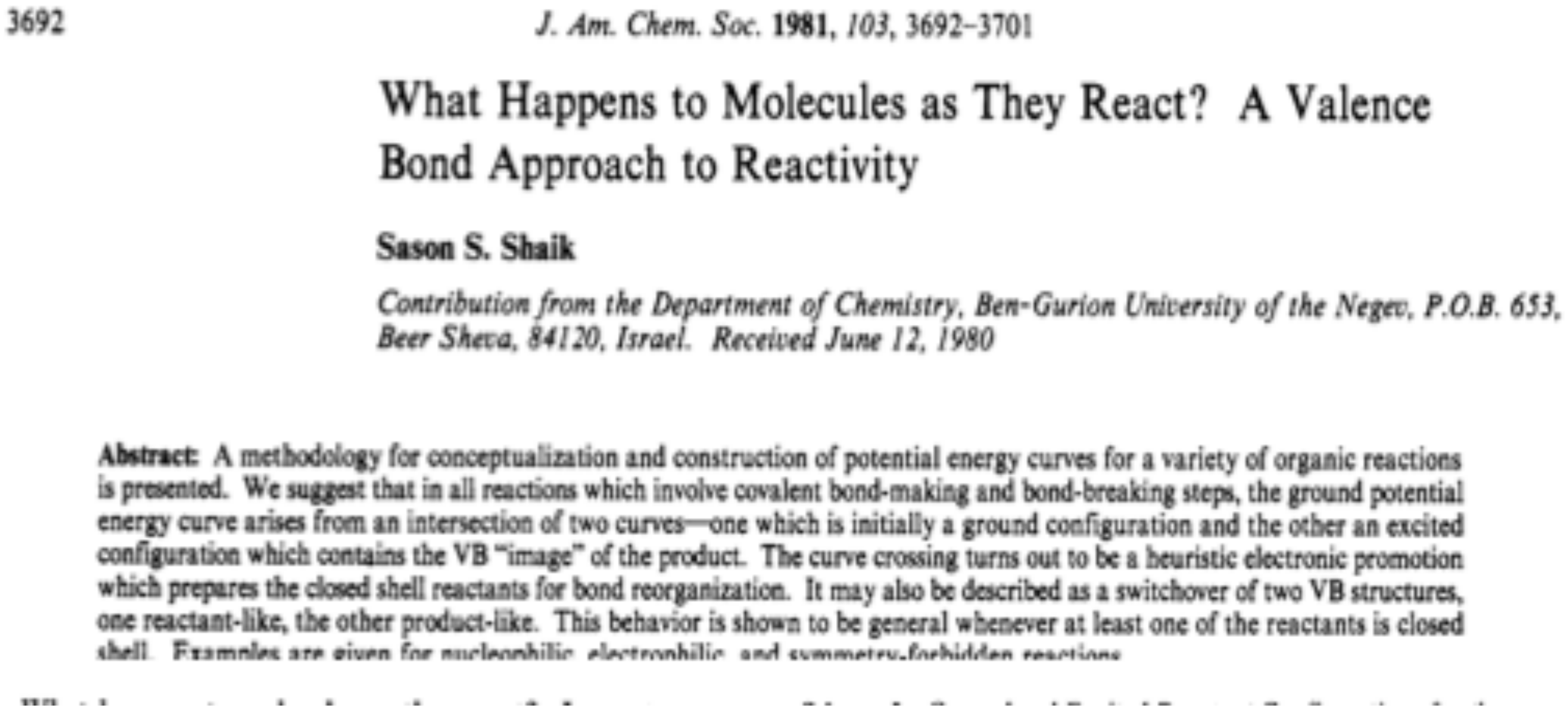
- At the beginning this was just an act of despair, sort of, “let’s see what will happen if…”.

- But as time went by, I realized that what I was doing was simply mapping the MO-based wave functions into a collection of VB-structures, with different weights (W_i):

$$\Psi_{\text{MO-CI}} \rightarrow \Sigma_i[w_i\Psi_{\text{VBS},i}]$$

- But more so, while doing that I found something very beautiful and general about the mechanism of barrier formation and electron reorganization in chemistry.

My excitement is quite clear from the title I have chosen for the paper, “What Happens to Molecules as They React?”



3692 J. Am. Chem. Soc. 1981, 103, 3692–3701

What Happens to Molecules as They React? A Valence Bond Approach to Reactivity

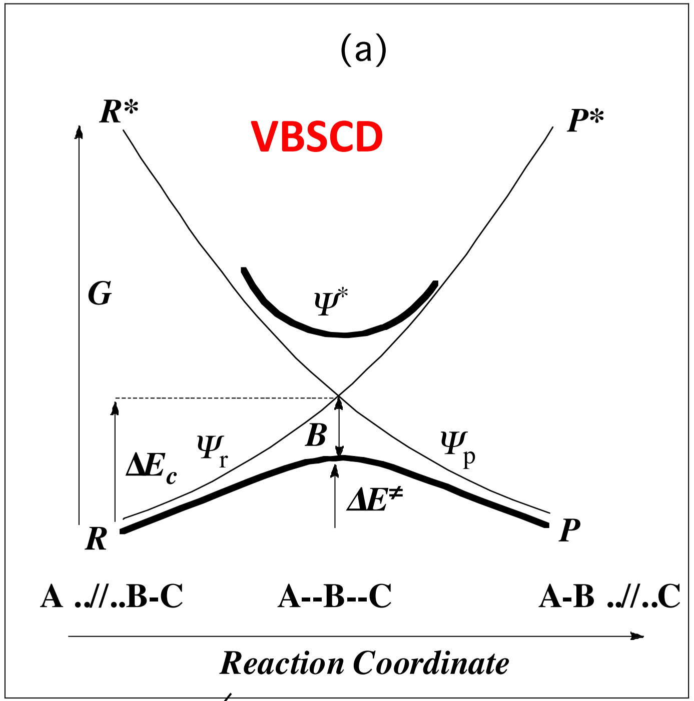
Sason S. Shaik

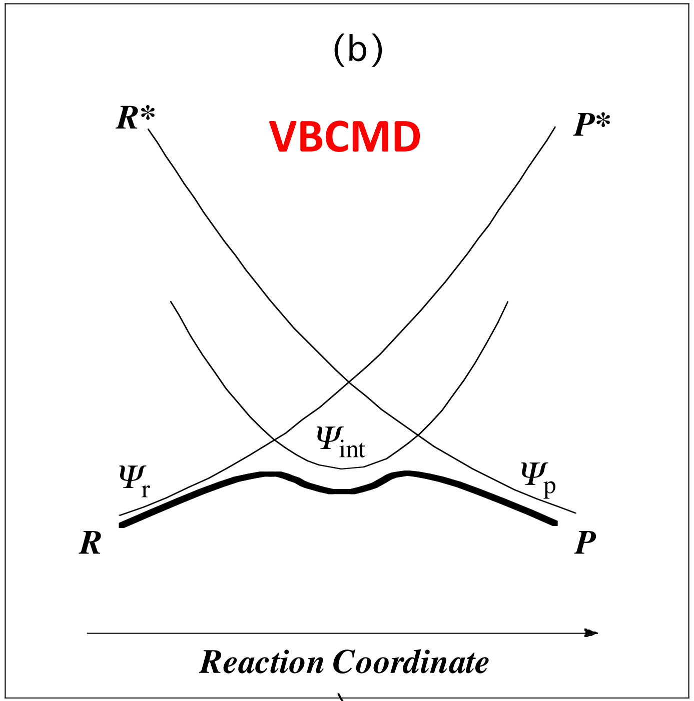
Contribution from the Department of Chemistry, Ben-Gurion University of the Negev, P.O.B. 653, Beer Sheva, 84120, Israel. Received June 12, 1980

Abstract: A methodology for conceptualization and construction of potential energy curves for a variety of organic reactions is presented. We suggest that in all reactions which involve covalent bond-making and bond-breaking steps, the ground potential energy curve arises from an intersection of two curves—one which is initially a ground configuration and the other an excited configuration which contains the VB "image" of the product. The curve crossing turns out to be a heuristic electronic promotion which prepares the closed shell reactants for bond reorganization. It may also be described as a switchover of two VB structures, one reactant-like, the other product-like. This behavior is shown to be general whenever at least one of the reactants is closed shell. Examples are given for nucleophilic, electrophilic, and symmetry-forbidden reactions

Even the refereeing process which took well over a year did not diminish my excitement that I was on a verge of “understanding” chemical reactivity.

The MO-VB mapping gave two archetypal diagrams that describe the major reactivity patterns in ANY reaction: All The "*Tora on a single foot*", or "in a nutshell":



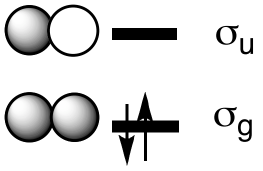


- Barrier formation in a single chemical step
- *R** is an FO-VB configuration in which the reactants are prepared for bonding to become *P*

- A Stepwise mechanism derived from a low-energy VB structure, which defines an intermediate.
- Internal catalysis

We will come back to these diagrams later. Let me digress at the moment and recall what you heard yesterday on the MO / VB relationship and what is the mapping good for?

- **Consider the simplest case of the H_2 molecule:**



$H_a—H_b$

$\Psi_{MO} = |\sigma_g(1)\overline{\sigma_g(2)}|$

$\Psi_{MO\text{-}CI} = |\sigma_g(1)\overline{\sigma_g(2)}| - c\bullet|\sigma_u(1)\overline{\sigma_u(2)}|$

Ψ_{MO} ⇩ $\sigma_g = a + b$

$\Psi_{MO\text{-}CI}$ ⇩ $\sigma_u = a - b$

$|a(1)\overline{b(2)}| - |\overline{a(1)}b(2)|$ $\quad |a(1)\overline{a(2)}| + |b(1)\overline{b(2)}|$

$(1+c)\{|a(1)\overline{b(2)}| - |\overline{a(1)}b(2)|\}$ $\quad (1-c)\{|a(1)\overline{a(2)}| + |b(1)\overline{b(2)}|\}$

Φ_{cov}	$\Phi_{ion(1)}$	$\Phi_{ion(2)}$	$(1+c)\Phi_{cov}$	$(1-c)\Phi_{ion(1)}$	$(1-c)\ \Phi_{ion(2)}$
$H_a\bullet\text{---}\bullet H_b$	$H_a{:}^-\ \ H_b^+$	$H_a^+\ \ {:}H_b^-$	$H_a\bullet\text{---}\bullet H_b$	$H_a{:}^-\ \ H_b^+$	$H_a^+\ \ {:}H_b^-$

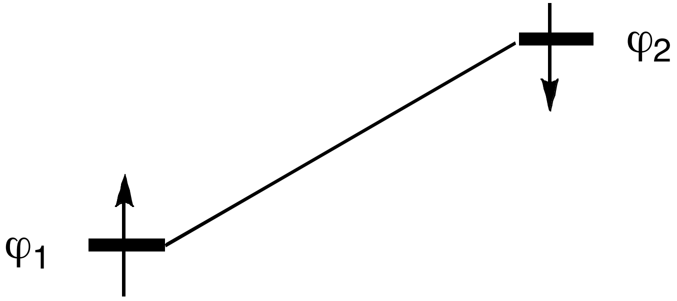
- **Thus, MO-VB mapping shows that the H-H bond is described mainly by a covalent structure with a smaller contribution from the ionic structures.**

What is so special about covalent structures?

The Covalent Structure of an A-B bond

$$\Phi_{cov} = N[|\phi_a\overline{\phi_b}| - |\overline{\phi_a}\phi_b|] = \phi_a(1)\phi_b(2)\{\alpha(1)\beta(2) - \beta(1)\alpha(2)\}$$

A Genral Bond Pair



$$\Phi_{1\text{-}2} = |\varphi_1(1)\overline{\varphi_2}(2)| - |\overline{\varphi_1}(1)\varphi_2(2)|$$

- The covalent structure couples the two spins to singlet state. It is stabilized by resonance and it minimizes e-e repulsion. Hence, the covalent structure dominates the wave function of polar-covalent bonds.

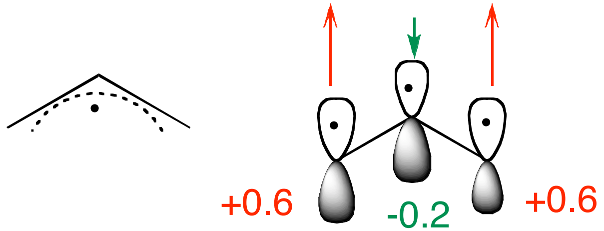
- We can take any two singly occupied orbitals couple their spins to generate a general bond-pair. Note that the orbitals are of general type and can be FOs or AOs, etc.

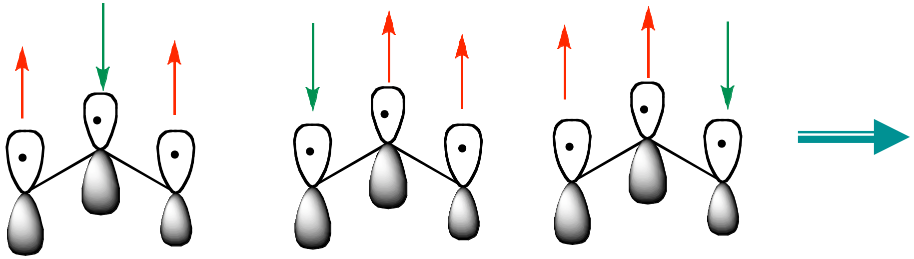
- It is possible to state that generally any MO or MO-CI wave function can be mapped into a set of VB structures

Is there any added benefit of looking at VB structures?

VB Structures provide immediate and lucid insight into chemical problems. Here is an example of the origins of spin polarization in allyl radical as emerging from EPR:

EPR





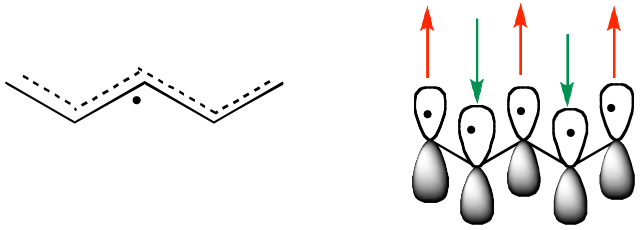
$|a\bar{b}c|$ $\quad$ $|\bar{a}bc|$ $\quad$ $|ab\bar{c}|$

$D_b = D_{QC}$ $\quad$ D_a $\quad$ D_c

- D_{QC} is spin-alternant, & hence having the lowest energy & it controls the spin density pattern, thus causing the spin-polarization.

$E_{rel} = 0$

The spin-alternant determinant of the pentadienyl radical shows that the negative spin density will now shift to the carbons flanking the central one. The next homolog will have it back on the central carbon, etc. So easy!

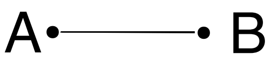


D_{QC}

How about VB interaction energies? Let’s recall what you heard from Philippe. Consider the interaction between two fragments A and B. This interaction depends on the spin coupling and the number of electrons.

- **Using a simple Hückel-type resonance integral β between the interacting orbitals, and S, their overlap we can write the following expressions:**

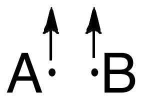
  - **Bonding energy:**



$E = 2\beta S$ **<0**

  - **Pauli Repulsion in VB Theory:**

Elementary Repulsion

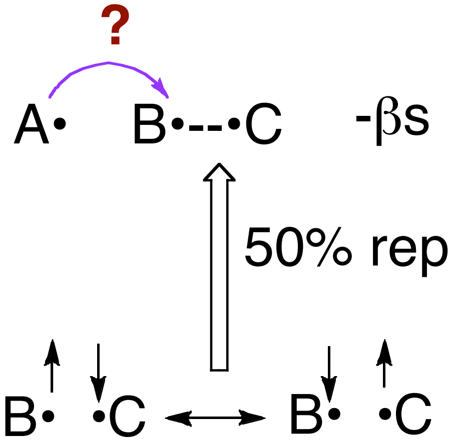


$-2\beta s$ **>0**

A: •B $-2\beta s$

A: :B $-4\beta s$

Nonbonded Interactions



$-\beta s$

It is seen that all the expressions are βS quantities multiplied by the number of electrons and having signs; positive for bonding and negative for repulsion. [VB Book, Ch. 3]

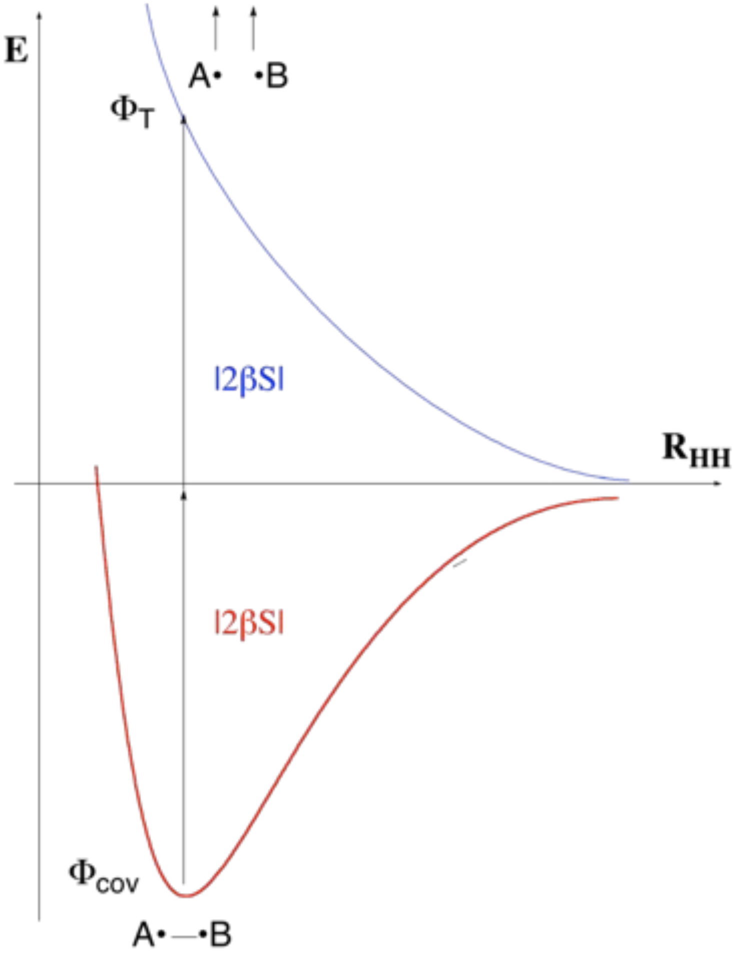
Something that will be useful to know is the Singlet –Triplet Excitation Energies in VB

- Consider A-B interaction with two electrons:
- As we just saw, the singlet and triplet energies are given as ±2βS.
- If we equate $D_{AB} = |2\beta S|$,

then ΔE_{ST} which is 4βS will be $\sim 2D_{AB}$

- If we include overlap in the normalization factors of the VB wave functions (e.g., *S* = 0.5), we will get that:

$2D_{AB} \sim \frac{3}{4}\,\Delta E_{ST}$

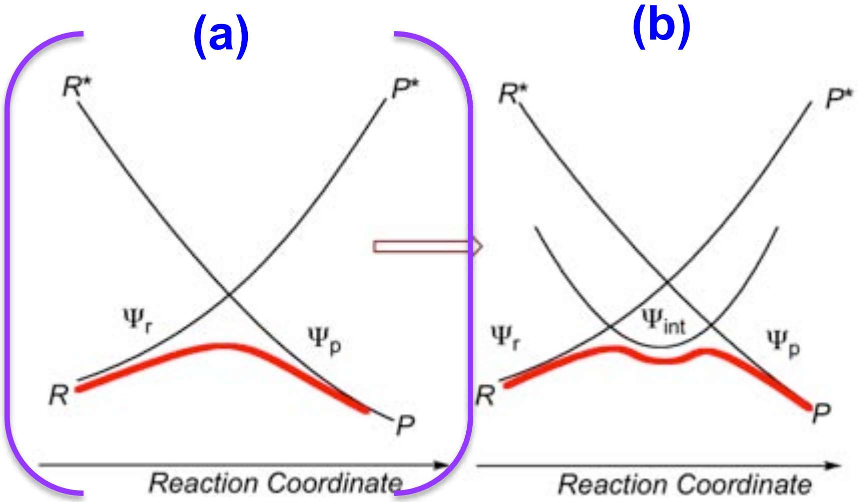


- Please note that in any event, the S→T excitation is related to the vertical bond strength D.

Let me return now to the conceptual tools with which we wish to look at reactivity:

These are two diagrams, which are based on VB-state correlations, which I introduced in the 1981 JACS paper to comprehend reactivity:

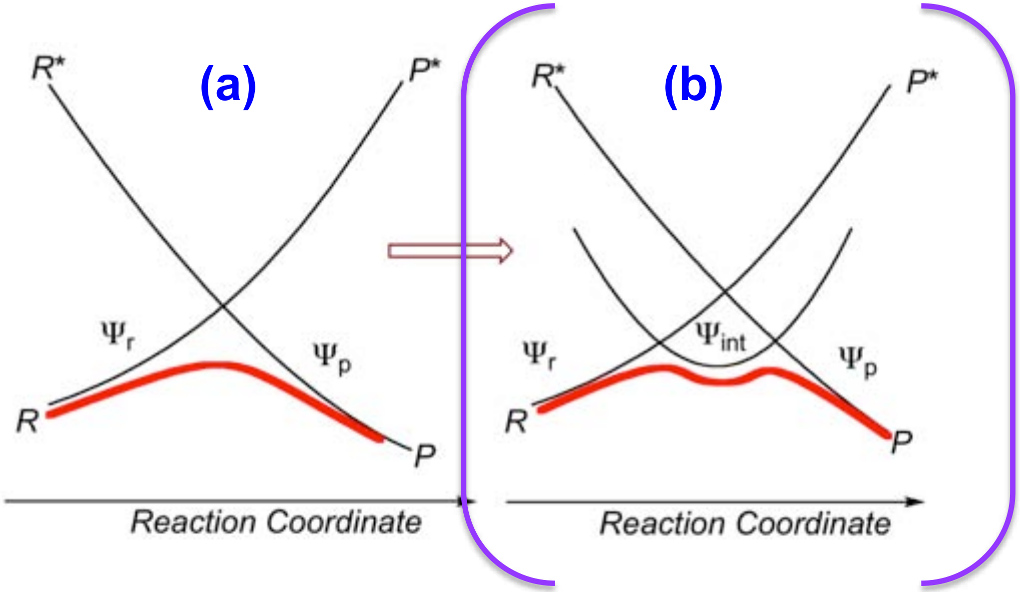
- **Diagram (a), which is called VBSCD, shows two state curves of reactants (R) & products (P) that intersect and mix to form the barrier and the TS for an elementary process.**



- **The state-curves of the VBSCD have two ground states that correlate to two excited states, *R** and *P**. These excited states are promoted electronic images of the ground states with which they correlate. So, the promoted states prepare the ground states for the bonding changes from *R* to *P*.**

The VB Configuration Mixing Diagram (VBCMD) in (b) is a bit more complex:

- Here, an intermediate state curve crosses the two principal curves, and the three-state mixing leads to a stepwise mechanism with an intermediate.
- The intermediate state has electronic structure different than that of *R* and *P*.

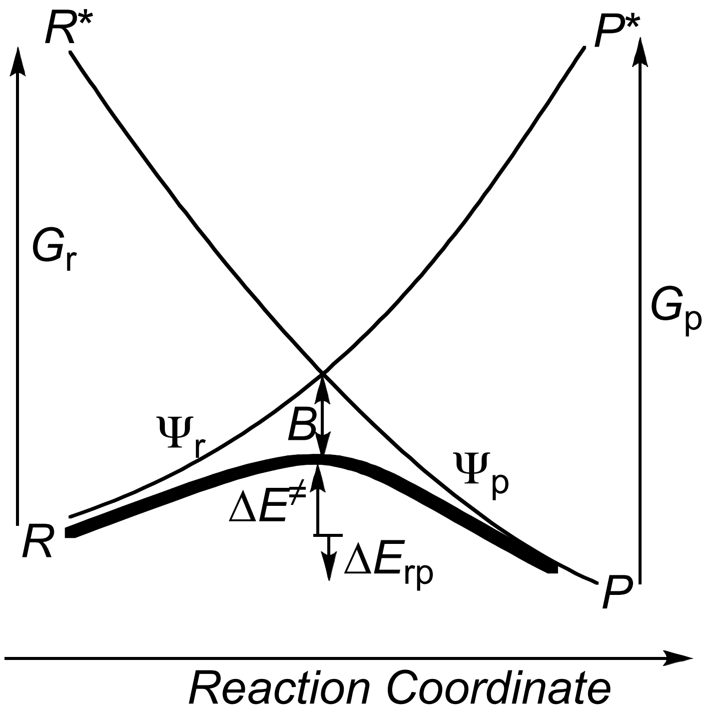


- Taken together the two diagrams can model a gamut of reactivity patterns, for all reaction types:
  - My collaborators and I have applied these diagrams to organic chemical reactions, inorganic chemical reactions, clusters, and metalloenzymes.

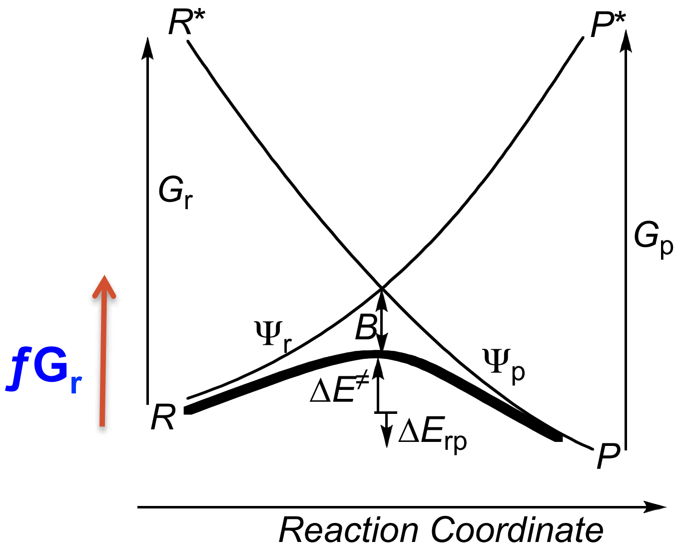
- Very much in parallel, Arieh Warshel has developed the EVB method and has applied similar diagrams as key tools for free energy simulations of enzymatic biochemical reactions.

A Few Words About the Promoted States in the VBSCD:

- **For example, in the promoted state *R**, we undo the pairing of the electrons in those bonds of *R* that have to be broken during the reaction, while we re-couple these electrons as in *P*. This prepares *R** to correlate to *P* & the same applies for *P** correlating to *R*.**
- **G_r and G_p are the promotion energies of reactants and products.**
- **B is the resonance energy of the TS due to the VB mixing at the crossing point.**



We can also derive barrier expressions from the VBSCD, by using the promotion energies, *G*, and the resonance energy of the TS, *B*, as a basis for such expressions:



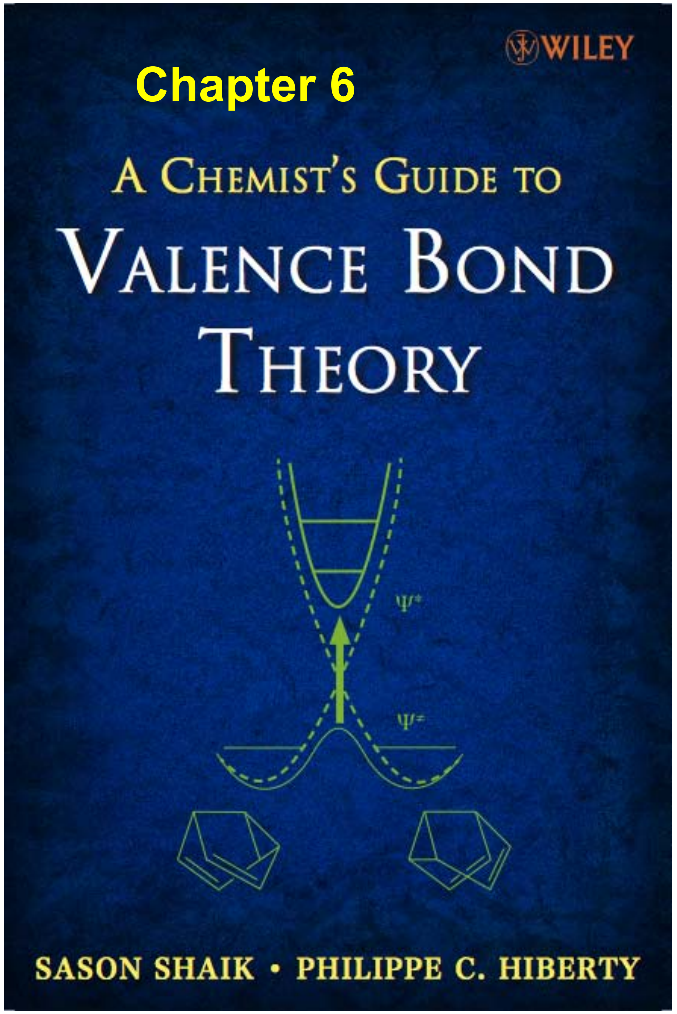
- The simplest expression is: $\Delta E^{\ddagger} = fG_r - B$

fG_r = the height of the crossing point at the reactant side.
It gauges the total deformation and repulsive interactions the reactants have to experience in order to achieve resonance with the product.

- A more explicit expression takes into account the reaction energy, the average promotion gap, G_0, and the average of the f factors, f_0:

$$\Delta E^{\ddagger} \approx f_0 G_0 - B + 0.5\,\Delta E_{RP} + 0.5\,\Delta E_{RP}^2/G_0$$

- Clearly, in order to apply the VBSCD to predict reactivity patterns in specific reactions, we need to learn how to construct the diagram from the VB building blocks and how to identify *R** and *P**, and assess G, B and *f* as well.
- This is done in great detail in Chapter 6 in the book, as well as in the reviews that are recommended on the website. You will also get some tutoring on that during the workshop.
- However, what I wish to do now is to bypass the detailed construction process and provide you with simple qualitative rules that allow to assign the promoted states for any desired reaction, and use the *G*'s to make quick assessment of reactivity



These rules are based on whether or not the oxidation states of the fragments change during the reaction.

To use the Rule, draw the covalent structures of reactants and products and count the number of electrons on each fragment. If this number changes, then the oxidation state changes, and vice versa if the number does not change.

Let us apply the rule to two archetypical reactions:

- **Here are the covalent structures for a H-abstraction reaction. It is apparent that there is no change in the oxidation sate of X, H, and Y:**

$$\mathrm{X}\bullet + \mathrm{H}\bullet\!-\!\bullet\mathrm{Y} \longrightarrow \mathrm{X}\bullet\!-\!\bullet\mathrm{H} + \bullet\mathrm{Y}$$

- **And here are the covalent structures for a proton-abstraction reaction. It is apparent that here X and Y change their oxidation states. In the forward reaction $\mathrm{X}:^{-}$ is reduced while •Y gains an electron, and vice versa in the reverse reaction:**

$$\mathrm{X}:^{-} + \mathrm{H}\bullet\!-\!\bullet\mathrm{Y} \longrightarrow \mathrm{X}\bullet\!-\!\bullet\mathrm{H} + \mathrm{Y}:^{-}$$

Once the oxidation states are assigned, this determine the nature of *R (*P**) and of the corresponding promotion energies:**

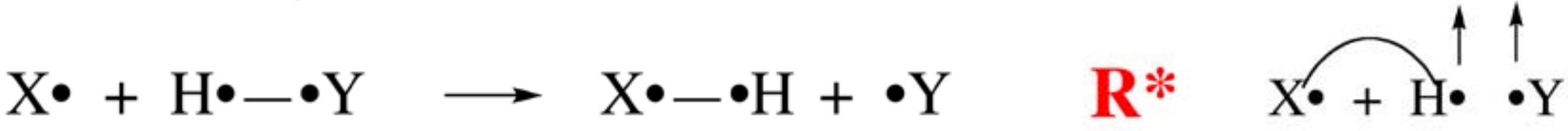
If you repeat the process for many other reactions, you will soon discover that the Promoted States in the VBSCD Involve two Elementary Excitations, depending on whether there are or aren’t changes in the oxidations states of the fragments:

- **The 1st Elementary Excitation**

Rule 1: No change in the oxidation state:

For reactions, which do not involve changes in the oxidation states of the reacting fragments, the bonds that are broken during the reaction are decoupled in the promoted state *R, to their triplet states, and the electrons are paired anew as in *P*.**

- **For example, in the H-abstraction reaction the *R** state would be the following:**



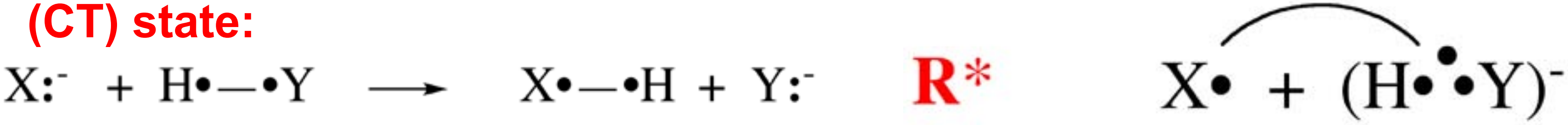
- **The corresponding promotion energy would then be given by the singlet-to-triplet decoupling energy of the bond electrons:**

$$G_r \sim \Delta E_{ST}(H\text{-}Y) \text{ and } G_p \sim \Delta E_{ST}(H\text{-}X)$$

The 2nd Elementary Excitations:

- **Rule 2:** **The fragments change their oxidation state during the reaction:**

For reactions, which involve changes in the oxidation states of the reacting fragments, the promoted state *R involves a charge transfer from the fragment that gets oxidized (losing 1e) to the fragment that gets reduced (gaining 1e). For example, in the proton-abstraction reaction *R** is the following charge-transfer (CT) state:**



$$X:^- + H\bullet\!-\!\bullet Y \longrightarrow X\bullet\!-\!\bullet H + Y:^- \qquad R^* \qquad X\bullet + (H\bullet\,\bullet Y)^-$$

It involves electron transfer from X:⁻ to the H-Y bond, while spin-pairing the electron on the X• with the excess electron in (HY)⁻ .

- **The corresponding promotion energy would then be the difference between the ionization potential (IP) of the anion and the electron affinity (EA) of the molecule:**

$$G_r = IP_{X:} - EA_{(H\text{-}Y)} \quad \text{and} \quad G_p = IP_{Y:} - EA_{(H\text{-}X)}$$

Let me illustrate now the use of the promotion energy in the VBSCD for making quick assessments of reactivity.

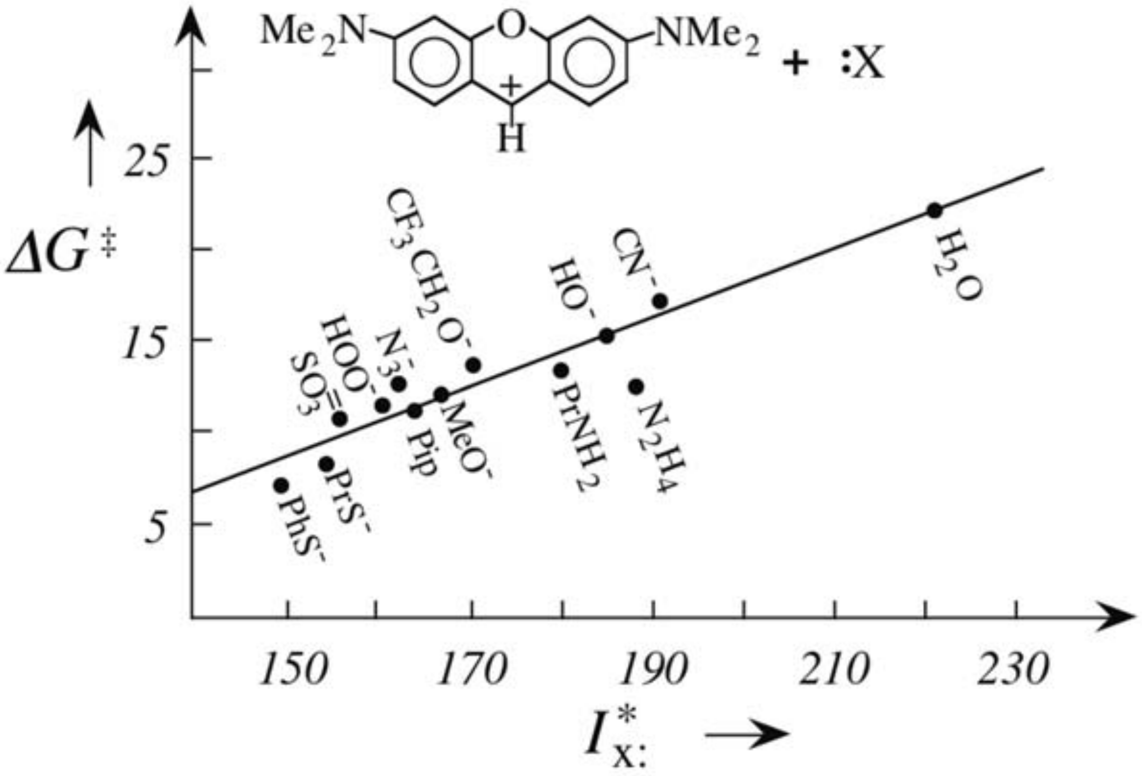
To do that, I have chosen three examples, out of the many given in the book (chapter 6) and the reviews.

Consider now the anion-cation recombination reaction $X:^{-} + R^{+} \rightarrow X\text{-}R$

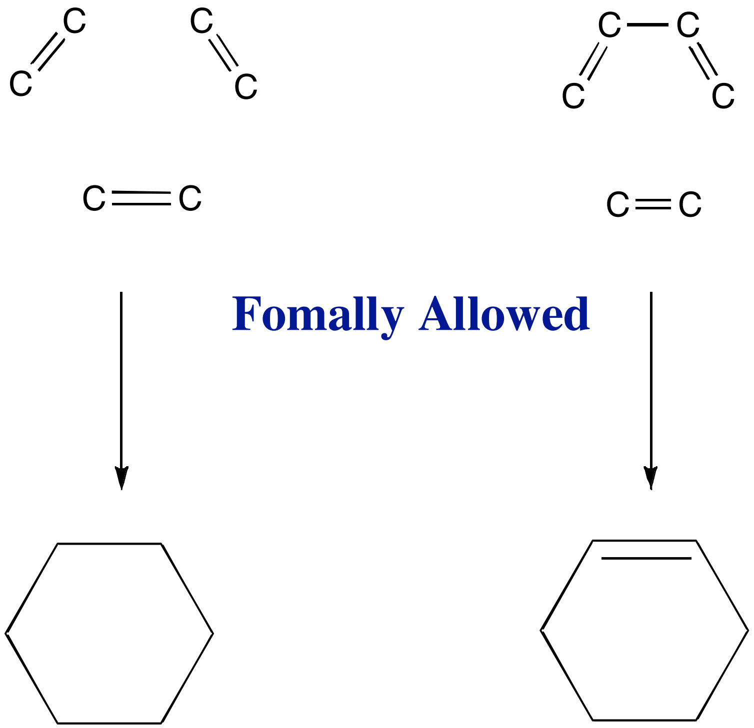
Since there are changes in the oxidation numbers of the fragments, the promoted state in the VBSCD is a vertical charge-transfer state, and,
$G_{CT} = IP_{X:}^{*} - EA_{R+}^{*}$

- **For a reaction series where the carbocation is common (Y-pyronin), the only variable of G_{CT} is the vertical ionization potential of the nucleophile $X:^{-}$**

- **Here is a plot of the experimental free energy barriers in aqueous solution vs. the vertical ionization potential of the anion $X:^{-}$ in the same solvent.**
- **Note the order brought by the VBSCD to the concept of nucleophilicity.**



Consider now the following two reactions which are both WH-allowed:



ΔH = -67 kcal/mol

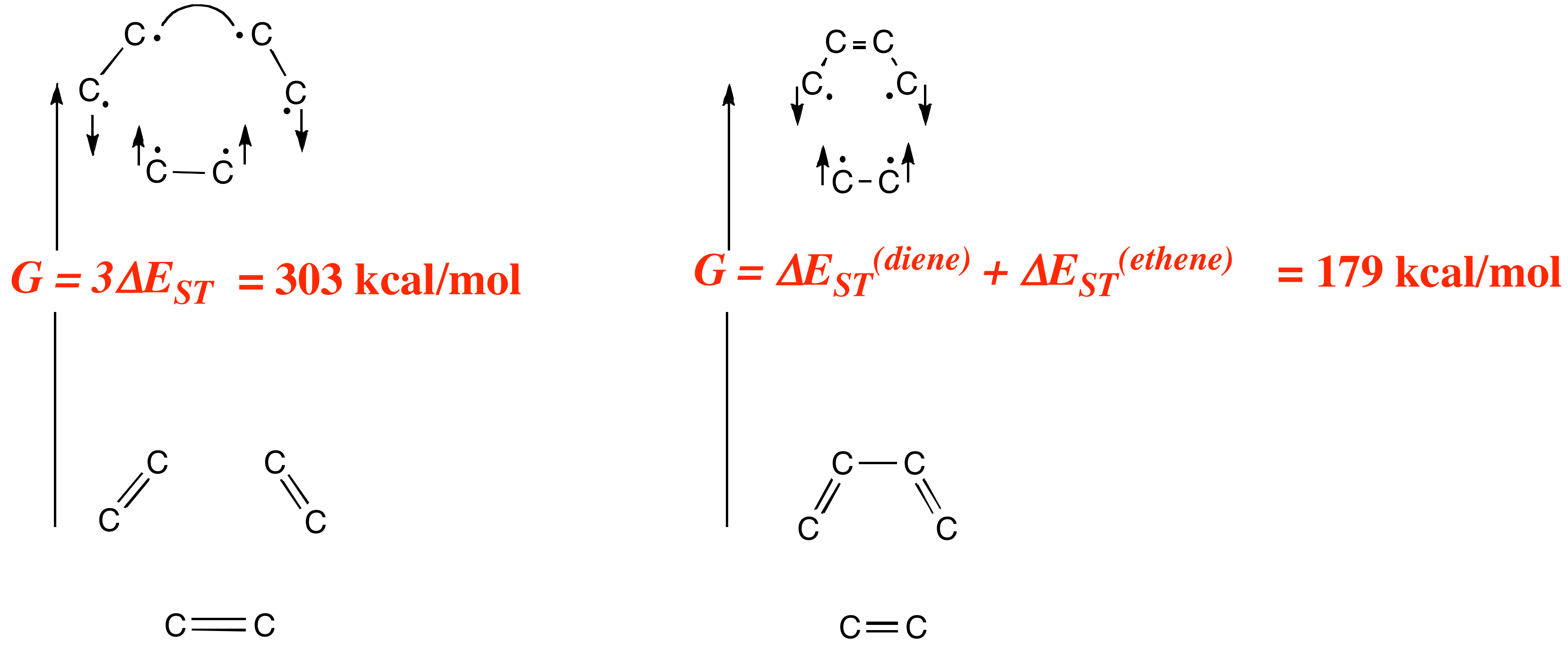
ΔH = -44 kcal/mol

$\Delta H^{\neq} = 49$ kcal/mol

$\Delta H^{\neq} = 22$ kcal/mol

It is seen that the reaction with the higher thermodynamic driving for has strangely a much larger reaction barrier. Why?

Since there are no redox changes, the *promotion energies* in the VBSCDs of the two reactions are singlet-triplet decoupling of the bonds that break during the reaction:

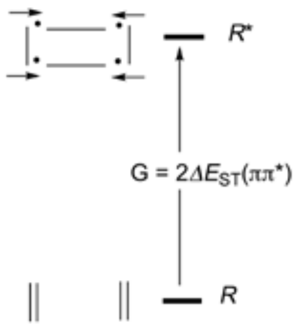


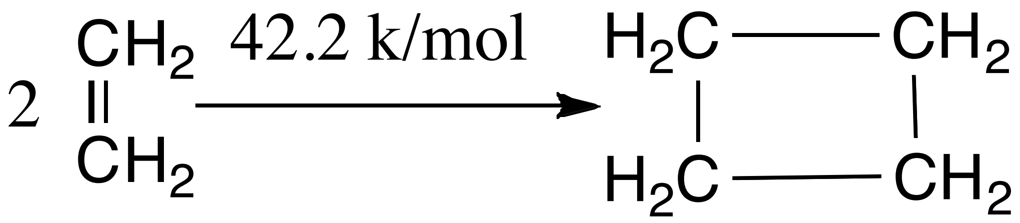
$G = 3\Delta E_{ST} = 303$ kcal/mol

$G = \Delta E_{ST}^{(diene)} + \Delta E_{ST}^{(ethene)} = 179$ kcal/mol

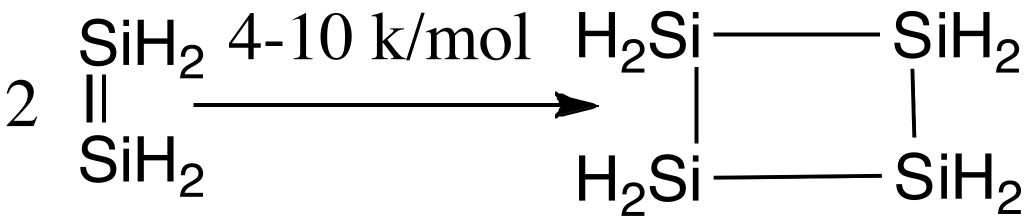
- **The barriers difference is due to the huge G value for the 2+2+2 reaction. The difference in the G's is due to ΔE_{ST} of the diene which is only 78 kcal/mol compared with 202 for two ethene molecules.**
- **If we take for example *f* = 0.25-0.3, then the difference of 124 kcal/mol in *G* values will predict correctly that the Diels Alder reaction should have a lower barrier than the 2+2+2 reactions, by 31-36 kcal/mol.**

And finally, here are two Forbidden 2+2 Reactions. Again, there is no redox during the reaction and hence, the promotion energies involve singlet-triplet decoupling of the two π-bonds:





$G_C = 2\Delta E_{ST}(\pi\pi^*) = 202$ kcal/mol



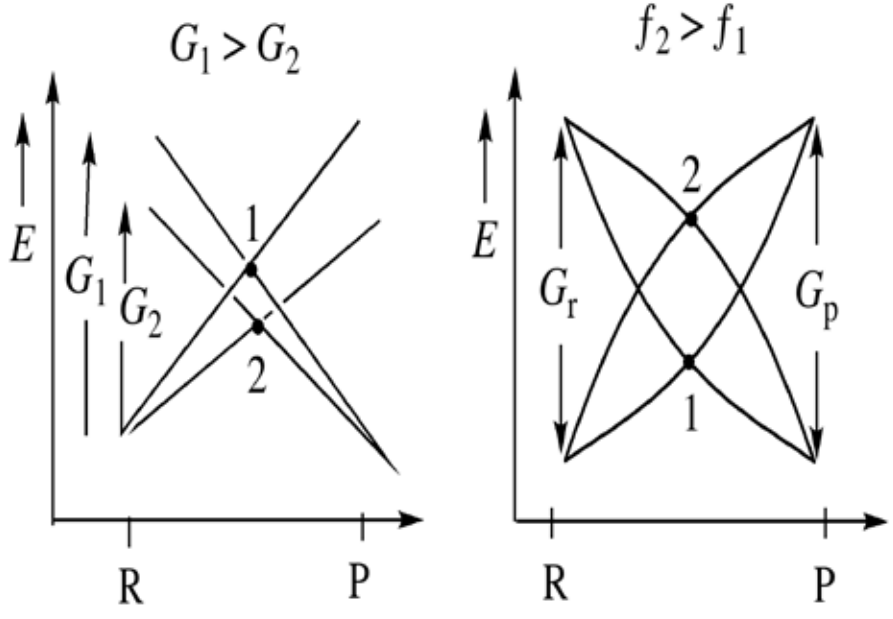
$G_{Si} = 2\Delta E_{ST}(\pi\pi^*) = 80$ kcal/mol

- **With a difference $G_C - G_{Si}$ = 120 kcal/mol, usage of f =0.3 leads to a barrier difference of 40 kcal/mol, thus highlighting the fact that the formally forbidden reaction of Si is in fact extremely fast!**

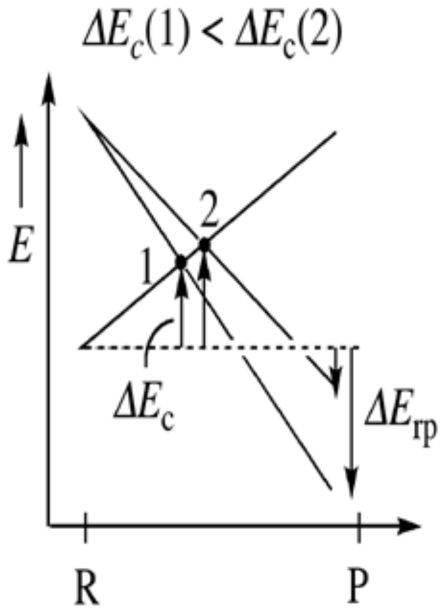
- **It is in fact faster than the Diels Alder reaction with G= 179 kcal/mol !**

The VBSCD enables to articulate the effects of the major barrier factors:

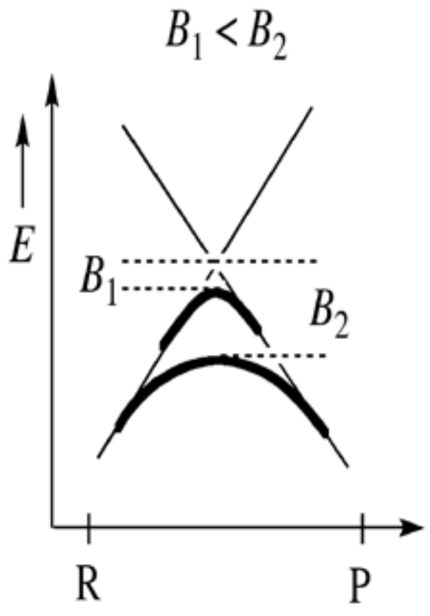
Promotion-state Effects



BEP
Rate-equilibrium



Symmetry & Trajectory



$$\Delta E^{\ddagger} \approx f_0 G_0 - B + 0.5\,\Delta E_{RP} + 0.5\,\Delta E_{RP}^2/G_0$$

Plenty of examples are given in Chapter 6 in the VB book and in the recommended reviews.

Having given you rules, with which to derive the VBSCD, I want to proceed to show you that one can construct the diagrams in a systematic quantum chemical mixing manner as done actually by the VB computations you will do in tutorial 3.

I will do so, using an S_N2 reaction. I do not expect you to understand everything I say at the moment it is said. So do not worry if you will not fully understand everything. I think the tutorial should fill the gap, and reading Chapter 6 in the book should further narrow the knowledge-gap.

Consider the S_N2 reaction: $X{:}^- + A\text{-}Y \rightarrow X\text{-}A + {:}Y^-$

- **We start by writing down the VB-structure set (VB basis set)**

$X{:}^- \quad A\bullet\!-\!\bullet Y$ $\qquad$ $X\bullet\!-\!\bullet A \quad {:}Y^-$ $\qquad$ $X\bullet \quad A{:}^- \quad \bullet Y$

6_R, $\Phi_{HL}(R)$ $\qquad$ 6_P, $\Phi_{HL}(P)$ $\qquad$ 7_{LB}

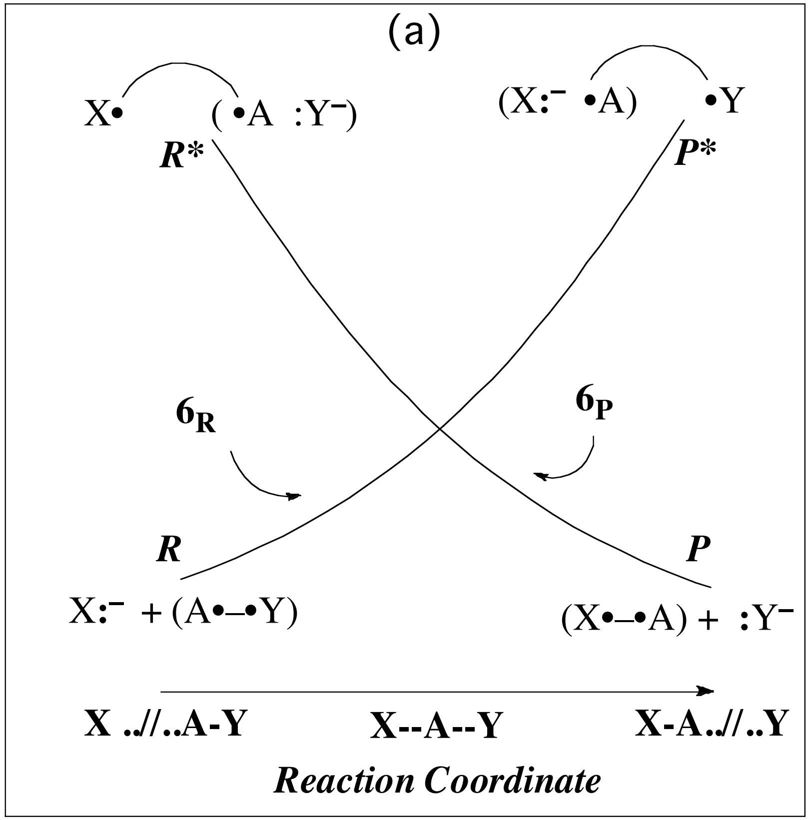
$X{:}^- \quad A^+ \quad {:}Y^-$ $\qquad$ $X{:}^- \quad A{:}^- \quad Y^+$ $\qquad$ $X^+ \quad A{:}^- \quad {:}Y^-$

8_{TI} $\qquad$ 9 $\qquad$ 10

The Φ_{HL} are the covalent structures, called after Heitler and London (HL)

Start with the Covalent HL Structures

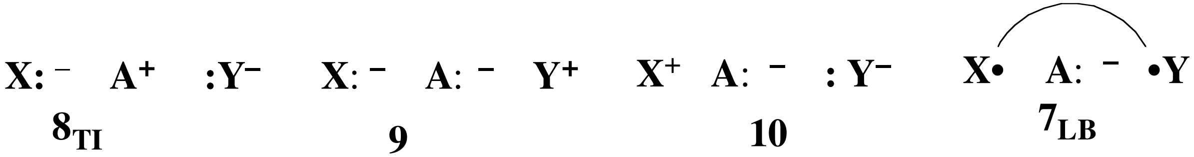
- **Disregard electrostatic stabilization*, focus on bonding and repulsive interactions:**

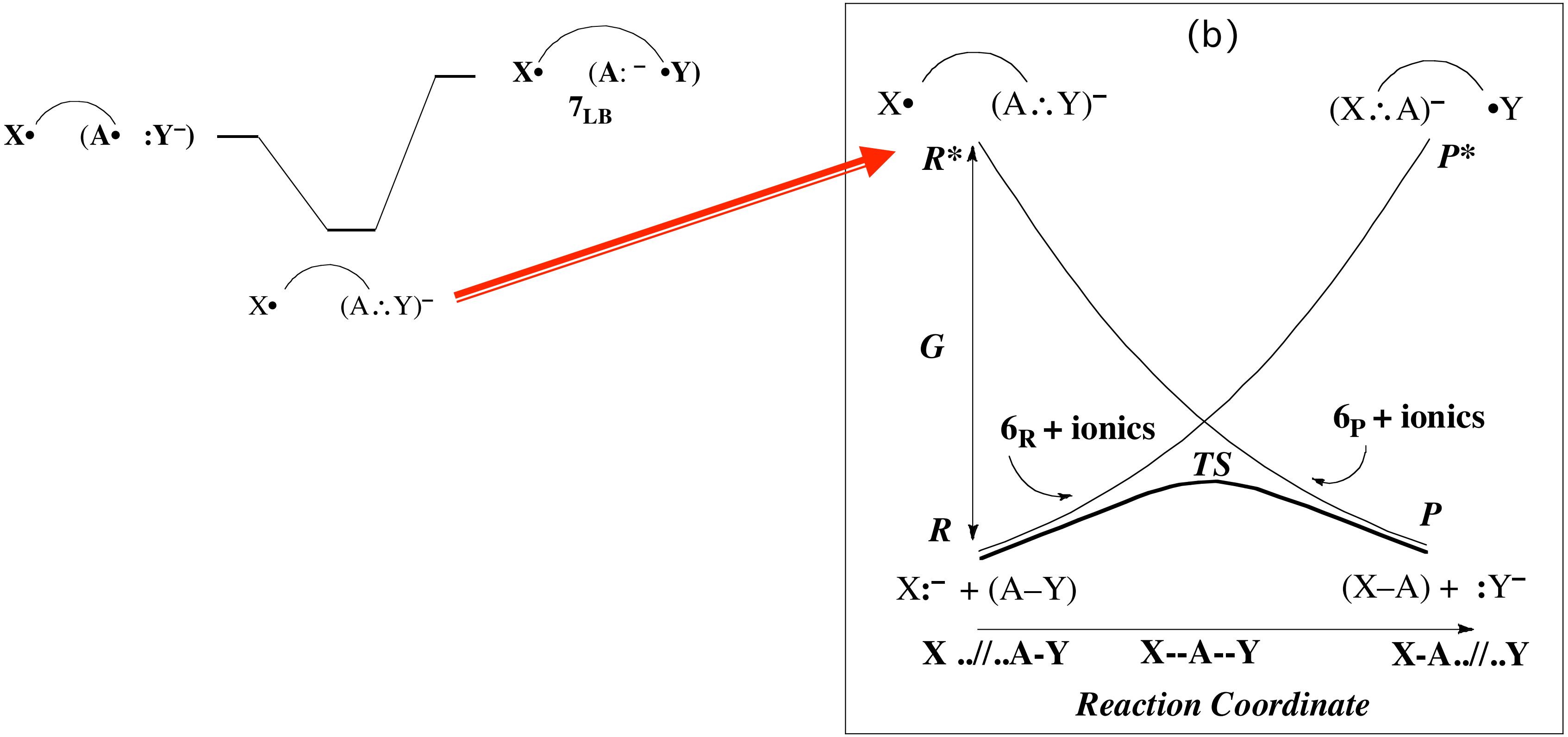


The two HL structures interchange along the reaction coordinate, since we break the bond and build-up a repulsive nonbonded 3e-interaction in the other linkage.

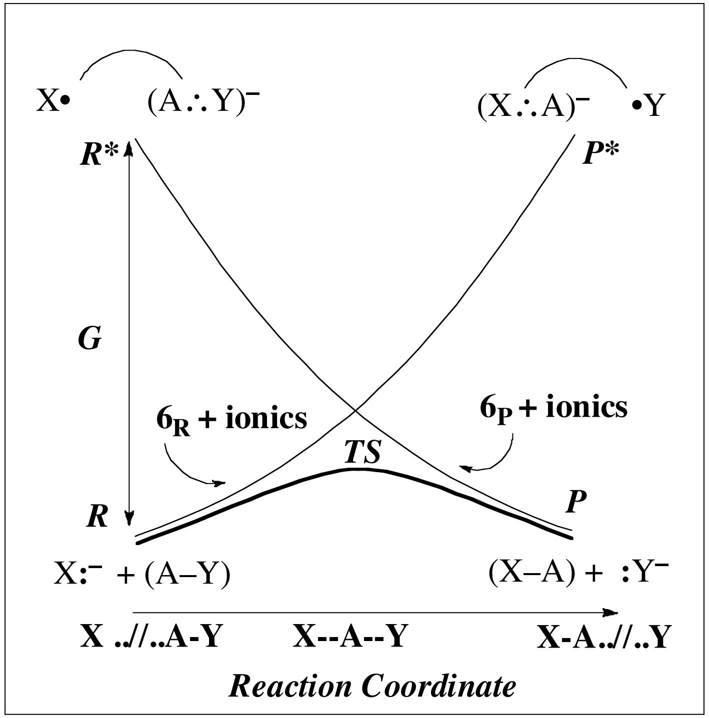
* Electrostatic interactions will generate ion-molecule clusters, e.g., X:⁻/A-Y

Mix now the secondary structures into the HL curves (6_R and 6_P) to form state curves:





Let’s present the diagram with the state curves and do the final avoided crossing between them:



- **The Charge transfer states are vertical states, namely they possess the same molecular geometry and solvent orientations as the ground states below them (non-equilibrium solvation). This is indicated by the asterisks:**

$$G = I_{X:}^{*} - A_{A\text{-}Y}^{*}$$

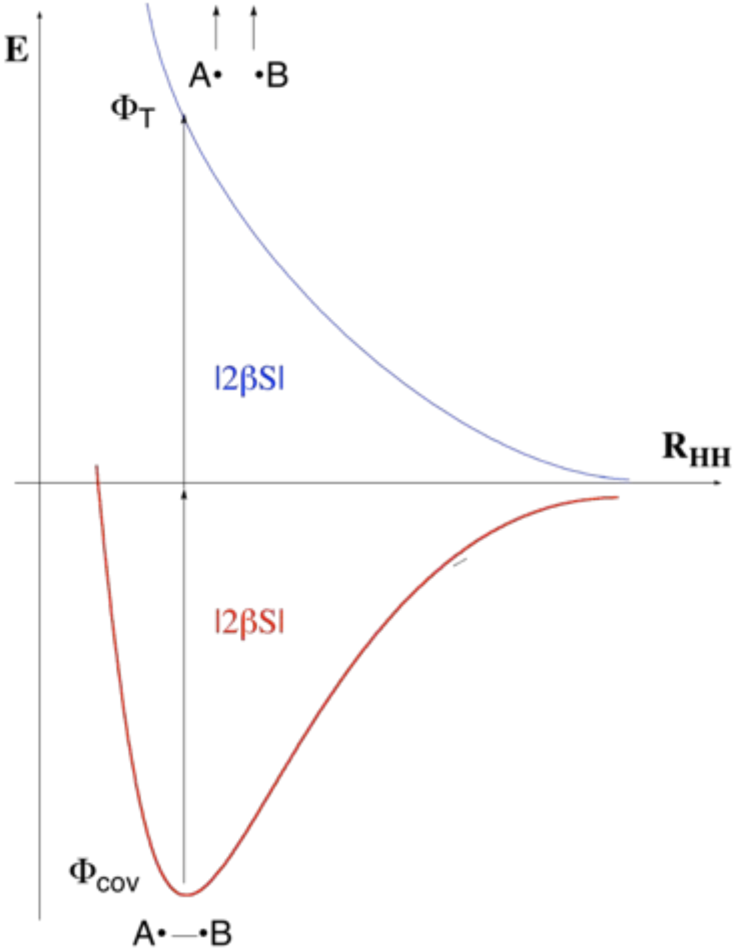
- **in the tutorial you will use PCM model which cannot give you non-equilibrium solvation. But you can use a semi-empirical estimation of these states (see JACS, 1984,** *106*,1227-1232 **).**
- **Alternatively, you can use the VBSM routine in XMVB.**

Having constructed an entire VBSCD is so many details, let me show now that it is possible to construct the VBSCD also in an intuitive way.

I will do so, using H-abstraction

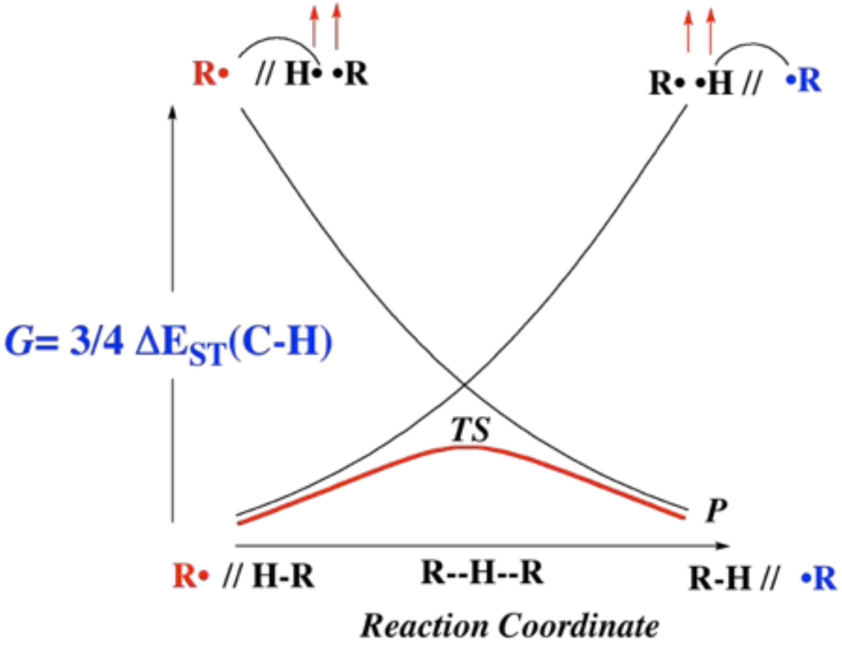
A Reminder: The Singlet –Triplet Excitation Energies in VB

- As we argued, if we neglect overlap, then the singlet and triplet energies will be given as ±2βS, & ΔE_{ST} ~ |4βS|



Consider now an identity exchange R• + H-R -> R-H + •R

- and focus on the two Lewis structures of the reactants and products.
- Starting with the reactants structure, and following it along the reaction coordinate, we are breaking the H-R bond, thus paying the price as $-2\beta S$. And we are also creating on the other side a repulsive non-bonded triplet R• •H interaction given as $-\beta S$. So the promotion energy gap between the state curves is: $\frac{3}{4}\Delta E_{ST}$

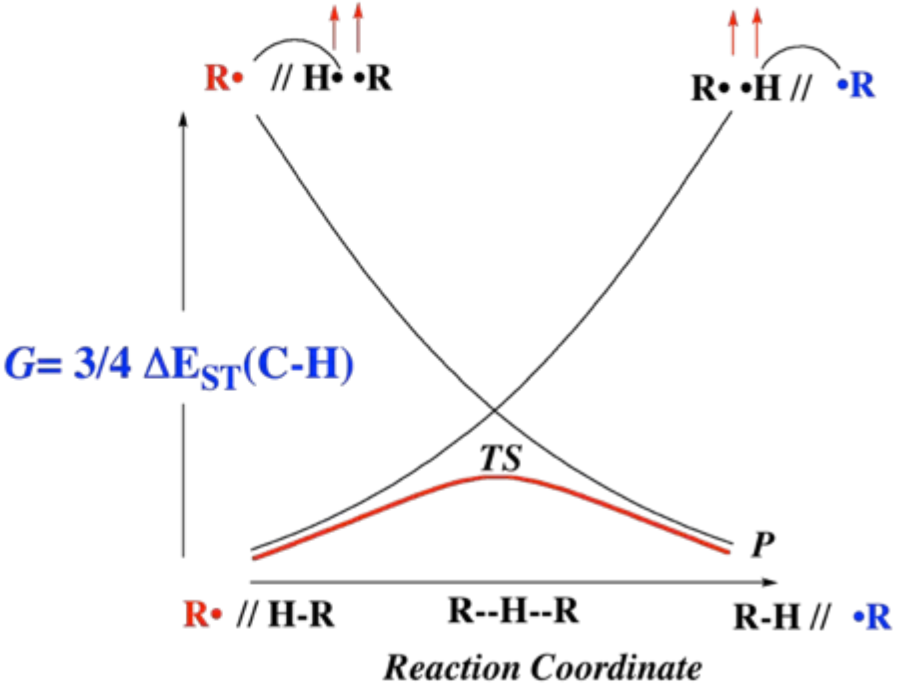


- Repeating the process in the reverse direction generates the second state curve, and again the promotion gap is $\frac{3}{4}\Delta E_{ST}$.
- Subsequently we let the state curves mix and avoid the crossing.

- Chapter 6 in the VB book shows the detailed constructions using the 8 VB structures, which account for all the ways of distributing the 3-electrons among the hybrid atomic orbitals of the fragments. It also uses fragment orbitals – "there are many ways to skin a cat"

- **If we include overlap (*S* = 0.5 for C-H) we can relate the promotion gap to the vertical bond strength 2$D_{C\text{-}H}$ and obtain the following expression which will be very handy later:**

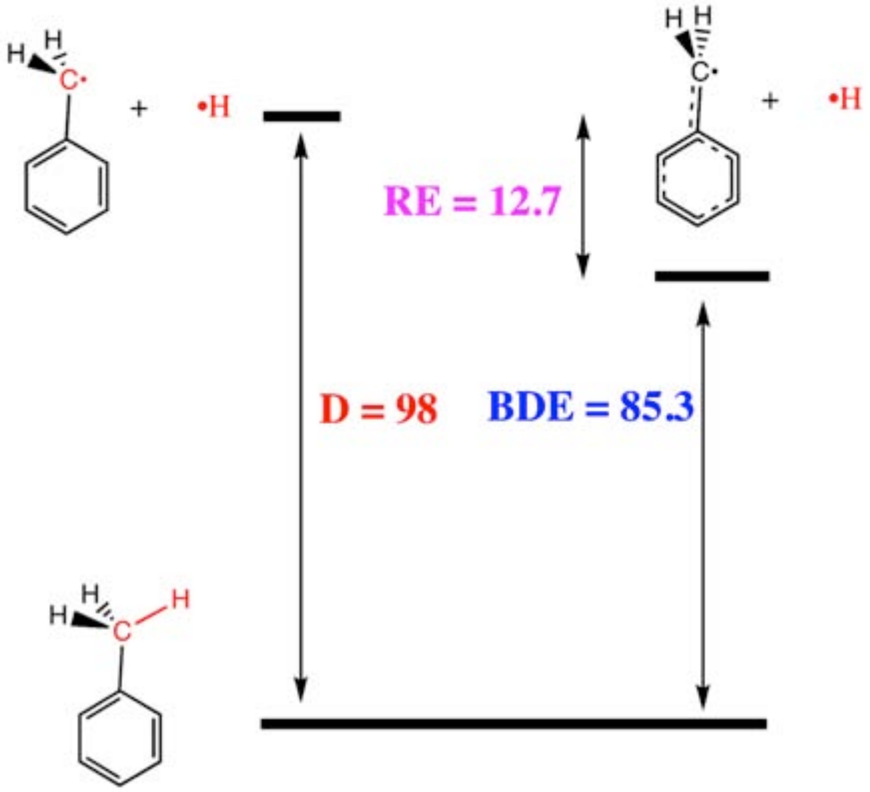
$$\frac{3}{4}\,\Delta E_{ST} \sim 2D_{C\text{-}H}$$



Exercises 6.3-6.6 provide different ways of estimating the reactivity factors. Ex. 6.6 shows also how the VB diagram can predict the barrier height and the conversion of the TS to a stable cluster for atom transfer reactions like Li + Li_2 -> Li_2 + Li

What is the difference between bond dissociation energy (BDE) and the vertical bond strength D?

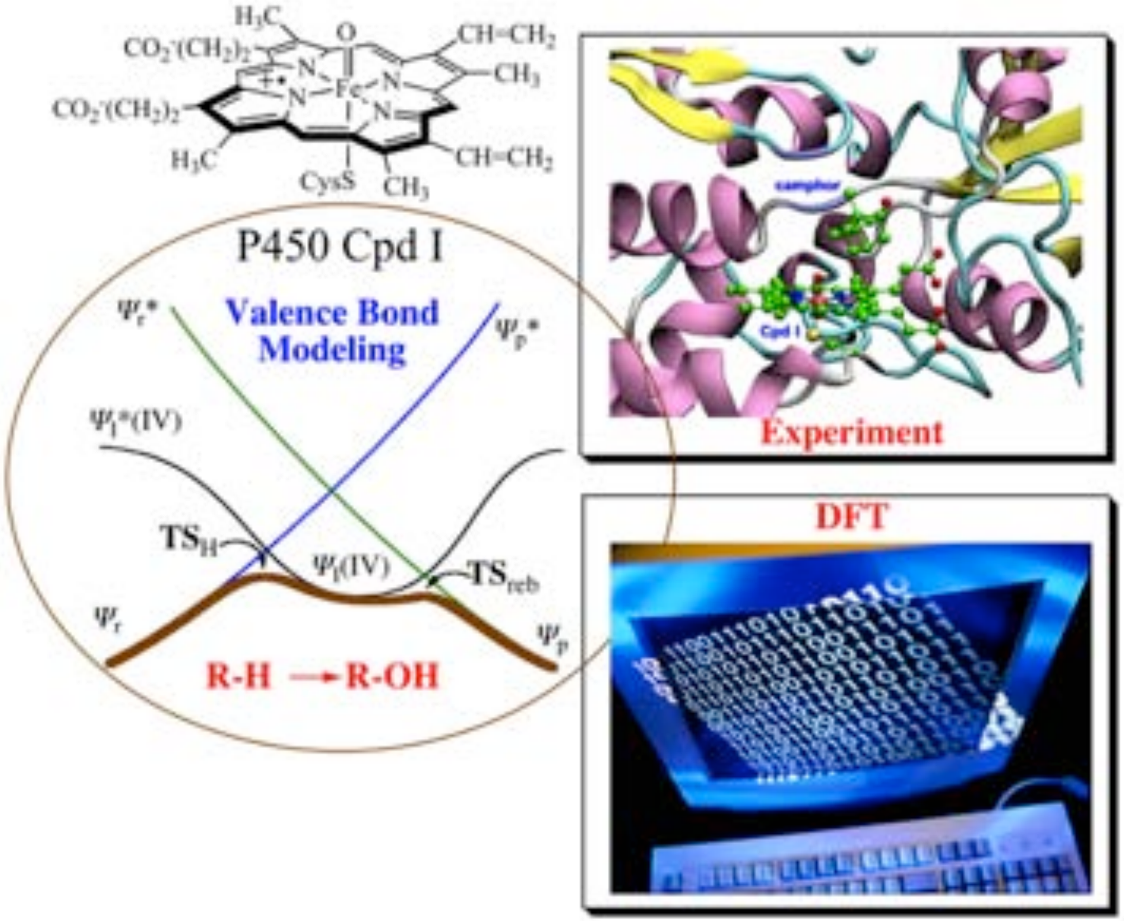
- **D - BDE = RE**
RE is the Reorganization Energy of the radical to become prepared for bonding.



- **The promoted state in the VBSCD <u>is a vertical state</u> and hence we use for the promotion gap vertical bond energy, D, and not BDE.**

- Now we are ready to delve into the chemistry of P450!

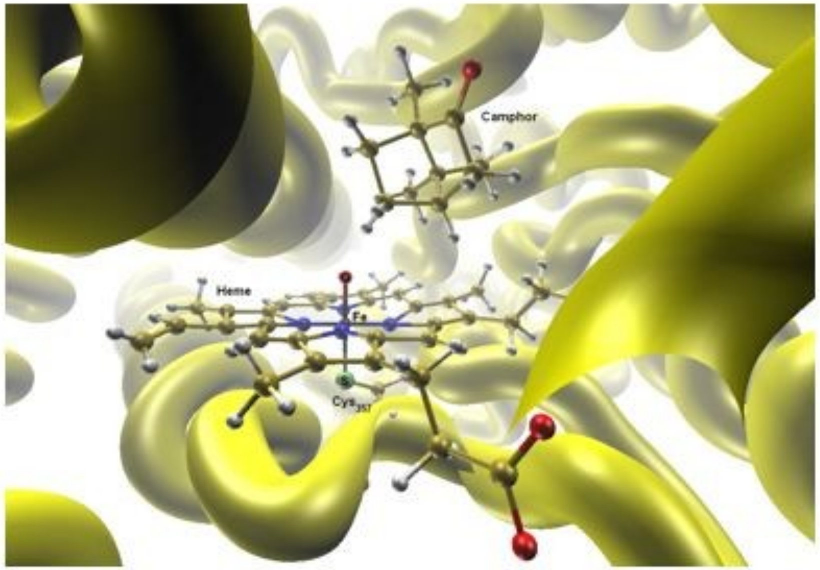
- And show how the VB model creates order, predicts mechanisms, and enables to estimate barriers from raw data



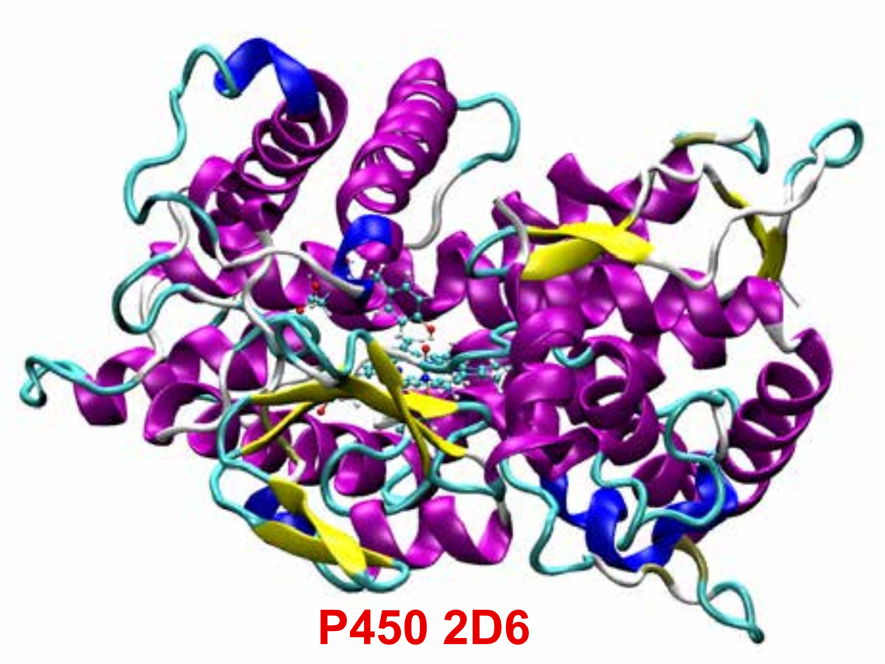
Cytochrome P450 is a large family of enzymes, generated by more than 4,000 different genes in the various forms of "life".

- **P450s activate O_2, and form an active species that oxidizes organic molecules as means of neutralization of *xenobiotics, and of* biosynthesis for example, of steroids, brain chemicals, molecules with anti cancer activity, etc.**

- **These enzymes which look like impossibly intricate cathedrals, are also ever so beautiful objects, so much so that I have been spellbound ever since I started investigating P450s…**

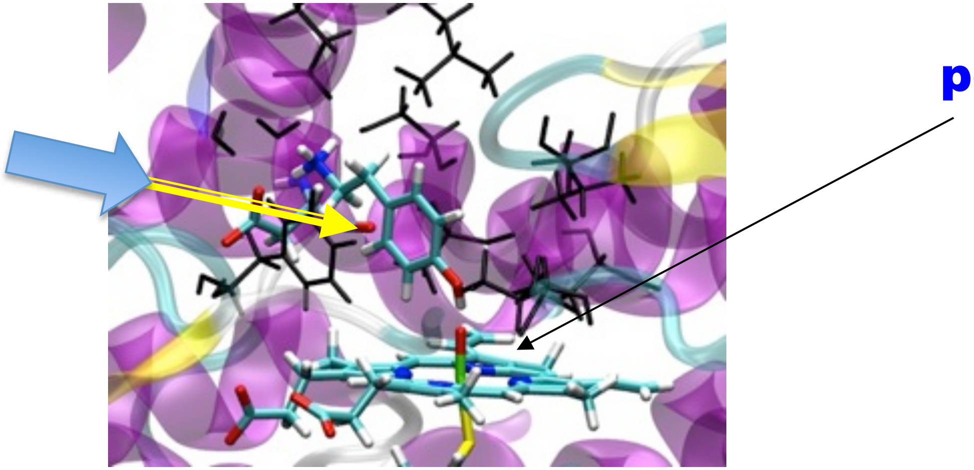


$P450_{cam}$



P450 2D6

Here is the Active Species of Cytochrome P450 2D6. It is an iron-oxo porphyrin ready to convert the precursor substrate to Dopamine in our brain:

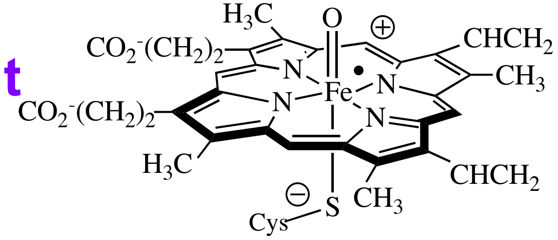


Precursor substrate

Iron-oxo porphyrin

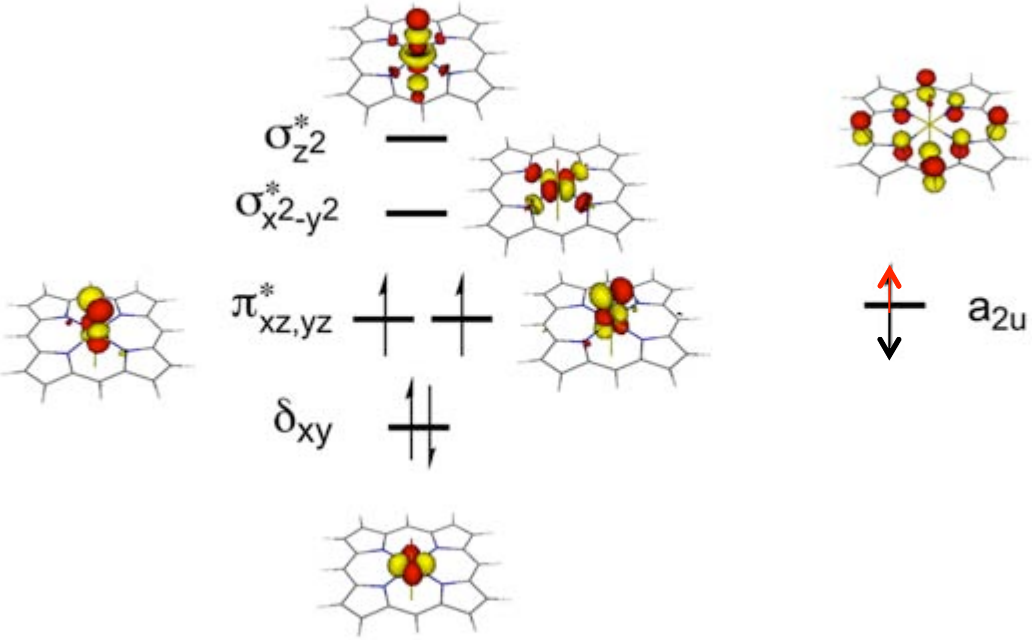
- It is apparent that there is a considerable structural complexity here.
- In addition the problem is electronically intriguing since the active species is a high valent iron-oxo porphyrin cation radical complex, which is called Compound I (Cpd I)

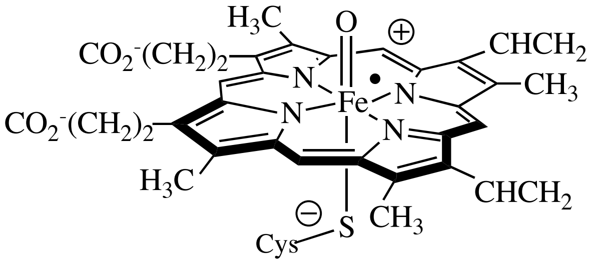
Cpd I



Cpd I has 3 unpaired electrons:

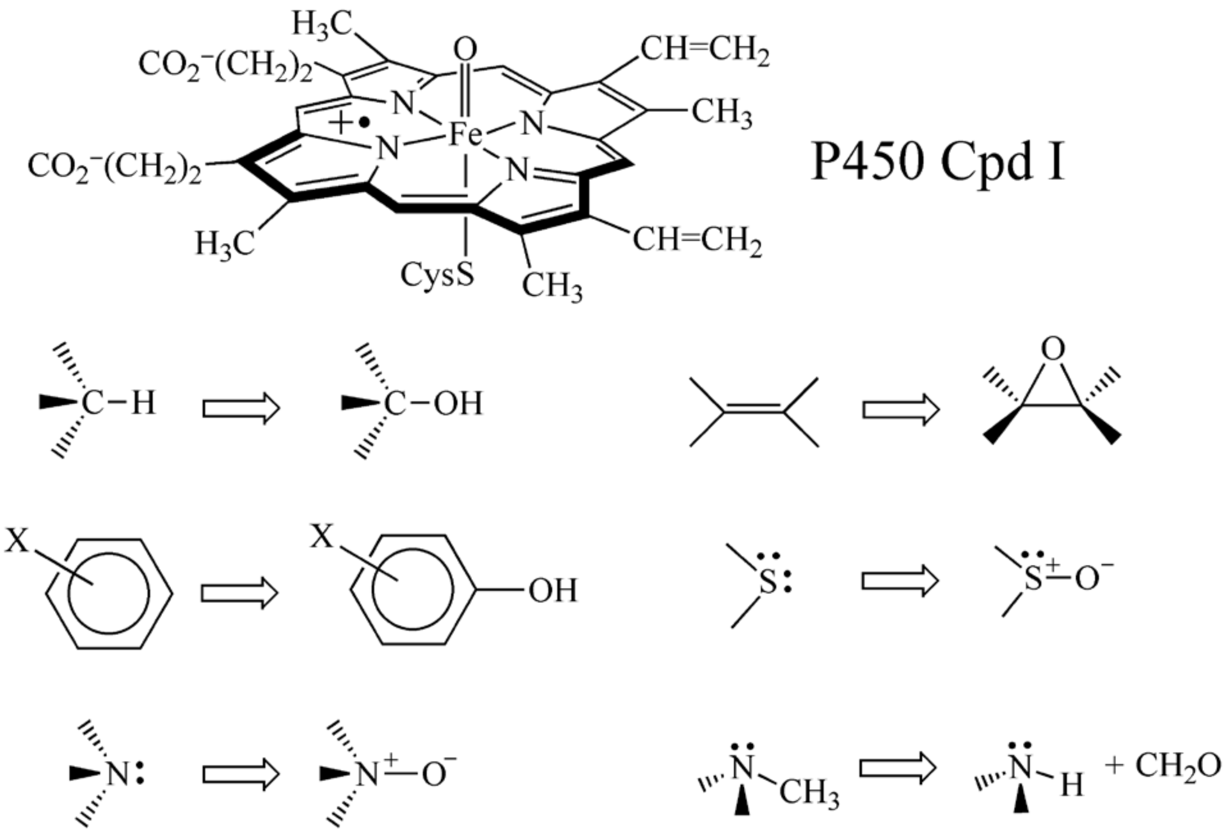
Two electrons reside in the π^* orbitals of the Fe=O moiety, which is an analog of the $^3O_2$ molecule, and the third electron resides in a porphyrin orbital, marked as a_{2u}.





As such, Cpd I possesses two virtually degenerate spin states, S=1/2 and S=3/2, depending on the spin direction in the porphyrin orbital, a_{2u}.

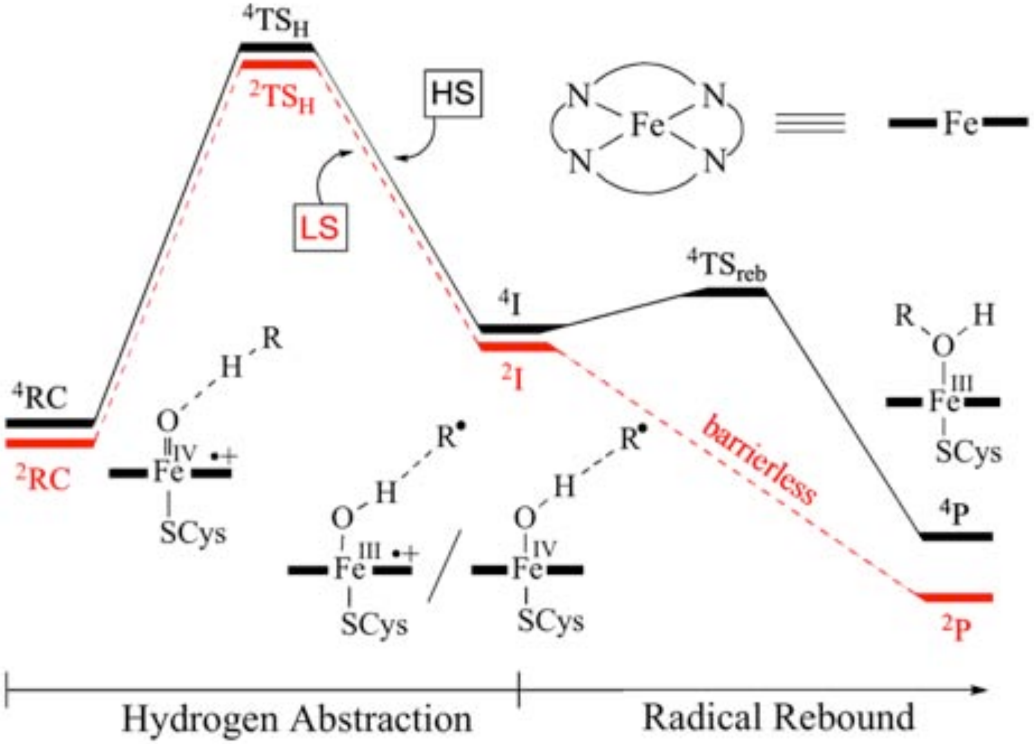
Here is a small selection of the oxidation reactions that Cpd I catalyzes:



- These processes involve the doublet and quartet spin states, which also exhibit different mechanisms.
- Additionally, these processes reveal a variety of reactivity patterns, which we wish to organize and comprehend.

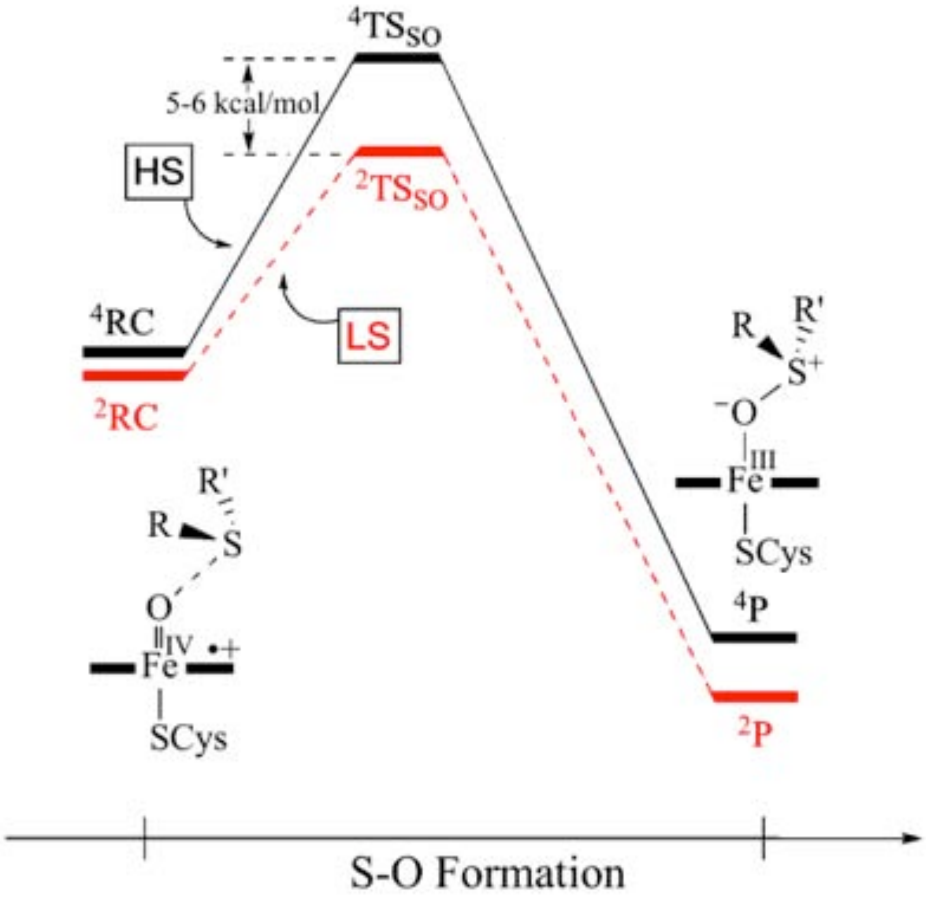
Here is the DFT and DFT/MM-calculated mechanism of alkane hydroxylation catalyzed by Cpd I :

- It is seen that Cpd I hydroxylates alkanes in a biphasic reaction, involving H-abstraction followed by radical rebound to form a ferric alcohol complex.



- Up to the intermediate junction, $^{4,2}I$, the two spin states are close, but they diverge at the rebound process, where the HS state has a rebound barrier, whereas the LS spin state proceeds in an effectively concerted manner.
- Both C=C epoxidation and aromatic oxidation are similar to alkane hydroxylation and hence are not shown.

And here is the DFT and DFT/MM-calculated mechanism of thioether sulfoxidation by Cpd I :



- It is seen that the sulfoxidation mechanisms are concerted on both spin states. Furthermore, now the LS state has a significantly smaller barrier compared with the HS state.

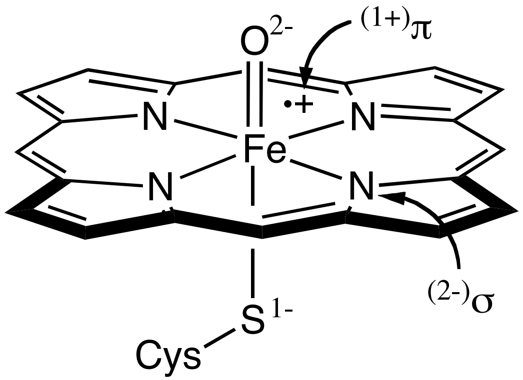
Can we understand all these rich features?

I hope to show you that "yes we can" by usage of VB theory.

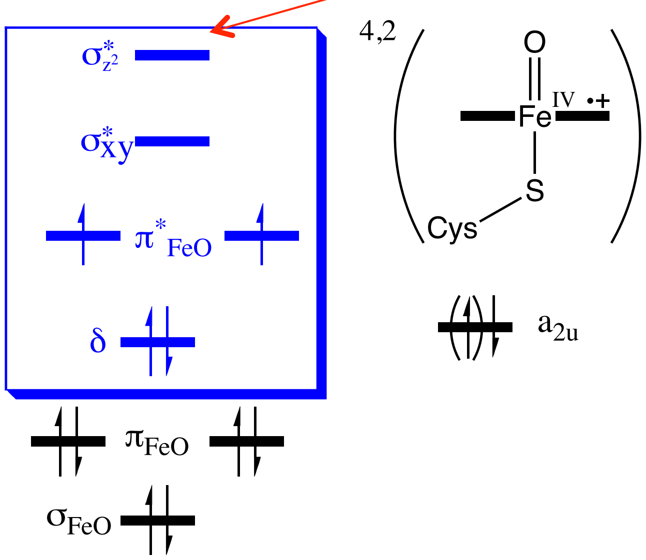
However, we first need to create bridges between VB Theory and the common language of Bioinorganic Chemists

Bioinorganic chemists use oxidation states, which are useful for keeping track of the number of d-electrons along the reaction pathway

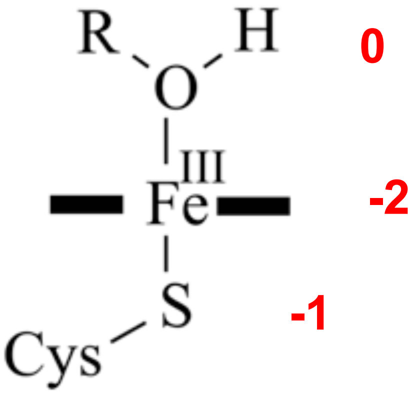
- **For example, the oxidation states in Cpd I are determined by assigning octet to all the ligands at the expense of Fe. As such, Fe should be Fe^{V}. But from spectroscopy we know that one oxidation equivalent is on the porphyrin. Hence we have $Por^{+\bullet}Fe^{IV}O$ with a d^4 configuration:**



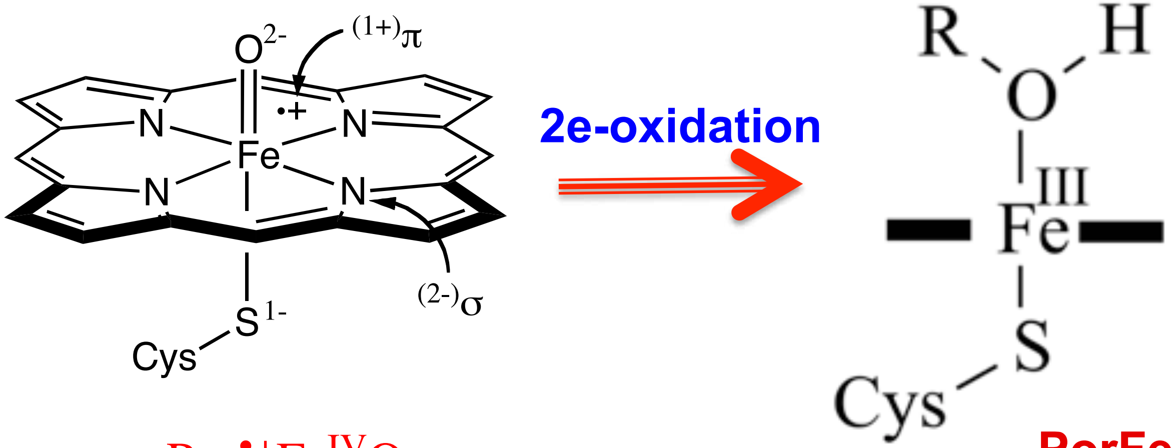
$Por^{\bullet +}Fe^{IV}O$



- **As the radical rebounds, we will have a ferric alcohol complex. Since the oxidation number of the alcohol is zero, we have Fe^{III} and closed-shell porphyrin.**



- **As such, the effective oxidation state of the heme complex changes along the reaction path, by two units, from Por+• Fe^{IV}O to PorFe^{III} (OHR).**



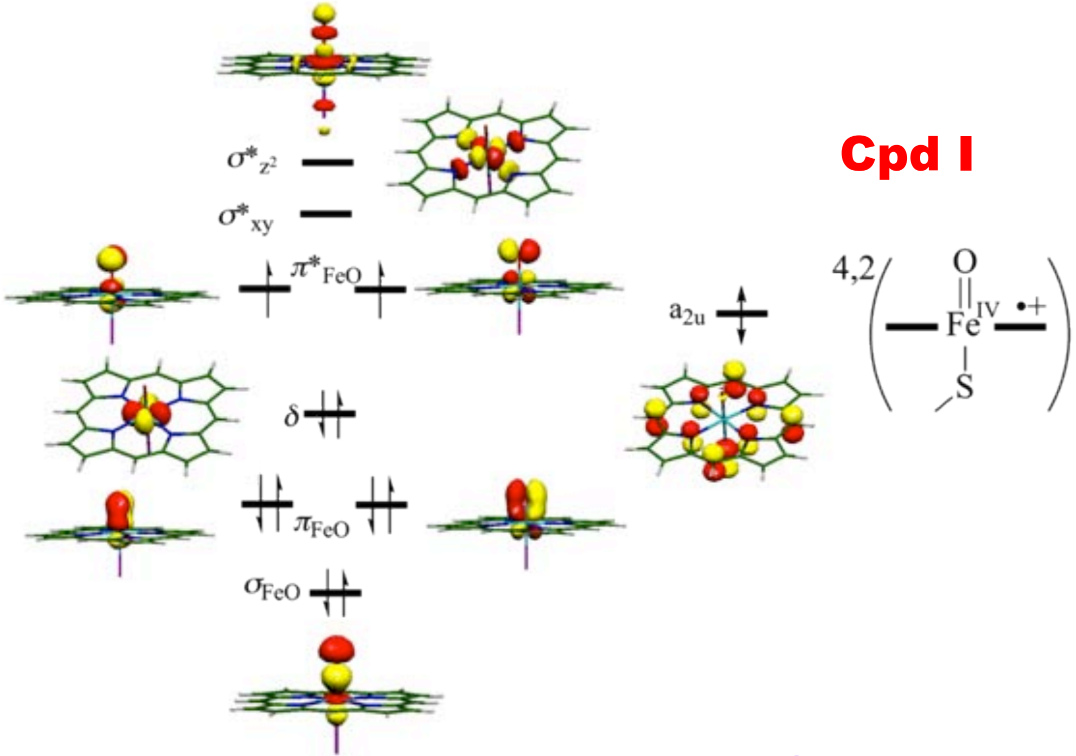
Por$^{\bullet +}$Fe^{IV}O

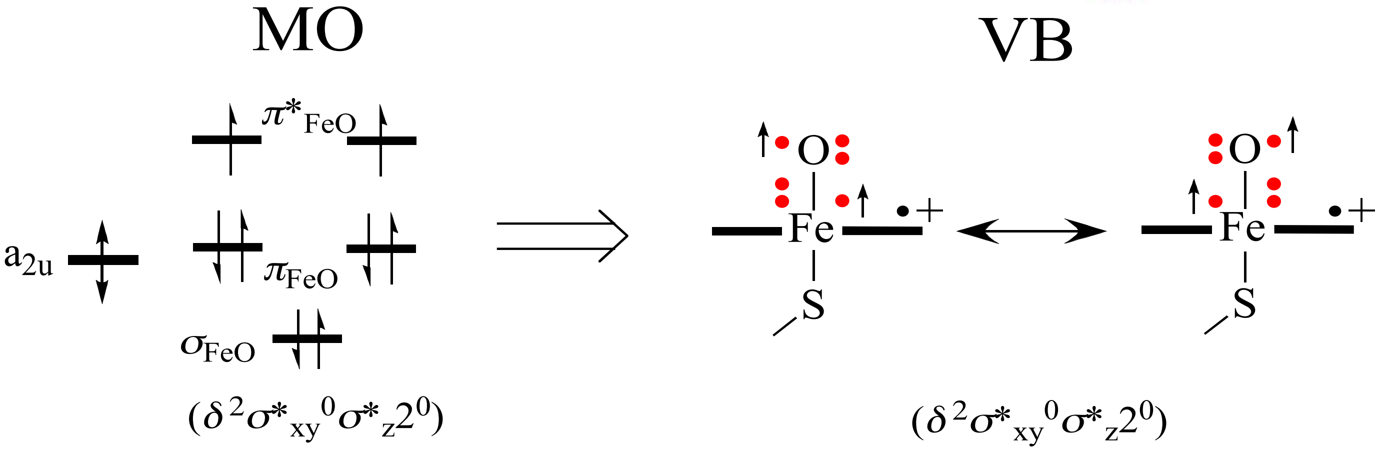
PorFe^{III} (OHR)

- **As I already argued, this oxidation state language can be naturally embedded in the VB model**

Bioinorganic Chemists, use MO language. So, let us Proceed to Bridge between MO and VB Descriptions for Cpd I

- Bridging of the MO description of Por$^{+\bullet}$Fe^{IV}=O to a VB language is simple, once one realizes that the Fe^{IV}=O moiety is analogous to triplet O_2, which in addition to the σ(Fe-O) bond it has also two 3-electron π-bonds in two perpendicular planes (recall Philippe's lecture).

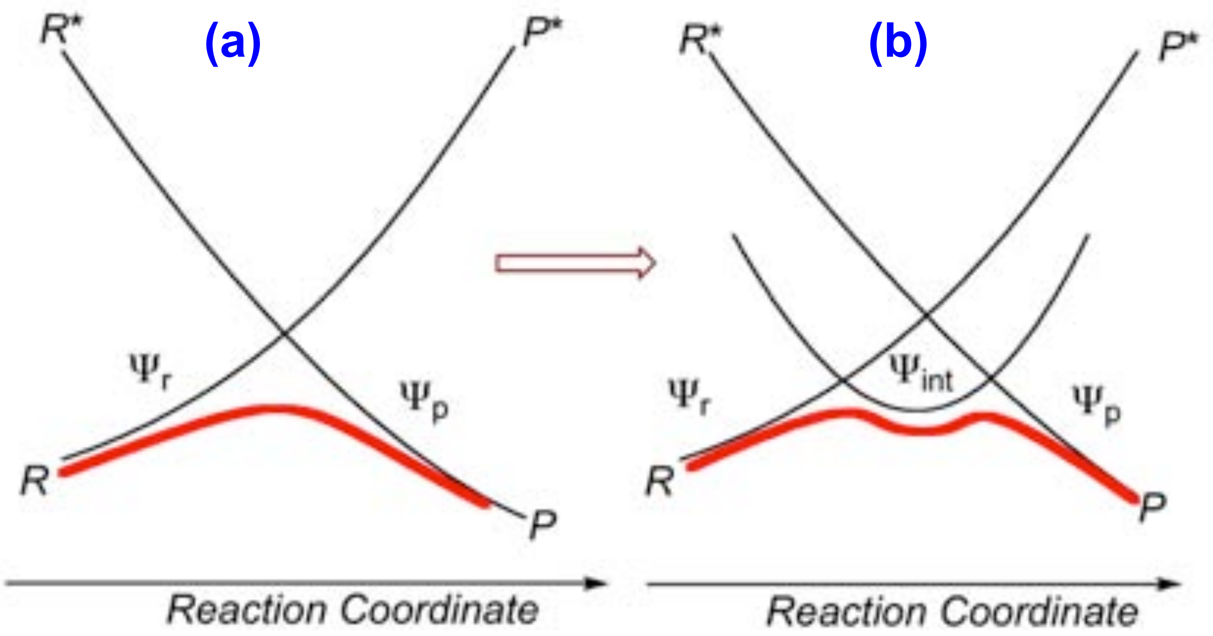




- Clearly the ferryl moiety (FeO) is a diradical

Now we are ready to apply the VB Diagrams to model reactivity patterns.

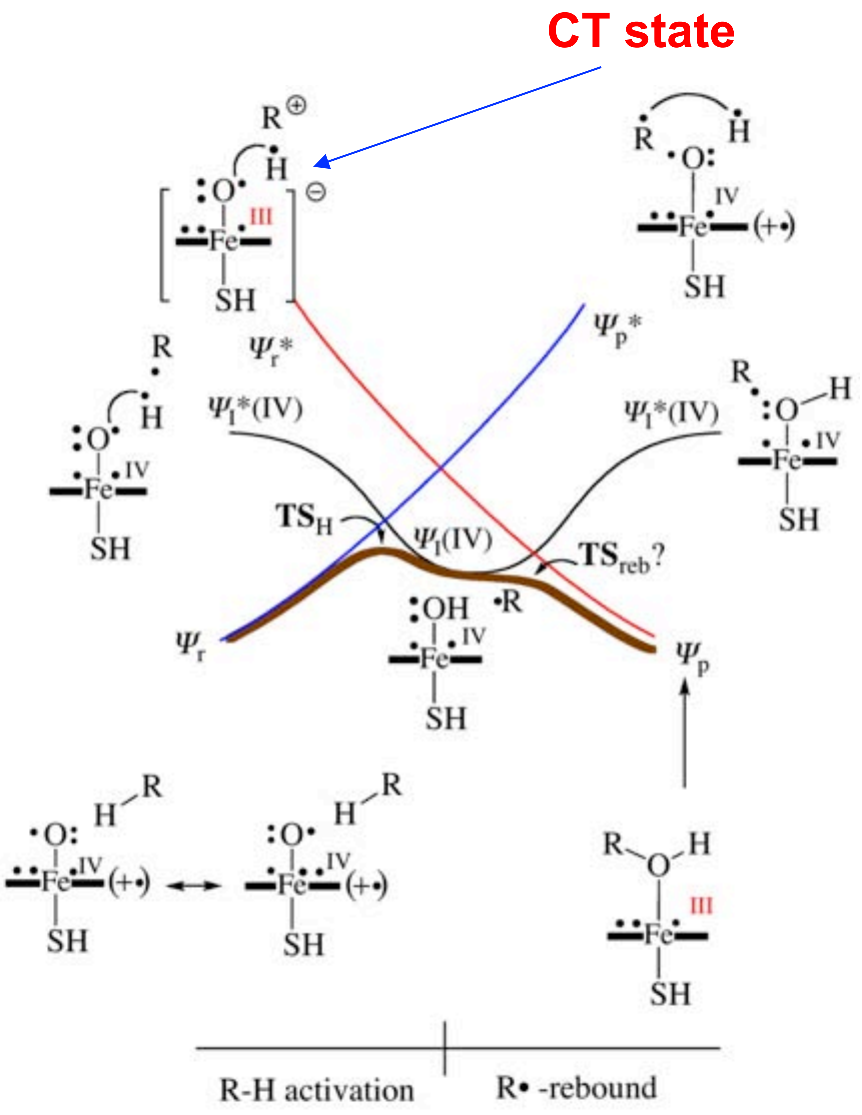
To refresh our memories, here are again the two diagrams, which are based on VB-state correlation:



- **Diagram (a), which is called VBSCD, handles an elementary chemical step, while diagram (b), so-called VBCMD describes stepwise reaction mechanisms.**

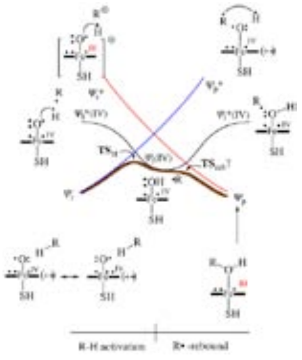
Here is the VB diagram for Alkane Hydroxylation by Cpd I

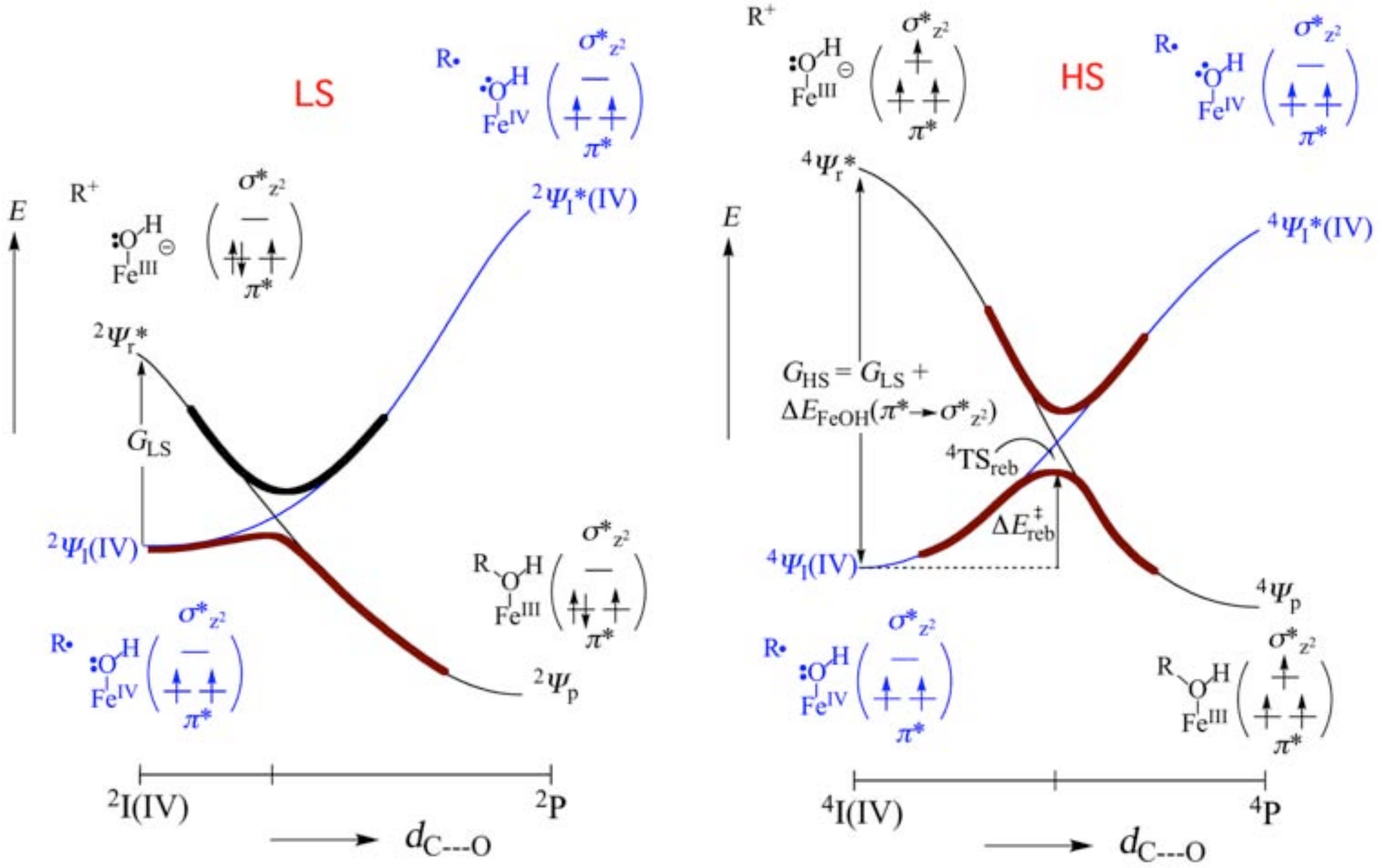
- By inspection of the oxidation states, one can see that the direct transformation of the alkane, R-H, to the alcohol product, R-OH, involves crossing of the ground state curve with a high lying charge transfer state curve.
- However, the process is catalyzed by an intermediate state wherein Cpd I uses its oxygen radical center to make a bond to the triplet decoupled H-R bond.
- This intermediate state cuts through the high ridge for direct oxo-transfer & splits the process into oxidative H-abstraction followed by radical-rebound to form the alcohol complex.



- This is a common feature for the two spin states.

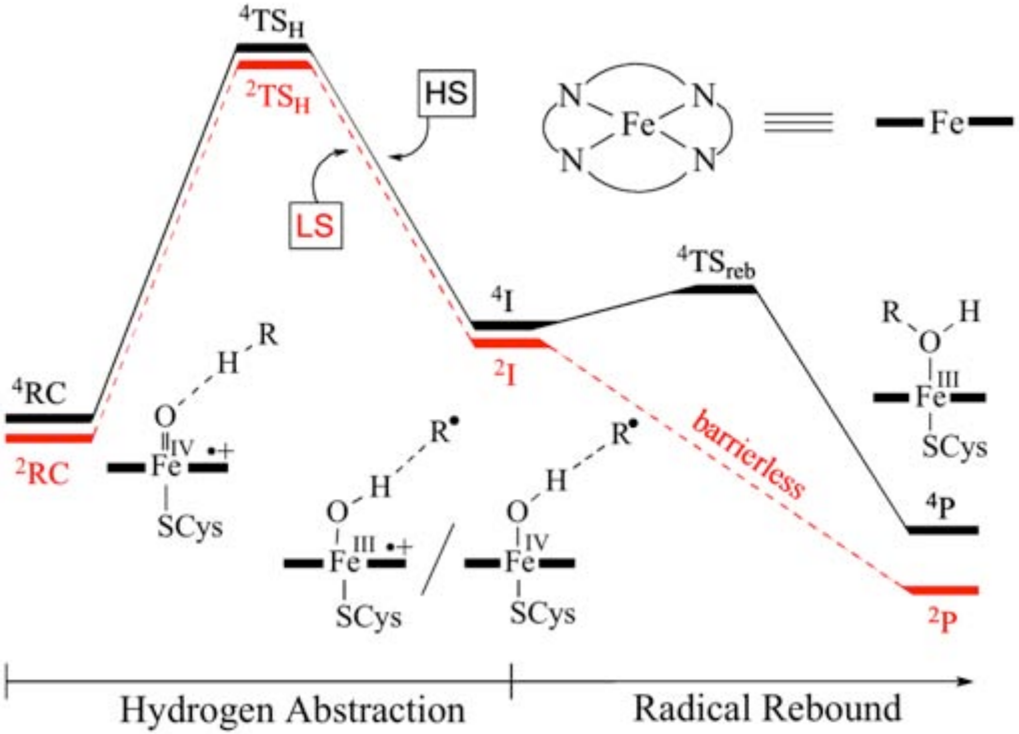
The difference between the two spin states occurs during rebound, as shown in the following VB diagrams going from $^{2,4}I_H$ to $^{2,4}P$:





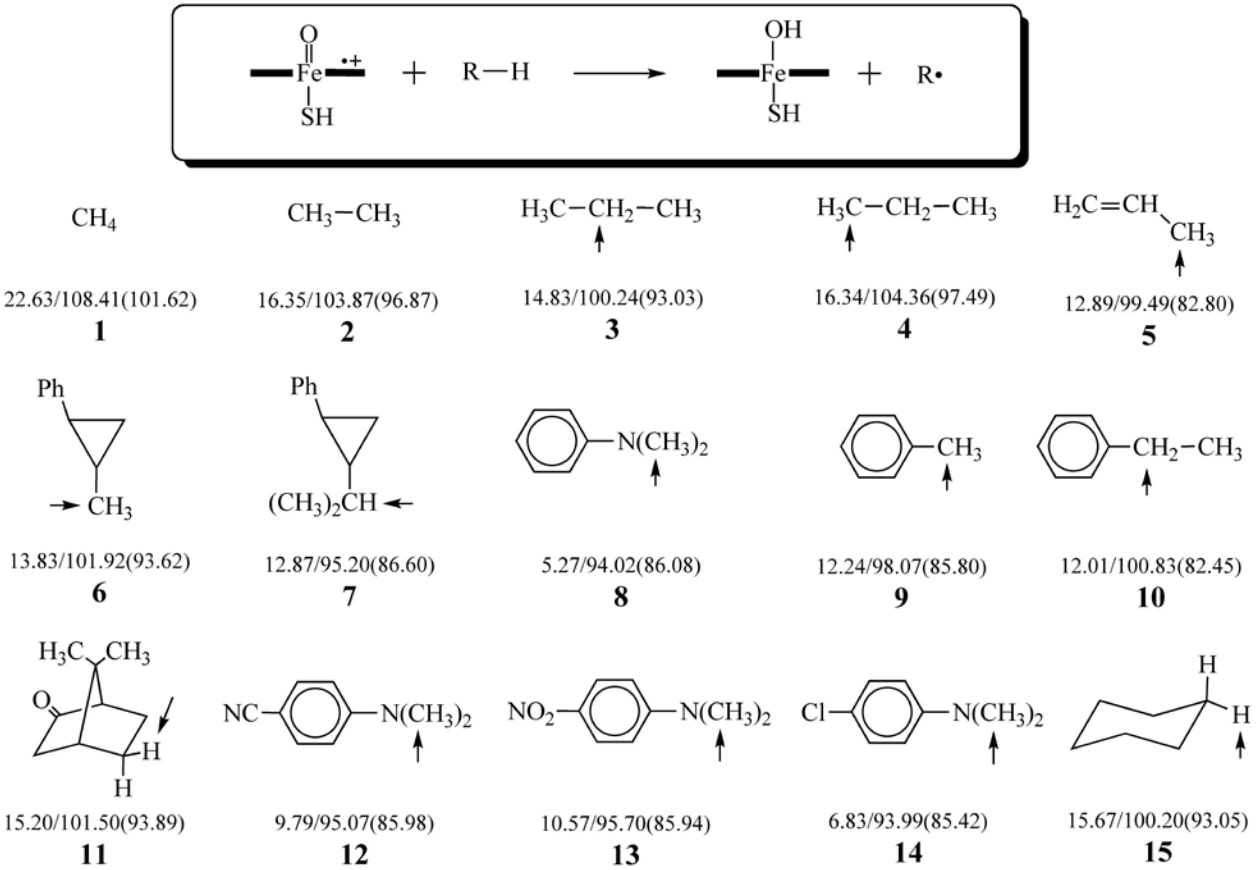
- It is seen that the promoted state for the HS process involves an additional excitation within the d-block, from the π^* to the $\sigma^*_{z^2}$ orbital.
- Since this is a sizable quantity, only the HS process, with the large promotion energy, has a rebound barrier, while the LS is barrier-free

Here is a reminder of the computational results for alkane hydroxylation:



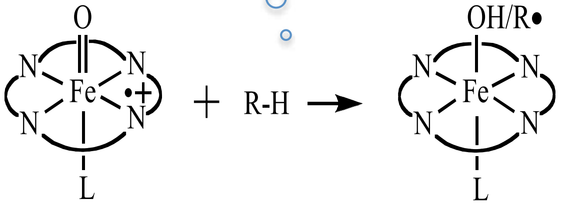
- It is apparent that VB diagrams predict correctly the bi-phasic character of the mechanism, as well as the stepwise HS vs. the effectively concerted LS processes.
- This prediction is amply supported by experimental and computational results.

Having elucidated the mechanistic scenarios and the spin-state differences, let us deal now with reactivity in the H-abstraction step, which is rate determining. Here are the reactions we looked at:



Different alkanes

Different Cpd I's



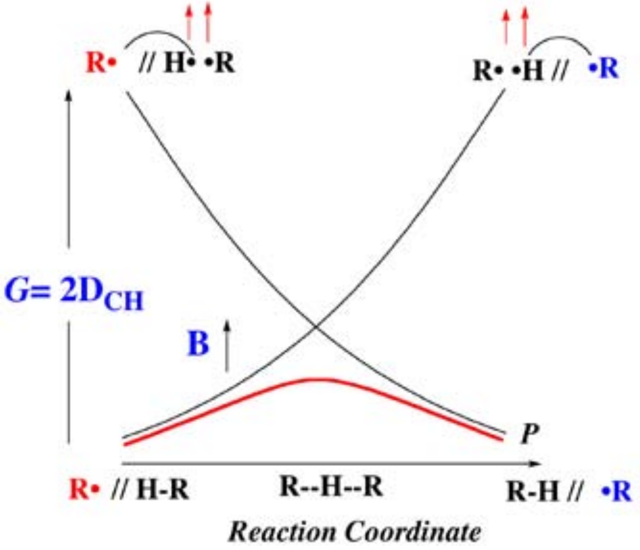
R-H = cyclohexane

L = SH, OAc, Cl, CF_3SO_3
15 16 17 18

So, now we have a large enough data base to apply the VB model quantitatively and see whether we can understand the trends

Before we can do so, let me say a few words about the reactivity factors, using an identity H-abstraction reaction.

- As we already argued, the promotion energy gap is well approximated by the vertical bond energy:
$G_r = 2D_{C\text{-}H}$
- Using semi-empirical VB arguments, leads to $f \leq 1/3$ (e.g., Ex. 6.6).
We use: $f = 0.3$ (ACIE2012).



- For B we have derived a few expressions that lead to close values:
- From semi-empirical VB arguments for an identity reaction:
$B \sim 0.5BDE$ (Book p 142 & Ex 6.5).
- For nonidentity reactions, X• + H-Y -> X-H + •Y, we derived the following expression (JACS, 2004, *126*, 13539):
$B \sim 0.5BDE_W$ w- the weakest of the two bonds.
- Finally, in the most recent study (ACIE 2012) we employed the following expression:
$B \sim 0.5BDE_{Av}$; $BDE_{Av} = 0.25(BDE_{HY} + BDE_{HX})$
which treats both bonds on equal footing.

Here is the VB model for the rate-determining H-abstraction step, cut out from the complete diagram:

- The simple expression for the barrier is:

$\Delta E^{\ddagger} = fG_r - B$.

The expression is useful if we have a reaction family wherein *f* and B are constants. In such a case, the variation in the barriers will depend only on G_r.

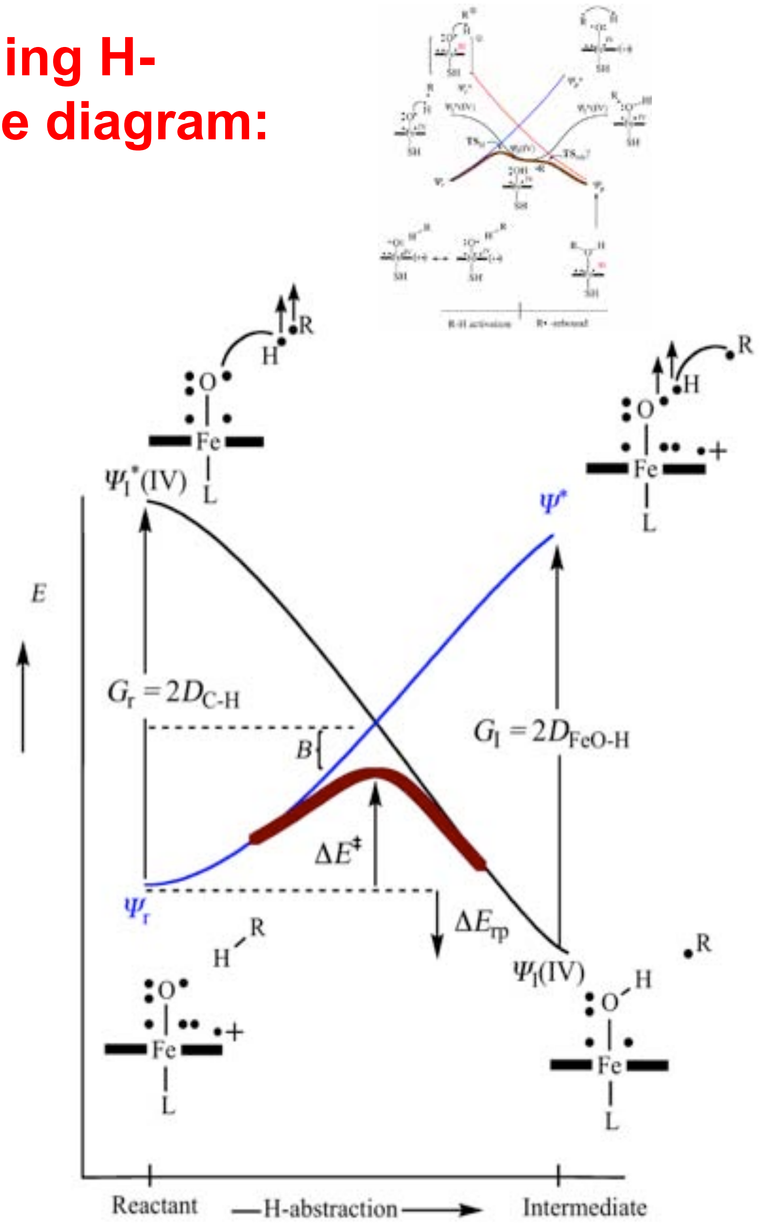
- As I just argued, using semi-empirical VB, it is possible to derive the following expressions for our limited series:

$G_r \sim 2D_{C\text{-}H}$

$f = 0.3$ &

$B \cong 0.5BDE_{weak} \sim 0.5BDE_{OH}$

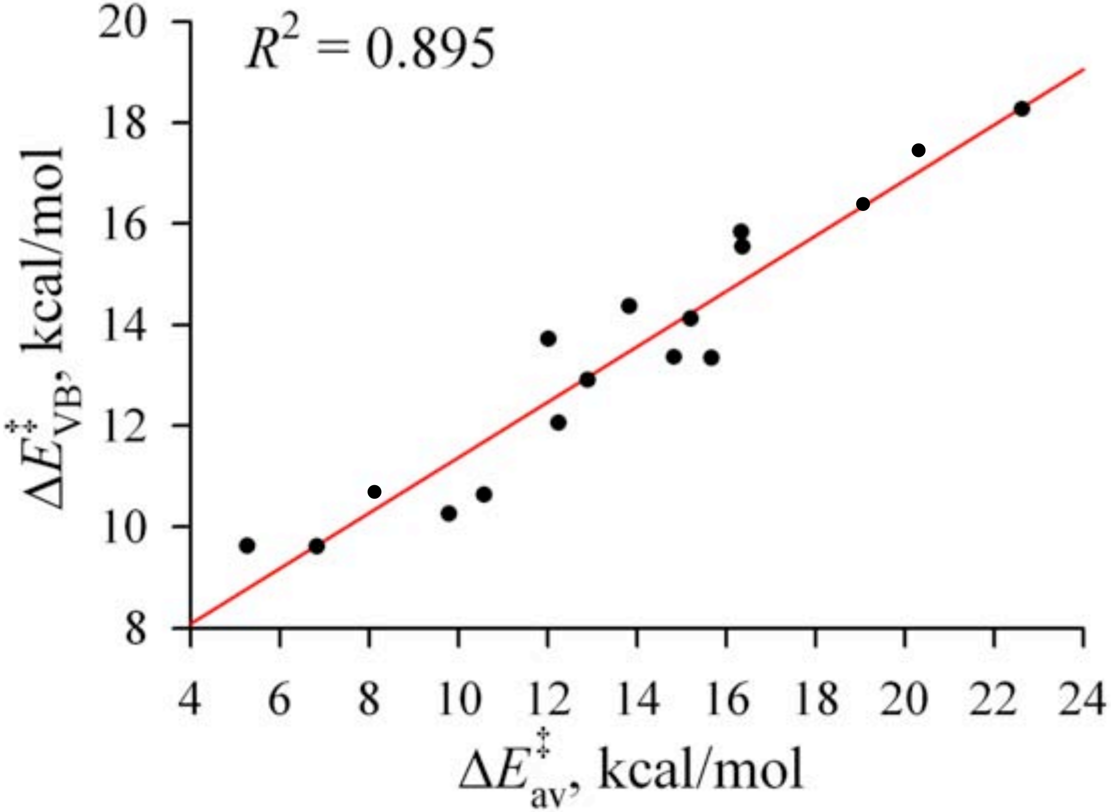
- As such, *f* and B are in principle constants and the simple equation is usable.



If indeed so, we can proceed to calculate barriers from raw data!

The correlation of the so-estimated VB barriers ($\Delta E^{\ddagger} \approx 0.3[2D_{CH}] - \frac{1}{2} BDE_w$) with the DFT computed ones is shown here:

- Considering the large variation of the alkanes and the different Cpd I species, I showed you before, the correlation is quite good.

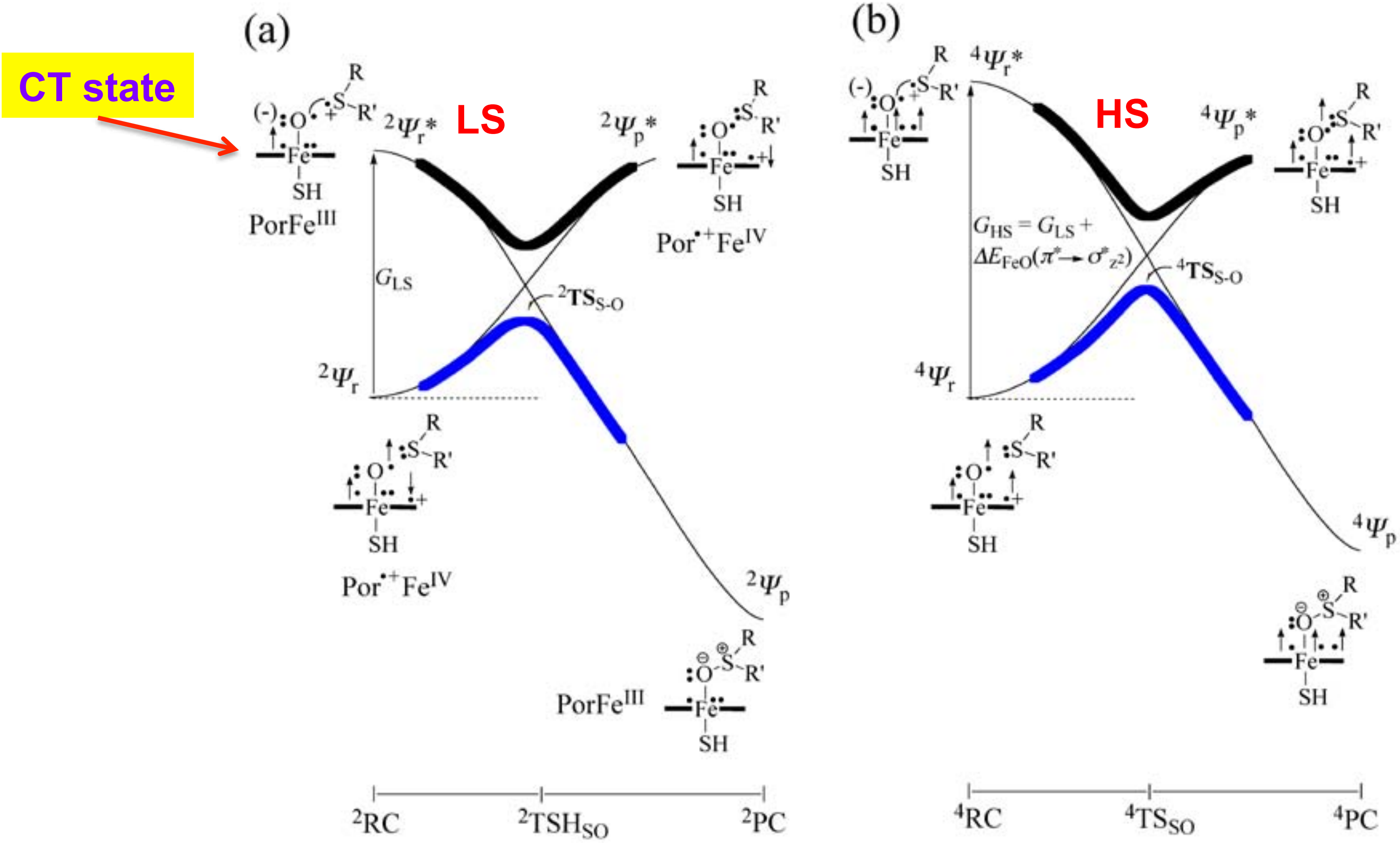


Shaik, Lai, Chen, Wang, ACR, 2010, 43, 1154

- This means that the VB model is capable of predicting the trends in the barriers of a key reaction of cytochrome P450 and for a variety of substrates and Cpd I species & all this from raw data.

- This is quite a powerful conclusion that emerges from the modeling.

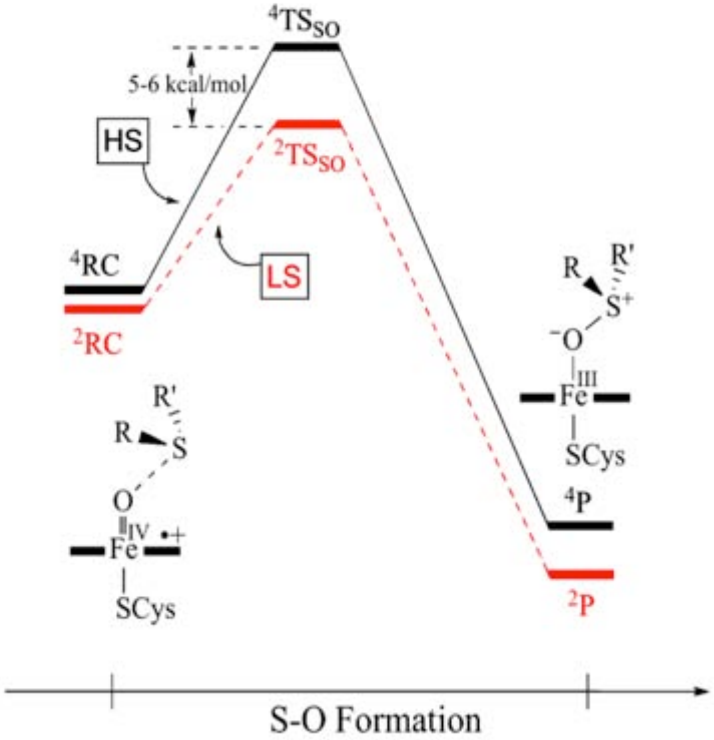
Here are the VB diagrams for sulfoxidation by Cpd I in the two states.



- As before, here too, the promoted states are charge-transfer states.

However, since there are no low-lying intermediate states here, sulfoxidation is a concerted reaction, in accord with experiment and with DFT. Furthermore, note that since $G_{HS}>G_{LS}$, sulfoxidation will proceed only via the LS state.

Here is a reminder of the DFT and DFT/MM results on P450 sulfoxidation



- It is apparent that the VBSCD model predicts well the concerted nature of the reactions, and the spin-state selectivity.
- The same prediction applies to other heteroatom oxidation processes, e.g., to amines, phosphines, etc.

The promotion gap, $G_{HS/LS}$ for sulfoxidation is the vertical charge transfer energy ($IP_{RR'S:}$-$EA_{Cpd\ I}$) without/with the spin-state dependent excitation within the d-block:

$$G_{LS/HS} = IP_{RR'S:} - EA_{Cpd\ I} \ + / \ \Delta E(\pi^* \rightarrow d_{z^2})$$

- **Using the simple expression for the barrier,**

$$\Delta E^{\ddagger} \approx f G_{LS/HS} - B,$$

we know from nucleophile-electrophile reactions, studied in the past, that B ~ 14.0 kcal/mol (roughly allylic resonance) & f~0.2.

- **Hence we can once again use raw data to calculate the barriers.**

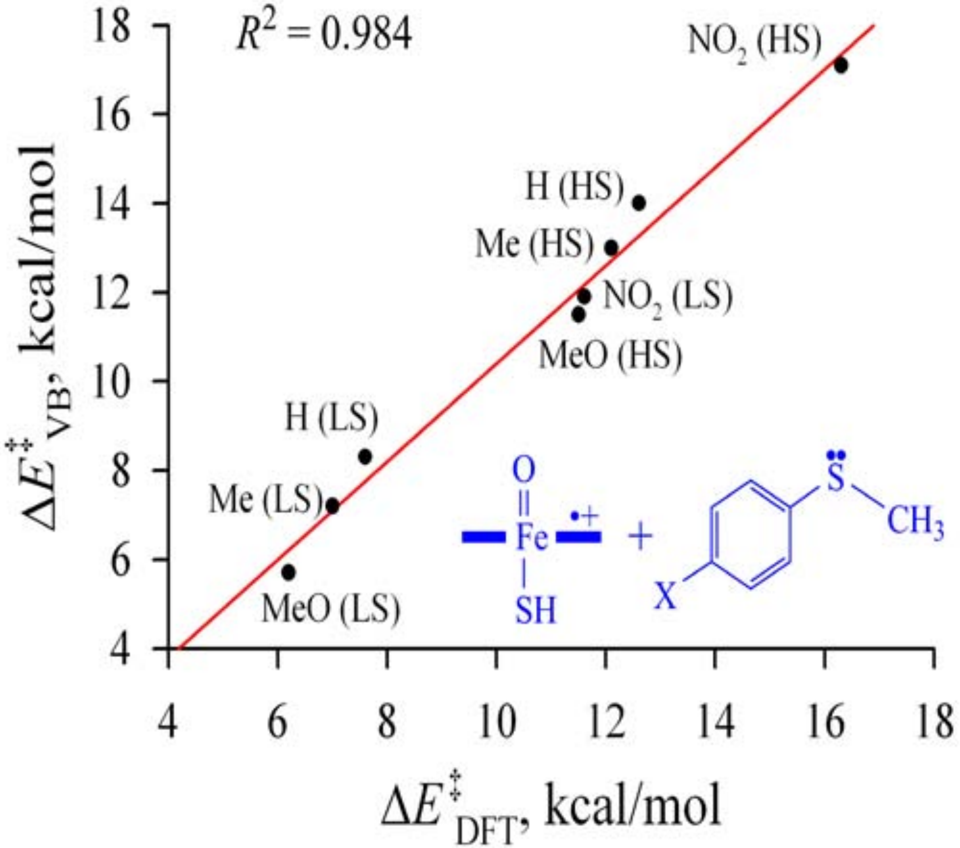
Here are the results:

- As shown by the plot, the so calculated VB barriers correlate well with the DFT barriers for both spin states.

- Moreover, the HS barrier is seen to be consistently larger than the LS one, because the HS gap is larger than the LS gap, by the excitation within the d-block:

$G_{HS} - G_{LS} = \Delta E(\pi^* \text{->} d_{z^2})$,

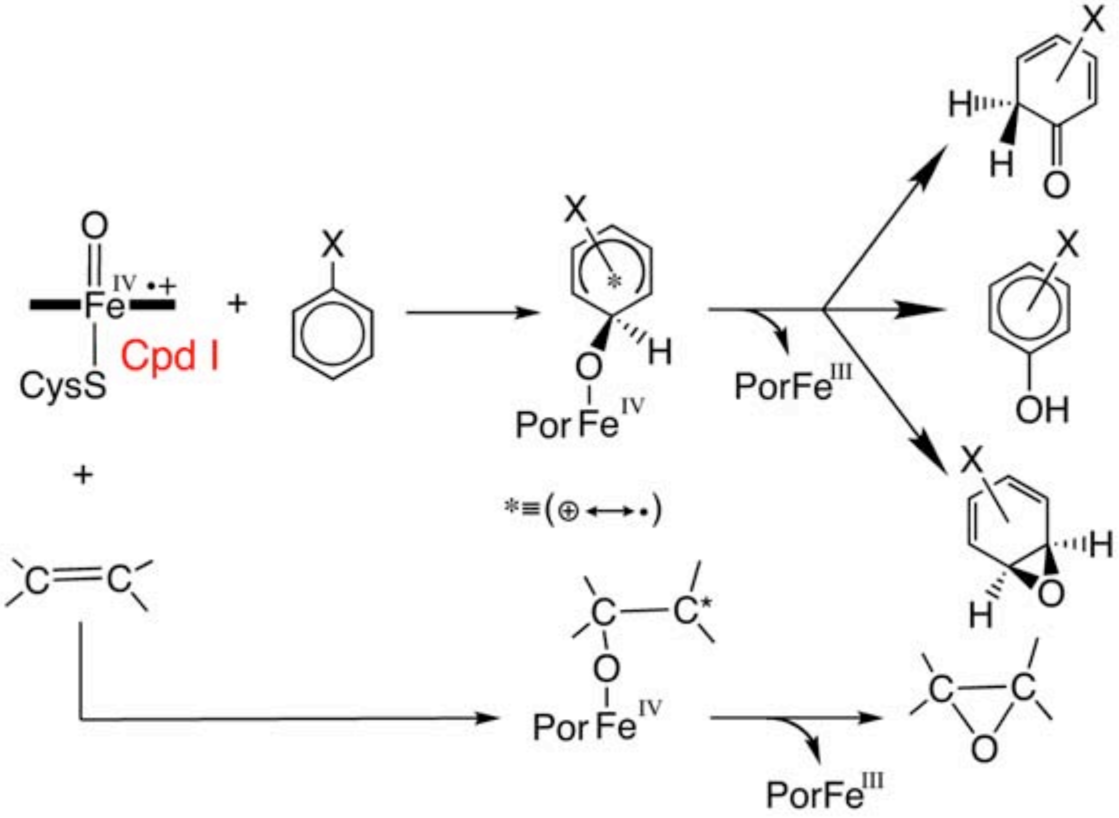
- The correlation with *IP*$_{RR'S:}$ is in line with experimental findings



Let us Turn now to Aromatic Activation and Double Bond Epoxidation:

- In both reactions, the π-activation is rate determining.
- In both cases, the reactivity was found to obey a dual correlation.

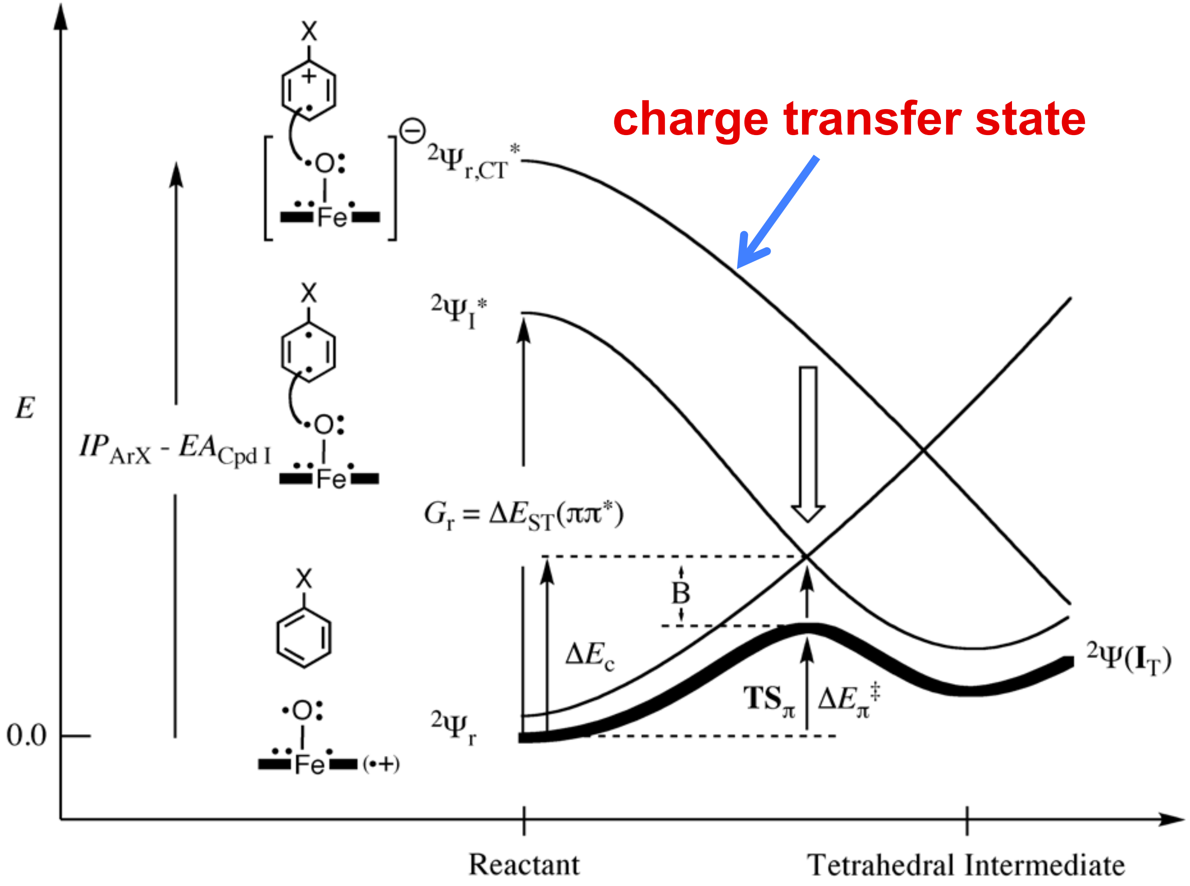
For example, Harvey et al and Ryde et al found that the Hammett plots for reactivity of substituted arenes require two types of σ_X-substituent constants, radical and polar constants, with a higher weight for the radical probe



Shaik, Milko, Chen, Lai, Schyman JCTC, 2011

The reason for the dual correlation is apparent from the VB diagram for aromatic activation by Cpd I:

- Thus, unlike C-H hydroxylation wherein the charge transfer state is far from the crossing point, in π-activation the charge transfer state is low lying, and therefore the charge transfer state mixes into the TS for π-activation


charge transfer state

- The result of this mixing is that the TS-resonance energy B increases with decrease in the IP value of the π-system. And hence the barrier has a dual dependence on both $\Delta E_{ST}(\pi\pi^*)$ & IP_{ArX}.

Shaik, Milko, Chen, Lai, Schyman JCTC, 2011

We have recently modeled the π-activation for a variety of arenes by Cpd I :

The VB barrier was determined by the simple expression:

$\Delta E^{\ddagger} \approx f G_r - B$,

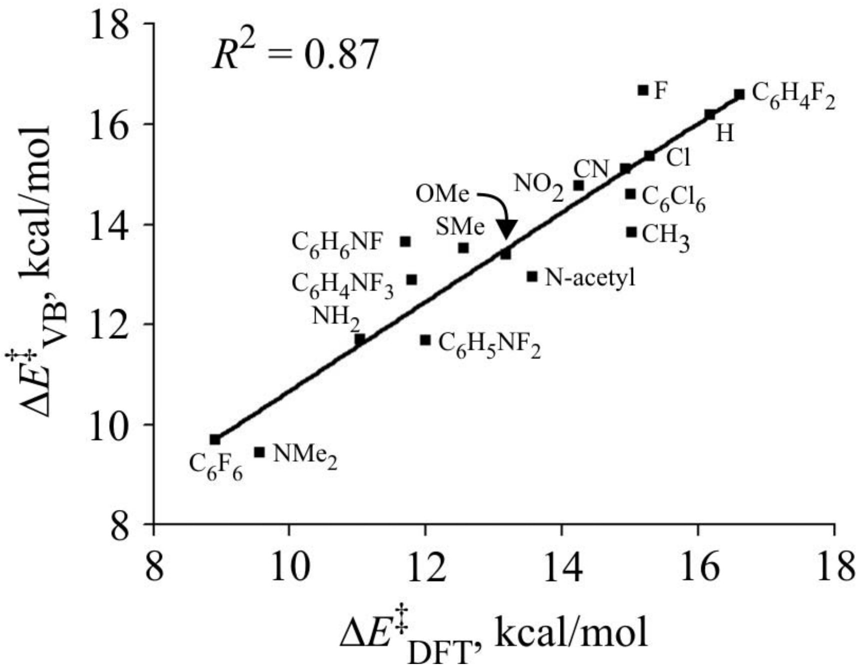
Where:

$G_r = \Delta E_{ST}(ArX)$

$B = B(1/IP_{ArX})$

$f = 0.3$

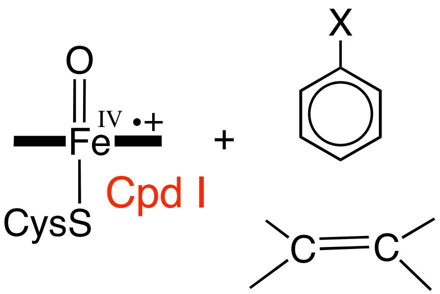
This enables us once again to calculate barriers from raw data



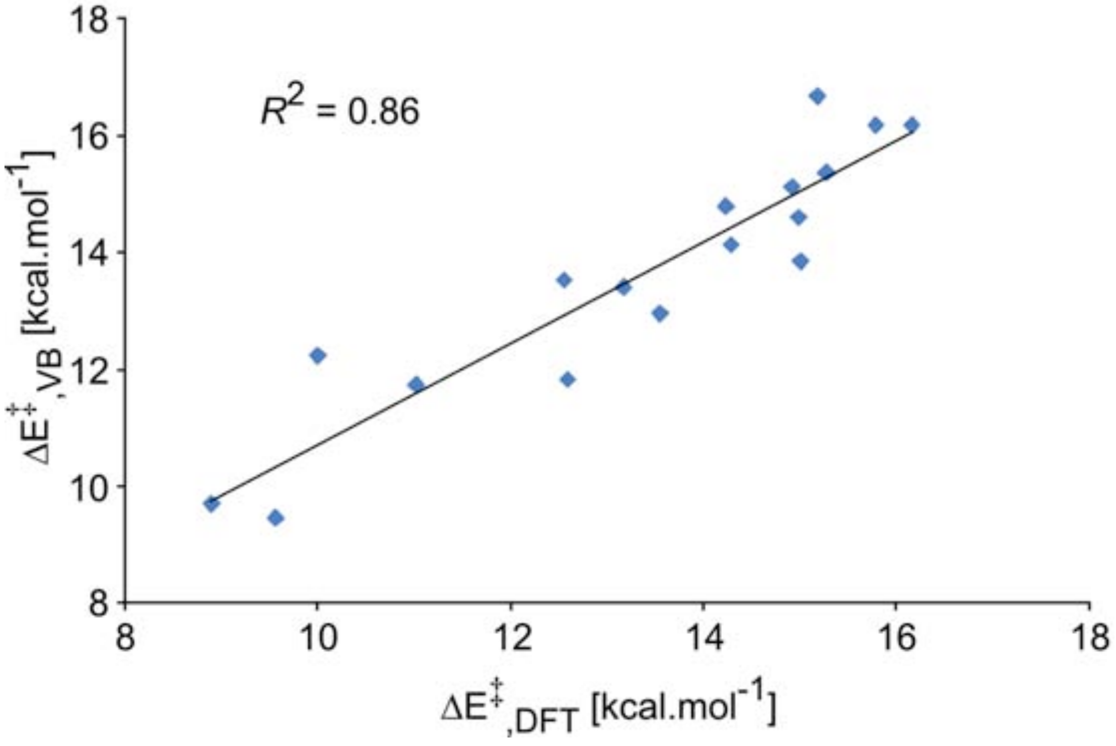
- **As shown by the plot, the correlation is reasonably good**
- **Furthermore, for some of the reactions, e.g., C_6F_6, C_6Cl_6, etc, we simply used the equation and calculated VB barriers based on raw data, and then used DFT results by other groups. As you can see, our predictions fall right on the nose**

Shaik, Milko, Chen, Lai, Schyman JCTC, 2011

Moreover, we recently found that the aromatics and the olefins lie on the same correlation line and have exactly the same expression for the barrier, which reveals the dual correlation noted experimentally:



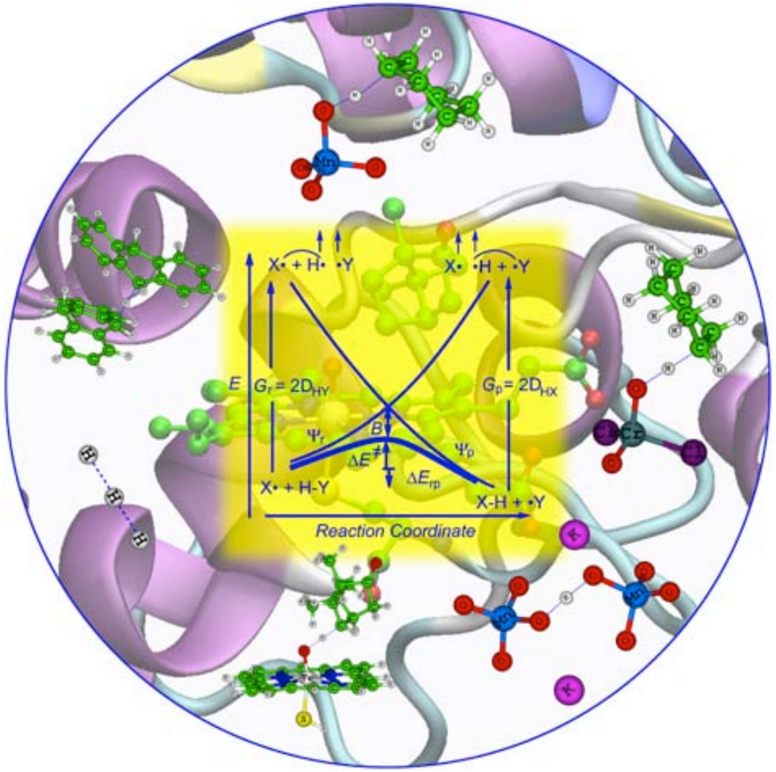
$$\Delta E^{\ddagger}_{VB} \approx 0.3\Delta E_{ST}(\pi) - B(1/IP_{\pi})$$



Shaik, Milko, Lai, in preparation

Let’s Try Something More Ambitious:

- H-atom transfer (HAT) is one of the fundamental processes occurring in nature and in oxidative chemistry:

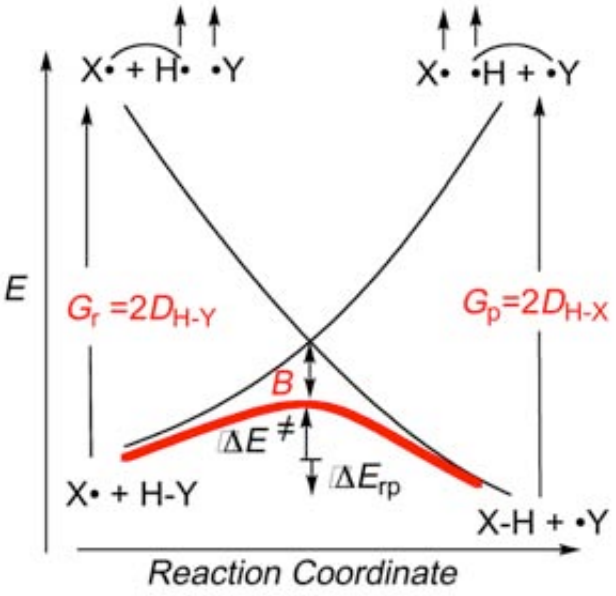


Most chemical oxidations begin with HAT. P450 and nonheme enzymes oxidize organic substrate by initial HAT. Heme enzymes, e.g., HRP, build the cell walls in plants by initial HAT from phenols. Cell membranes are destroyed by HAT. Proteins turn plaques by HAT. DNA damage occur by HAT. HAT occurs during combustion and in atmospheric processes…

The list is endless, attesting to the immense importance of HAT.

Our ambitions goal is to achieve a unified treatment of H-abstraction, namely, for any reaction, starting from $H\bullet + H_2 \rightarrow H_2 + \bullet H$ all the way to P450, and what’s in between.

We shall try to do that by initially estimating barriers for H-abstraction using raw data, and then by deriving insight from these 'numbers'.



For this purpose we must use the explicit expression for the barrier:

$\Delta E^{\ddagger} \approx f_0 G_0 + 0.5\, \Delta E_{rp} + \Delta E_{rp}^2/2G_0 - B$

Where,

$G_0 = D_{HY} + D_{XH}$ (the average promotion gap)

$f_0 = 0.3$

$B = ½\,[BDE(av)] = ¼\,[BDE_{HY} + BDE_{HX}]$

$\Delta E_{rp} = BDE_{HY} - BDE_{HX}$

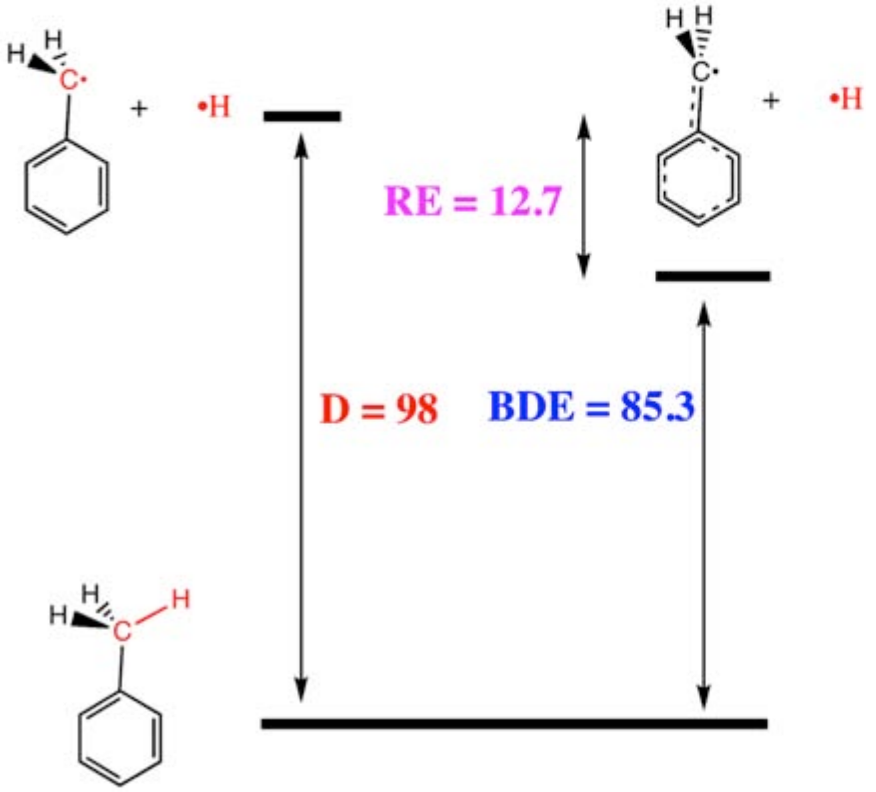
- All one needs for the applications are BDE and D data.

Here is a reminder about the difference between bond dissociation energy (BDE) and the vertical bond strength D?

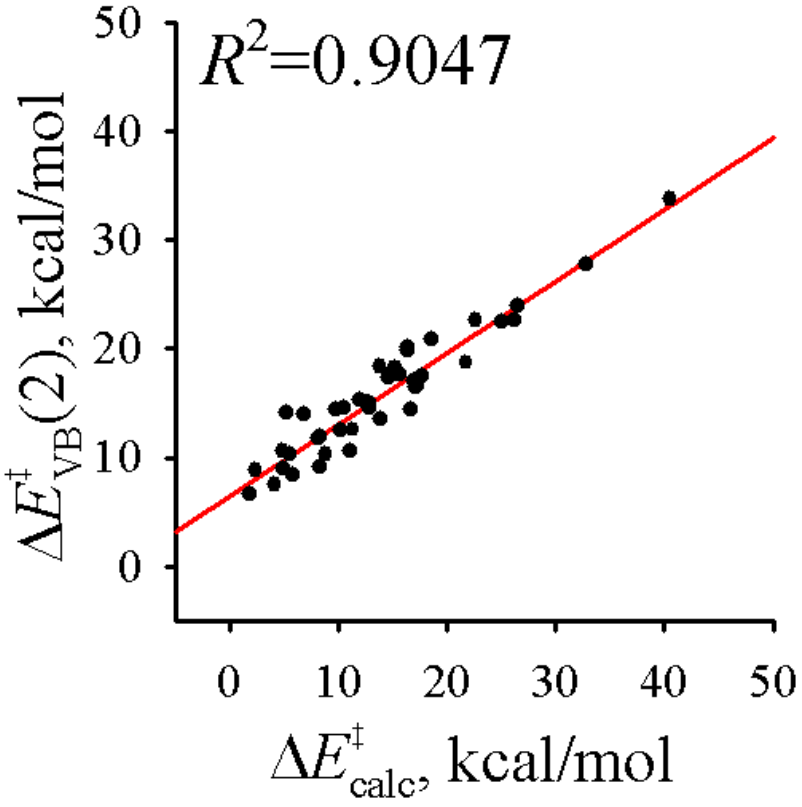
- RE = D – BDE

RE the Reorganization Energy of the radical to become prepared for bonding & it involves both geometric and electronic terms.

- RE should be large for delocalized radicals, and zero for atomic radicals.



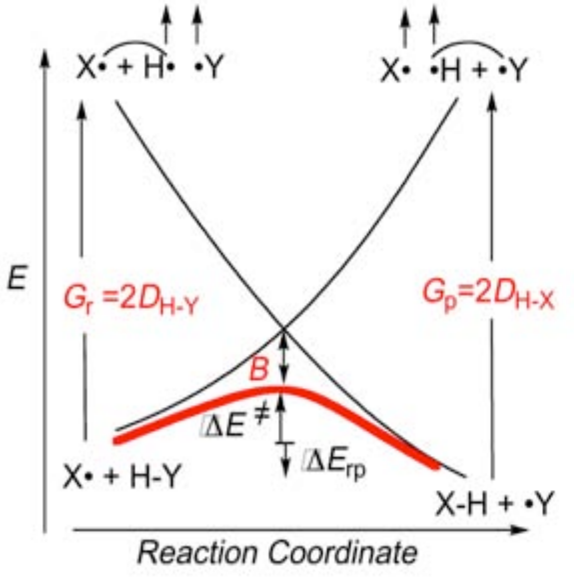
- Here is the plot of the so calculated VB-barriers vs. CCSD(T)/CBS and DFT barriers for 45 reactions including simple H-abstraction reactions (X• + H-Y -> X-H + •Y; X,Y = H, F, Cl, Br, CH_3, SiH_3, GeH_3, OH, SH, HCC, $NCCH_2$, etc), of identity and nonidentity processes, as well as, all the P450 cases I just showed you.



- It seems that the VB model can indeed predict trends in barriers of many seemingly unrelated reactions, and to do so based on raw data.

Our ambitious goal turns out to be successful: We can indeed estimate the barriers for a most fundamental reaction in nature, and do so on a back of an envelope!

Let us try to gain some insight into these successful numbers, by looking at individual barriers:



- To make life simpler, I will consider an identity reaction, X• + H-X ➔ X-H + •X.
- The corresponding barrier is:

$\Delta E^{\ddagger}_{XX} = fG - B = 0.6D_{HX} - \frac{1}{2}BDE_{HX}$

Since $D_{HX} = BDE_{HX} + |RE_{X\bullet}|$,

then the identity barrier is simply:

$$\Delta E^{\ddagger}_{XX} = 0.1[BDE_{HX}] + 0.6|RE_{X\bullet}|$$

This in turn means that a major factor of the identity barrier will, be the reorganization energy that is required "to prepare the radical X• for bonding".

Let us see how this works.

Here are Identity Reactions, BDE/RE values, VB- barriers ($\Delta E^{\ddagger}_{XX}$ = 0.1[BDE_{HX}] + 0.6|$RE_{X\bullet}$|) & reference barriers:

X• + H-X	BDE/$RE_{X\bullet}$	ΔE^*_{VB}	ΔE^*_{expt}	ΔE^*_{theor} ccsd(t)∞/DFT
H + H_2	104.2/0.0	10.3	9.8	
CH_3 + CH_4	104.9/6.9	14.4	14.3	14.9/14.6
F + HF	136.3/0.0	13.5		13.8/-
HCC + HCCH	132.9/0.1	12.2		11.6/12.8
$NCCH_2$ + CH_3CN	95.5/10.7	16.0		17.6/-
Allyl + propene	82.6/16.9	18.4		-/19.4
C_6H_7 + C_6H_8	69.5/20.4	19.2		-/20.6
DHA_{yl}+ DHA	72.8/15.4	16.5		-/17.2

- The VB model can reproduce experimental and high level barriers for identity reactions.
- The major factor of the barrier is RE, which is the “preparation energy” of the radical.

I will now move on to nonidentity reactions, and try to address a recent “hot” debate:

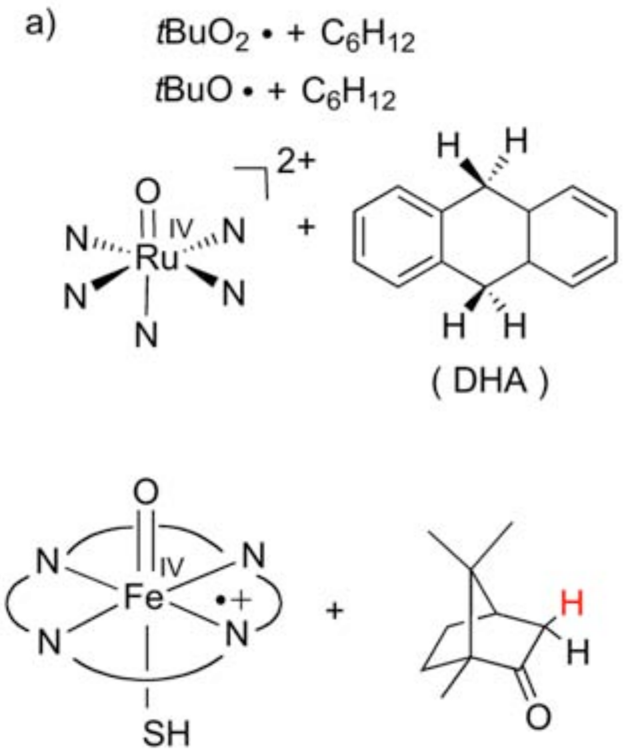
- **Many in the community are of the opinion that H-abstraction requires a radical abstractor.**

- **However, in the 1960s it was pointed out that closed shell reagents like Cl_2CrO_2 and $K^+MnO_4^-$ abstract hydrogen atoms from alkanes. Recently, with the work of Mayer and others like Ruchardt, this has become a focal topic, so much so that the following question is being posed in the recent literature:**

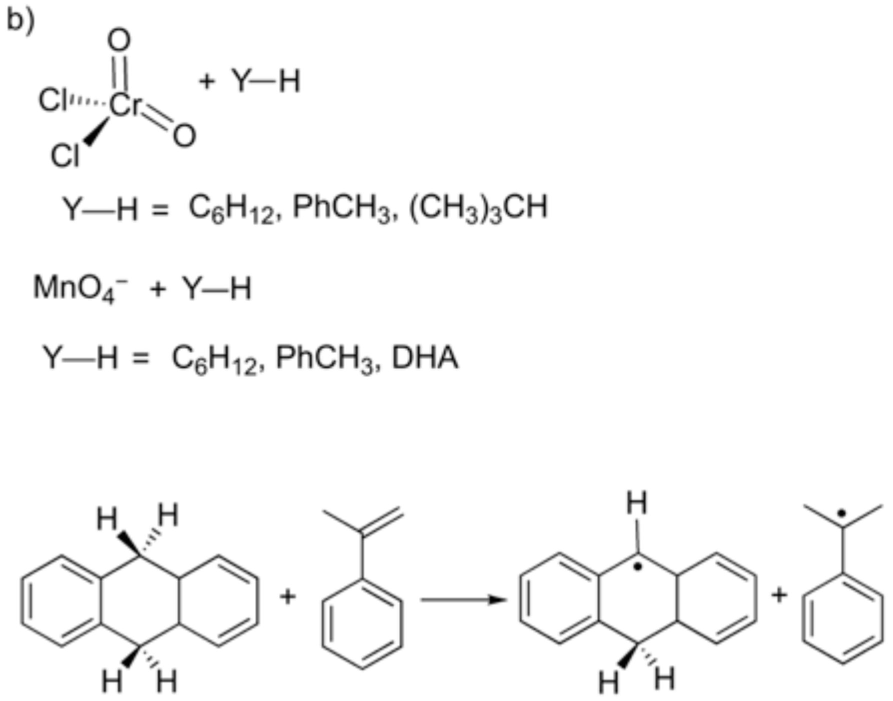
Do We Need at All a Radical to Abstract a Hydrogen Atom?

To address the debate, I will apply the VB expression to predict experimentally known barriers for the nonidentity reactions, which include radical and closed-shell abstractors:

Here are some of these reactions:



Open shell



Closed shell

The VB barriers were estimated by use of the explicit expression for the barrier:

$$\Delta E^{\ddagger} \approx f_0 G_0 + 0.5\,\Delta E_{RP} + \Delta E_{RP}{}^2/2G_0 - B$$

As before:

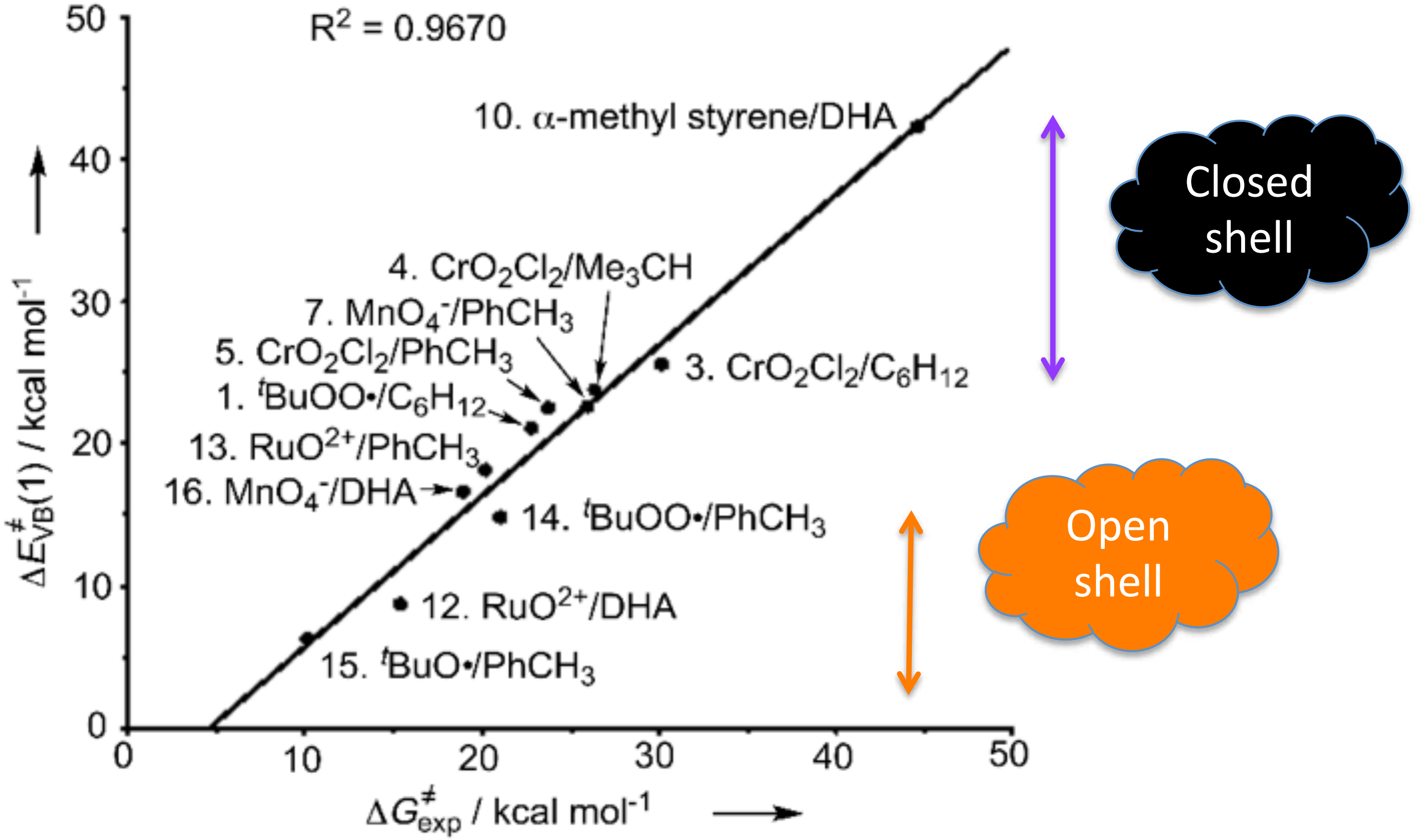
$f_0 = 0.3$

$B = ¼\,[BDE_{HY} + BDE_{HX}]$

$\Delta E_{rp} = BDE_{HY} – BDE_{HX}$

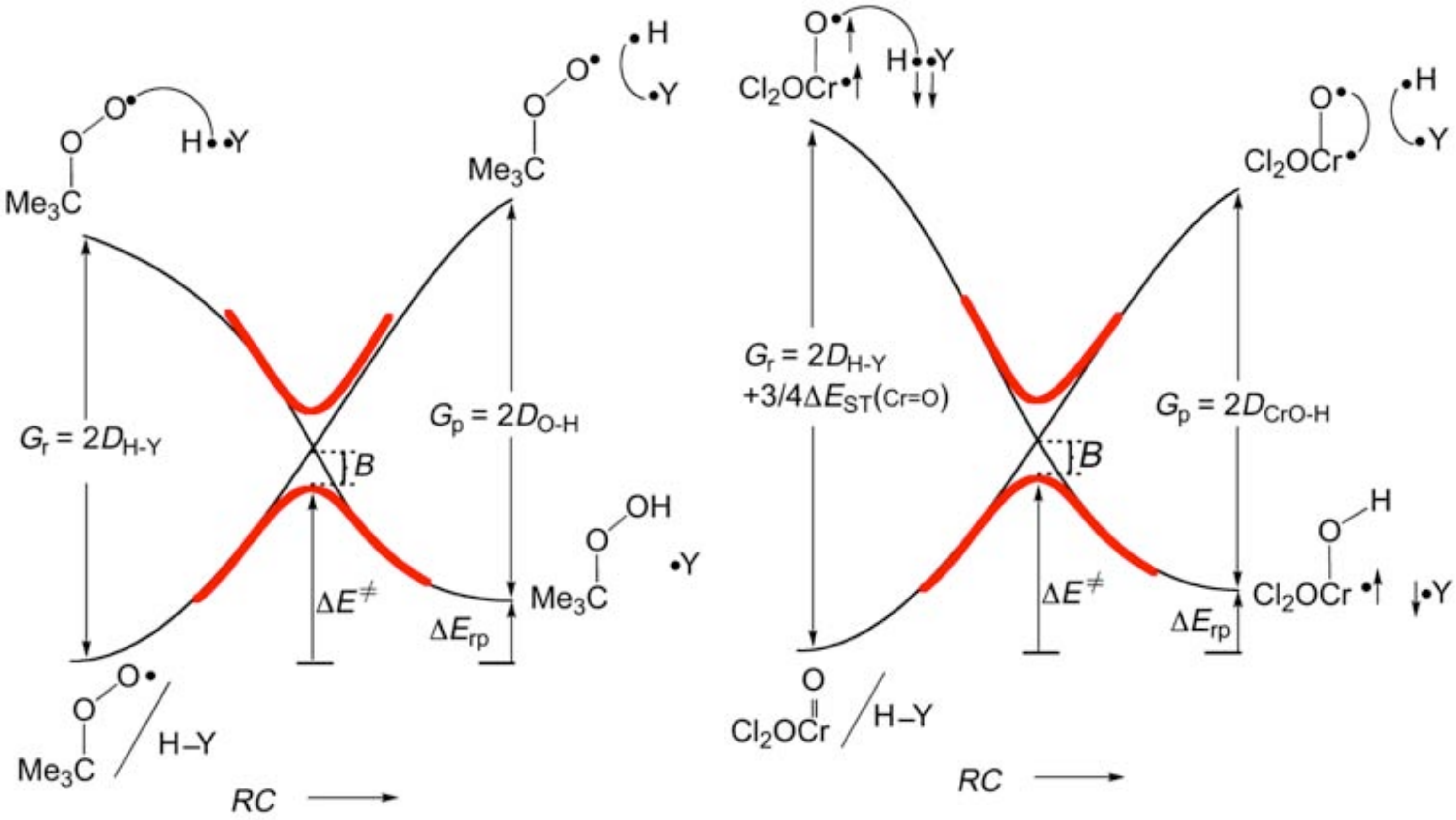
- **However, G_0 which is the average promotion gap, depends now on whether the abstractor is a radical or a closed-shell molecule.**

Here are the predicted VB barriers plotted again the experimental free energies of activation $\Delta E^{\ddagger}\,(1) \approx f_0 G_0 + 0.5\,\Delta E_{RP} + \Delta E_{RP}{}^2/2G_0 - B$



- **The VB barriers predict very well the experimental trends.**
- **Note that the closed-shell abstractors have higher barrier than the open-shell radical abstractors.**
- **Can we provide insight?**

Yes, we can! Here are the VBSCDs for an oxyl radical abstractor compared with a closed-shell oxo abstractor, having the same ΔE_{rp}



- It is seen that the closed-shell abstractor has a higher promotion energy due to the need to prepare a radical at the Cr=O bond by triplet de-coupling of the corresponding π-bond electron pair. And this is the root cause of the higher barrier for Cl_2CrO_2 compared with the oxyl radical having the same reaction driving force.

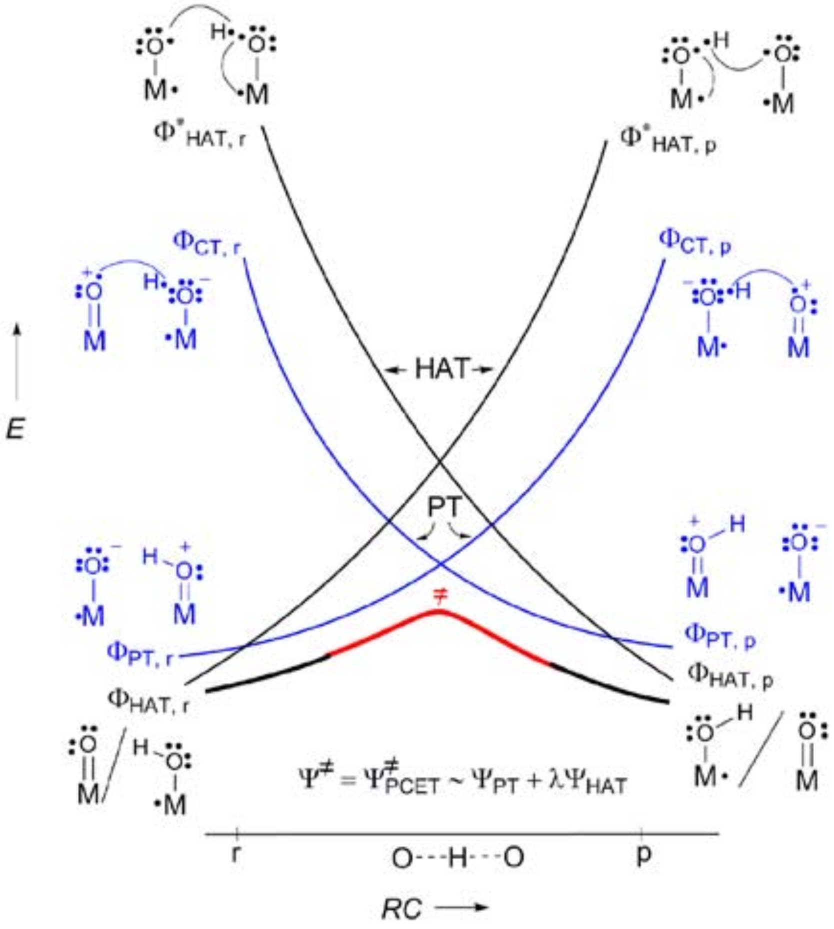
Back to the question:
Do We Need at All a Radical to Abstract a Hydrogen Atom?

- The answer of the VB modeling is:

NO we don’t. But then we must usually pay for this with the cost of creating this radical along the reaction coordinate.

- This is a good point to stop and start to summarize this section of my talk which tells part of a broader story, which is ongoing.
- More insight is discussed in a recent review in ACIE and in Chem. Sci. Both articles are in the website of the Workshop.

  - For example, here is the VB diagram showing the relationship between HAT and the proton-coupled electron transfer (PCET) mechanisms, and the blending of these two limiting mechanisms of H-abstraction.

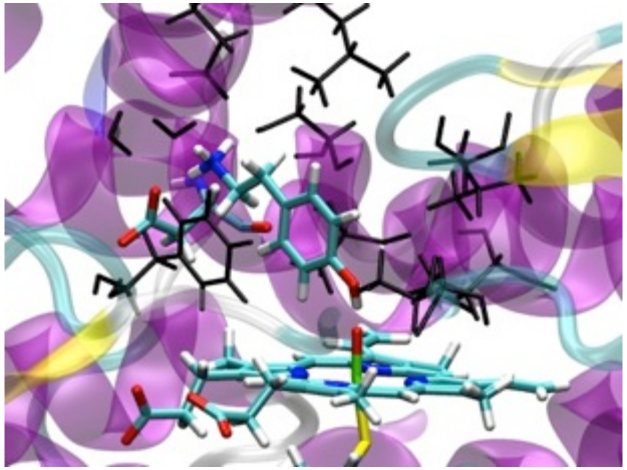


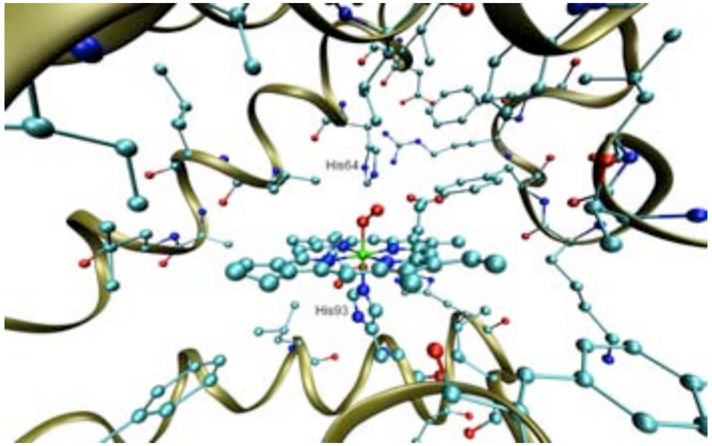
Lai, Li, Chen, Shaik, ACIE 2012, 51, 5556
Li, Danovich, Shaik, Chem. Sci. 2012, 3, 1903.

Thus, to summarize this part:

- **VB modeling is a useful interface between experiment and theory, and between computations (generating numbers) and understanding.**
- **It can create order, predict mechanisms, & estimate barriers for complex reactions from raw data, thus providing insight into Bioinorganic Chemistry and Chemistry, in general.**

- **The model follows the Coulson dictum: it provides not only numbers but also insight. It enables to see the forest from the trees.**





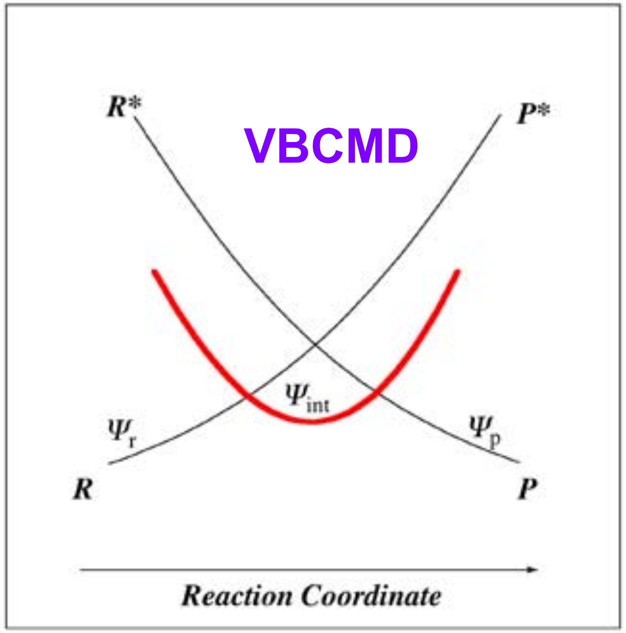
H• + H-H ➔ H-H + •H

In Summary of Stories 1 & 2, Thanks to:

Wenzhen Lai (47 reactions!),
Chunsen Li (more than 30 reactions)
Hui Chen (CH activation)
Petr Milko (arene activation)
Yong Wang
Usha Dandamudi
Patric Schyman
&
Samuel de Visser (2008, Cpd I)
Devesh Kumar (2008, Cpd I)

Let’s turn to the short stories, which try to show the amount of insight provided by VB theory in a wide variety of problems.

Some Examples of VBCMD



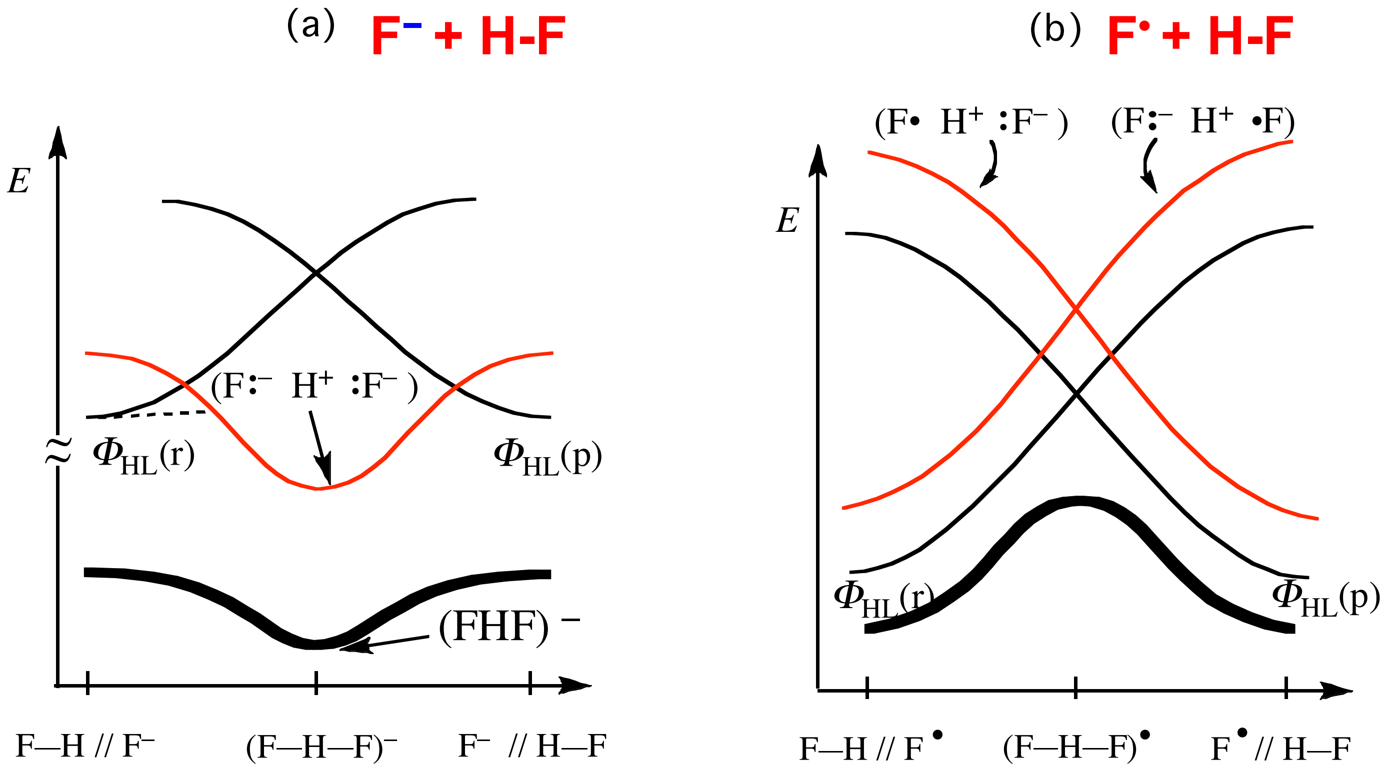
- **Intermediate curves have two origins:**

(a) Ionic Structures that are usually high in energy, cross <u>well</u> below the HL curves, leading to a stepwise mechanism, e.g., S_N1 or S_N2_{Int}

(b) There are many excited states other than *R and *P**. These excited states may get low enough and cross the main curves that describe the reaction *R* → *P*. Since these excited states are NOT related to the *R* → *P* and* and R* → *P* state curves, we call such cases "foreign states". We have seen one in P450 hydroxylation.**

- **I will proceed with a few examples focusing on ionic structures.**

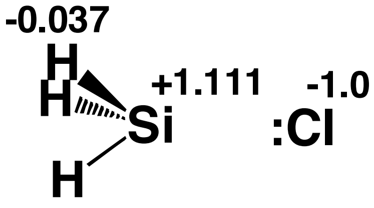
The Impact of a Single Electron

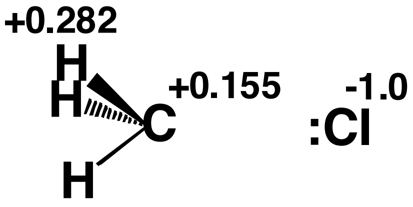


- With one electron less, the ionic structure loses at least 50% of its stabilization and rises in energy. The result is that the $(FHF)^{\bullet}$ species is a high energy TS (20 kcal/mol higher than F + HF), compared with the highly stable $(FHF)^{-}$ where the triple ionic structure, $F:^{-}\ H^{+}\ {}^{-}F:$ is of very low energy.

S_N2(C) vs. S_N2(Si)

- We know that nucleophilic displacements on carbon proceed via a TS, which is pentacoordinated. By contrast, in the case of silicon the pentacoordinate species is a stable intermediate. Why?
- Let' s have a close look at ionic structures of C-Cl and Si-Cl bonds:





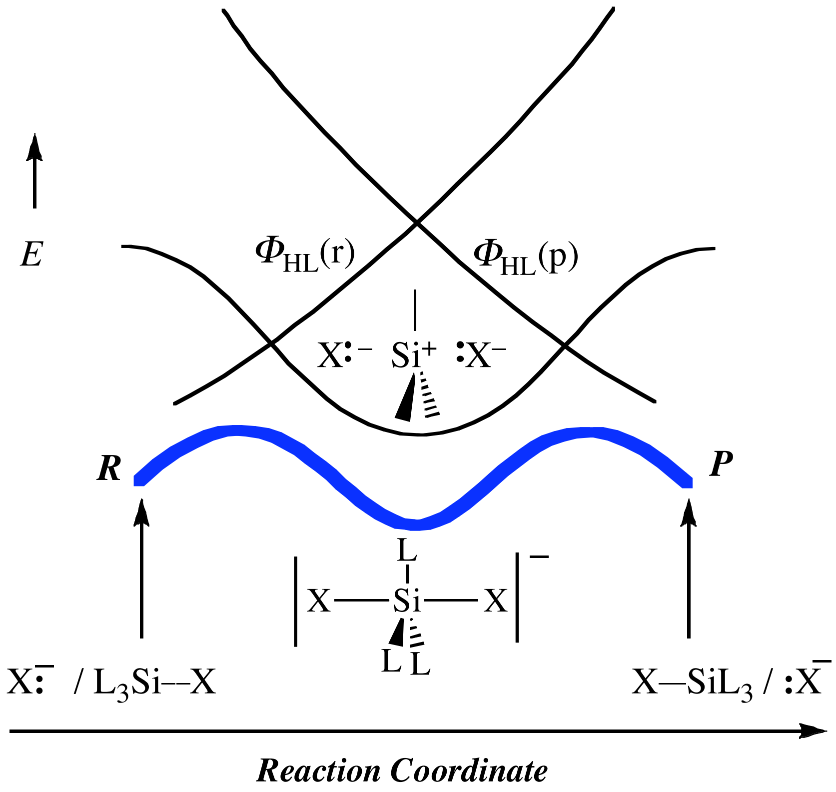
R_{ion} = 2.22 Å $\quad$ R_{ion} = 2.48 Å !!!

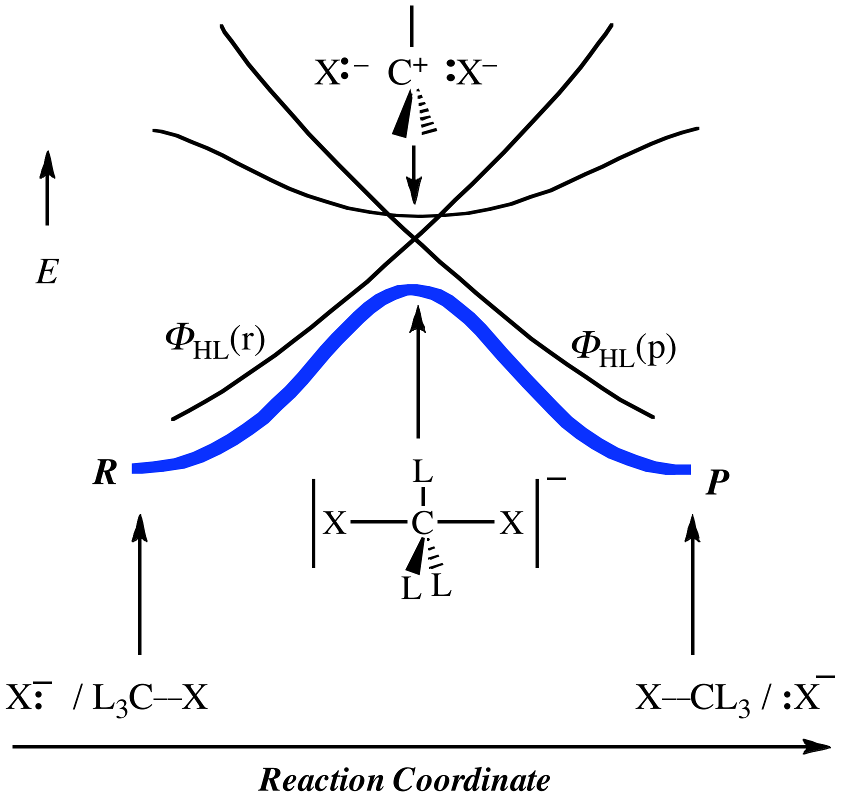
R_{cov} = 1.97 Å $\quad$ R_{cov} = 1.81 Å

$R(SiH_3^+)$= 0.31 Å $\quad$ $R(CH_3^+)$= 0.67 Å

R_3Si^+ is a small ion in the direction of the C_3 rotation axis, small like a proton. Thereby it will allow close approach of anions and significant electrostatic stabilization. This is due to the positive charge delocalization in Si vs. delocalization in C.

S_N2(C) vs. S_N2(Si) - Origins of Hyper-coordination

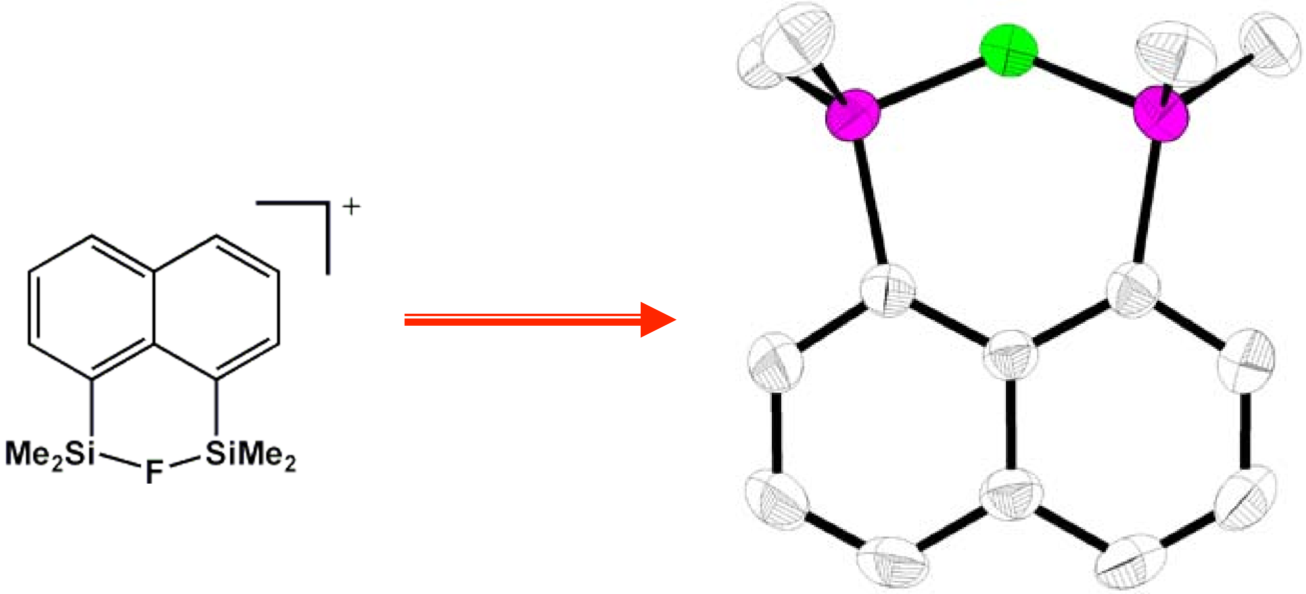




The triple ionic structure for Si is very stable, since all the positive charge is localized on Si. This makes Si$^+$ effectively small like a proton.

An Interesting Manifestation of the Small Size of Si$^+$ and the Ensuing Electrostatics:

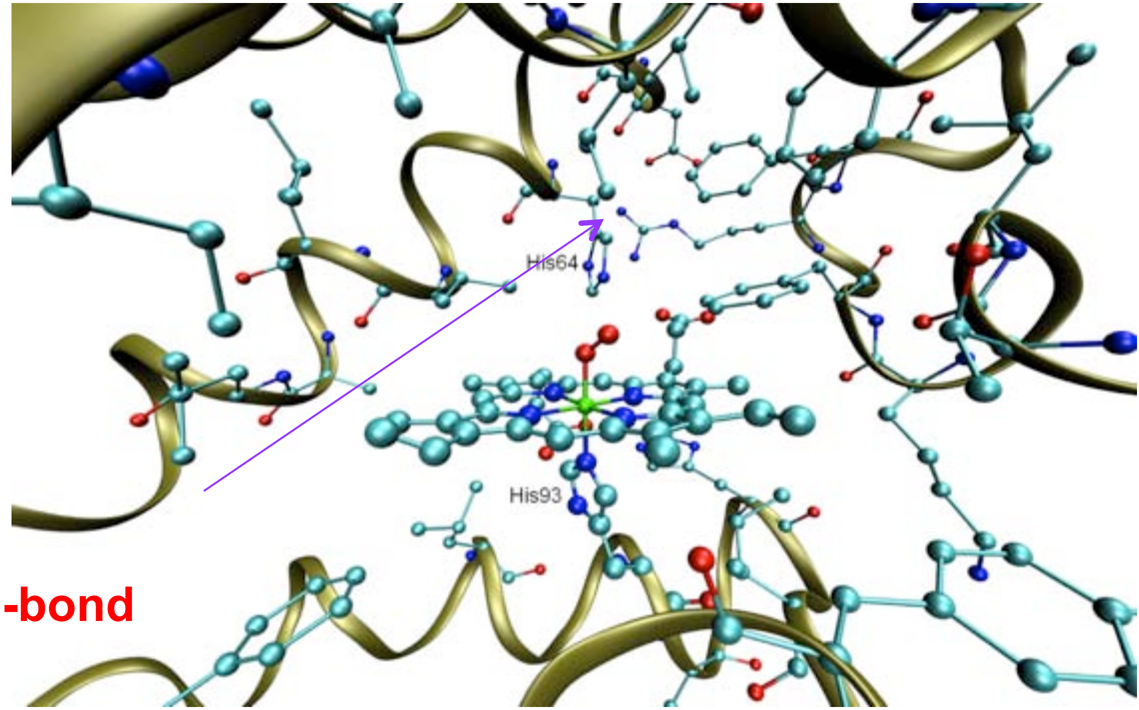
- Thus, we have a ymmetric (Si---F---Si)$^+$ cation due to low energy Si$^+$:F$^-$ $^+$Si structure:



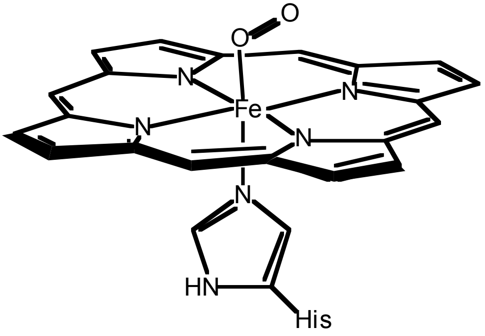
The carbon analog has <u>an asymmetric C-F…..C$^+$ Structure</u>! It has an intact C-F bond and a C+ center on the other side.

Mueller, Hirao, Shaik, *Organometallics*, 2011, 30, 4087

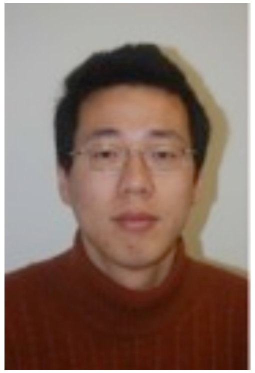
Let me turn now to the 4th Story by showing that VB reading of a complex wave function of the Oxy-Mb can resolve controversies and provide a paradigm for future understanding in bioinorganic chemistry.



H-bond



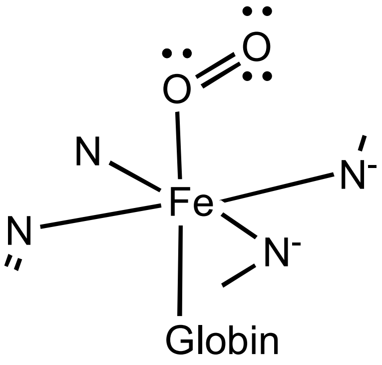
$Mb\text{-}O_2$; $Hb\text{-}O_2$



H. Chen. M. Ikeda-Saito & S. Shaik, JACS 2008;
Shaik & Chen, JBIC 2011

The Pauling-Weiss Controversy

- In 1936 Pauling and Coryell measured the magnetic susceptibility of both "free" Hb & Oxy-Hb . They found Hb to be high-spin while Oxy-Hb was diamagnetic. Based on the diamagnetism, they suggested the model (a), which involves coupling of diamagnetic Fe(II) and $^1O_2$

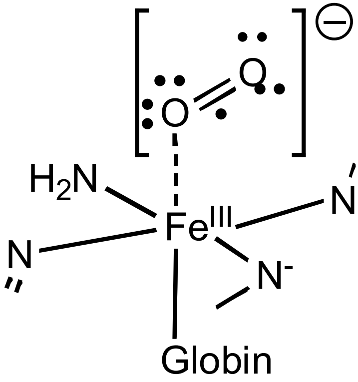


(a)

$Fe^{II}•O{=}O$

$Fe^{II}(S{=}0)•O_2\ (S{=}0)$

- In 1964 Joseph Weiss considered spectroscopic data and chemical behavior of model Fe•O_2 complexes in solution, & argued in favor of another model, in which Fe^{II} transfers an electron to O_2 and the two "radicals" couple to a singlet spin to give the complex described in (b):



(b)

$Fe^{III}•(O{=}O)^-$

$Fe^{III}(S{=}1/2)•O_2^-\ (S{=}1/2)$

Chen, Ikeda-Saito Shaik, JACS 2008;

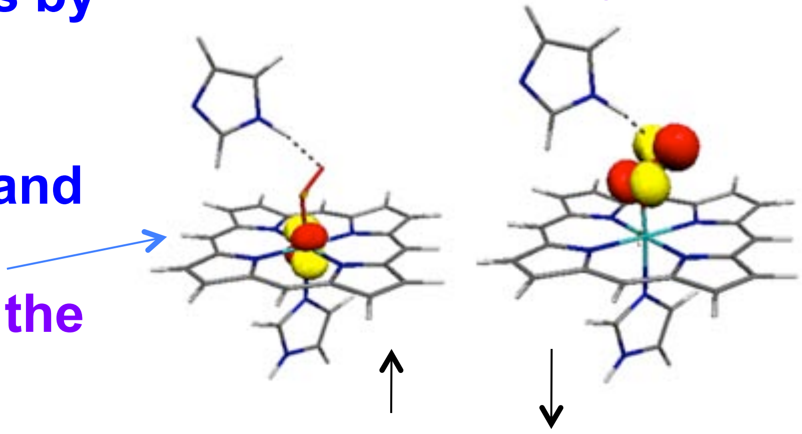
This Pauling-Weiss controversy started a 50-years debate on the nature of the Fe-O_2 bonding in oxy-heme enzymes. I wish I had sufficient time to tell you this fascinating story. But I don't…

- **So, let me jump to the end of the debate, when DFT calculations became available:**

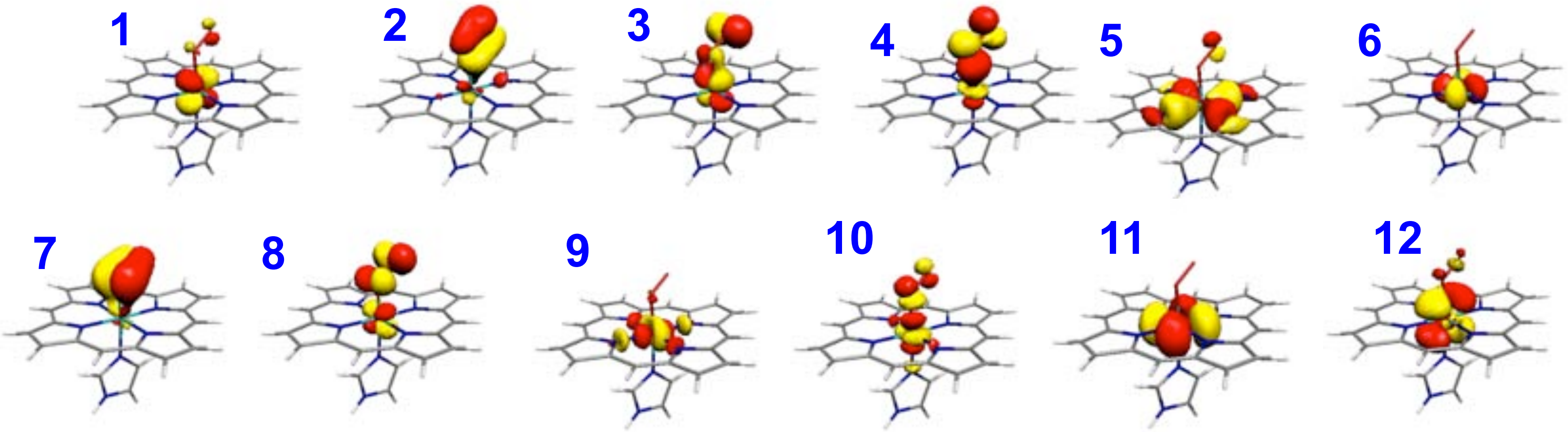
- **Thus, DFT & DFT/MM calculations by many groups (Rovira, Parrinello, Thiel, Morokuma…) showed significant negative charge on O_2 and gave an open-shell singlet ground state, with one electron on Fe and the other on O_2.**

- **This description strongly supported the Weiss model, but not the Pauling's model.**

The NSOs of Oxy-Mb:



By contrast, CASSCF/MM revealed ONLY closed shell CSFs:

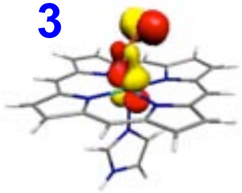


Singlet (CSF)	
$1^2 2^2 3^2 4^2 5^2 6^2 7^2 8^0$	66.5 %
$1^2 2^2 3^0 4^2 5^2 6^2 7^2 8^2$	23.6%
Others	<1%

- This result seems to lead to the conclusion that Pauling was right, Weiss was wrong, and DFT is useless. But, is it really so?
- VB reading of the CASSCF wave function shows that the answer is definitely NO!

Here are the main elements of the VB ‘reading’ of the CASSCF Wave function:

3



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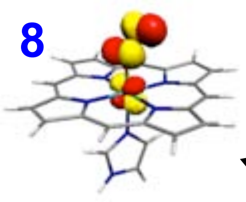


bonding-antibonding pair of π-MOs

- The CAS/MM wave function is 90% a TCSCF wave function wherein all the orbitals are doubly occupied except for ϕ_3 and ϕ_8, which are either vacant or doubly occupied. The TCSCF wave function which can be written as follows:

(1) $\Psi_{TCSCF} = N\,\{a|\ldots \phi_3 \overline{\phi_3}| - b|\ldots \phi_8 \overline{\phi_8}|\}$; a and b are coefficients.

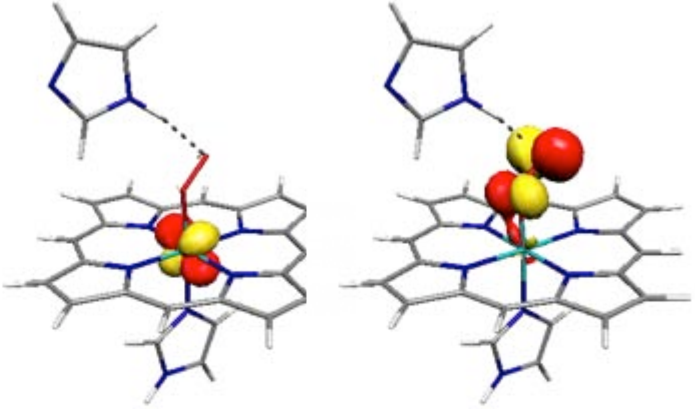
- Much like in the classical textbook example of H_2, the TCSCF wave function in equation (1) can be transformed to a GVB wave function:

(2) $\Psi_{GVB} = N_{GVB}[|\ldots \psi_1 \overline{\psi_2}| - |\ldots \overline{\psi_1} \psi_2|]$;
$N_{GVB} = 1/2[1 + S^2]^{1/2}$ $S = <\psi_1 | \psi_2> = (a^2-b^2)/((a^2+b^2)$

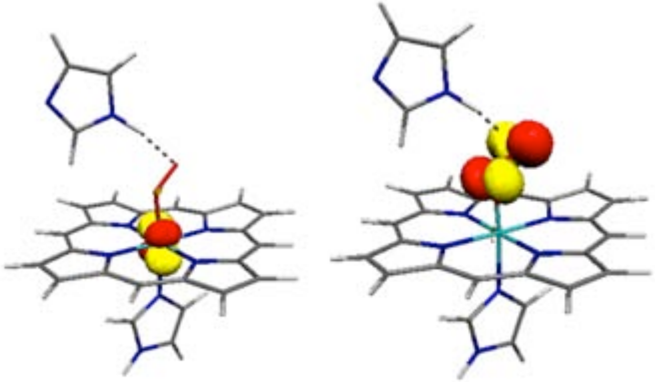
- The GVB wave function describes a bond-pair: two electrons, one in ψ_1 the other in ψ_2 , which are spin paired like in the famous Heitler-London-covalent wave function, having an $\alpha\beta-\beta\alpha$ spin wave function.

So, Is DFT Wrong?

- Here are the transformed singly occupied orbitals for the CASSCF/MM wave function, shown alongside the singly occupied DFT natural spin orbitals:



CASSCF/MM GVB orbitals

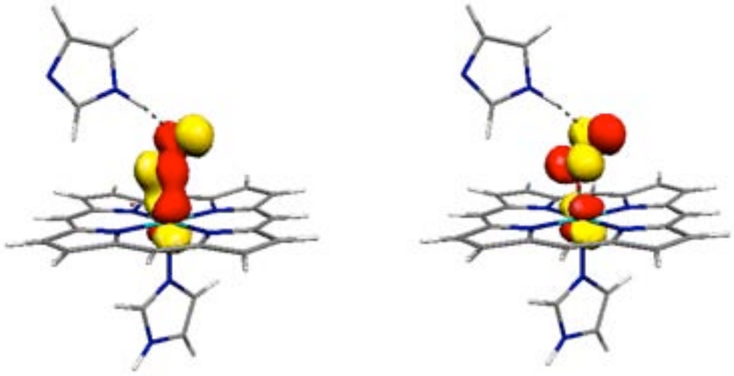


DFT/MM NSOs

- Clearly, the DFT/MM &CASSCF/MM descriptions are virtually identical. The DFT determinant is not spin adapted! But this is easy to remedy…
- Furthermore, we found that both DFT and CAS have about the same negative charge on O_2, ~ -0.5 , and a singlet-triplet gap of 7.4-8 kcal/mol.
- It therefore follows that, DFT is OK, CASSCF is OK, and Weiss was right while Pauling was wrong...

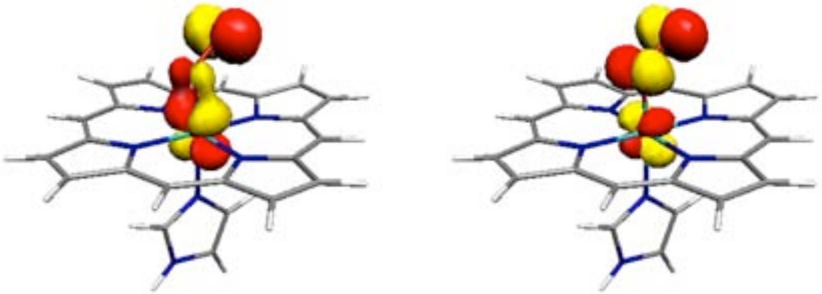
Further Support of DFT

- One can further strengthen the case for DFT by inspecting the occupation numbers in the Kohn-Sham Natural Orbitals vis-à-vis the CAS/MM Orbitals:



1.35e 0.61e

KSNOs



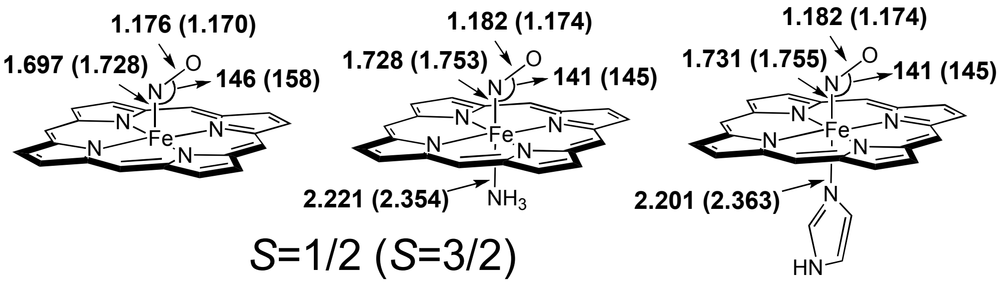
1.46e 0.58e

CAS-MOs

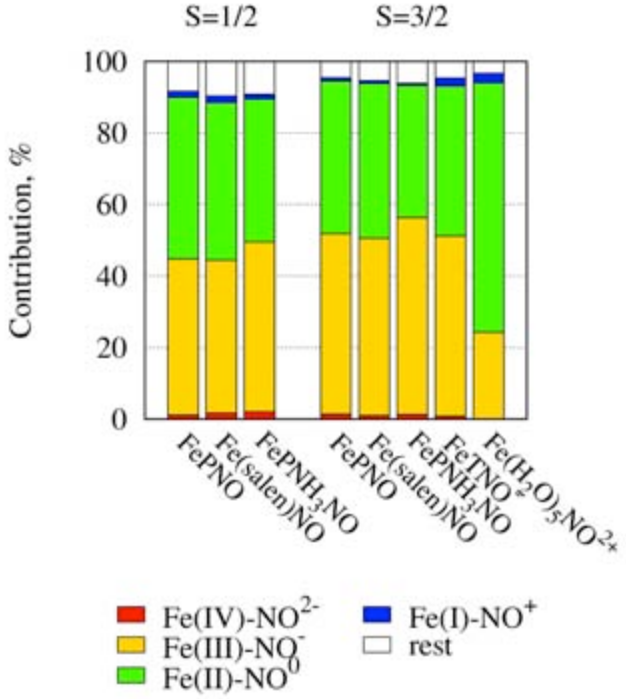
- The occupation numbers are close, and it is apparent that by breakage of the spin symmetry, DFT is trying to emulate a TCSCF situation in order to account for the missing static correlation in the single KS-determinant.

VB Reading of Complex Wave Functions can be done routinely for example, the analysis of

Nitrosyl Complexes, $\{Fe^{II}\ NO\}^7$, for which there has been a two-decades old debate on the oxidation state of Iron.



- **The VB-reading was done by localizing the CASSCF orbitals and re-doing the CAS with these localized orbitals, which in turn, generates a VB-type wave function.**
- **Doing so it was possible to tell that Fe-NO is described mainly by:**
  $Fe^{III}NO^{1-}$ & $Fe^{II}NO^{0}$ and has 2.5 bonds between Fe and NO.
- **End of Dilemma**



Radon, Pierloot et al, JPCB, 2010

The final Story concerns
Photochemical
Reactivity – Sorry but no time left.

Read Ch. 6,11 and some of Ch. 7.
Philippe will tutor conical intersection.

I have a feeling I have talked enough and it is time to conclude:

- I have tried to project the unique and wide-ranging insight that VB theory offers a into so many areas of chemistry:
- It creates order, predicts mechanisms, estimates barriers for complex reactions, enables one to think about excited states and photoreactivity, and it elucidates also complex MR/MC wave functions. And there are many, many more topics, like bonding, etc …
- I think it is time to bring back VB theory into the classroom and into the research desk of chemists!

81-84

84-2012…

96-2012…

92-2012…

94-99…