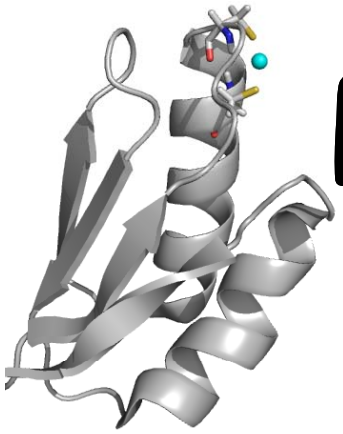
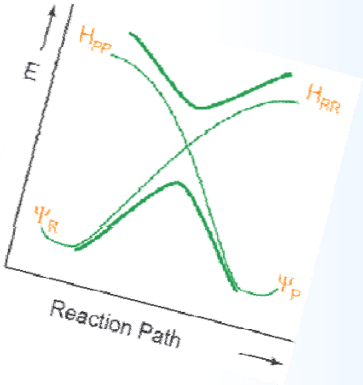


VB/MM Insights into Enzyme catalysis



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The Hebrew University of Jerusalem

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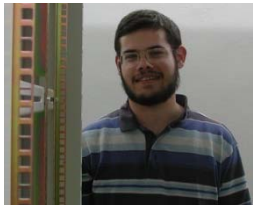
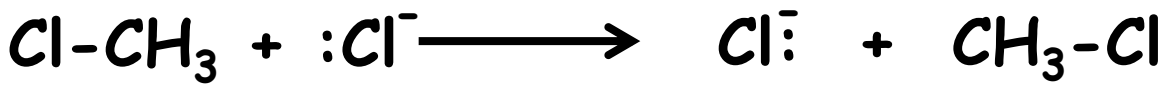


Interested post-docs are most welcome to the group to continue with this and other interesting projects

$$$ Israel Science Foundation (ISF)
Human Frontiers of Science Program (HFSP)
Alex Grass Center for Drug Design and Synthesis of Novel Therapeutics

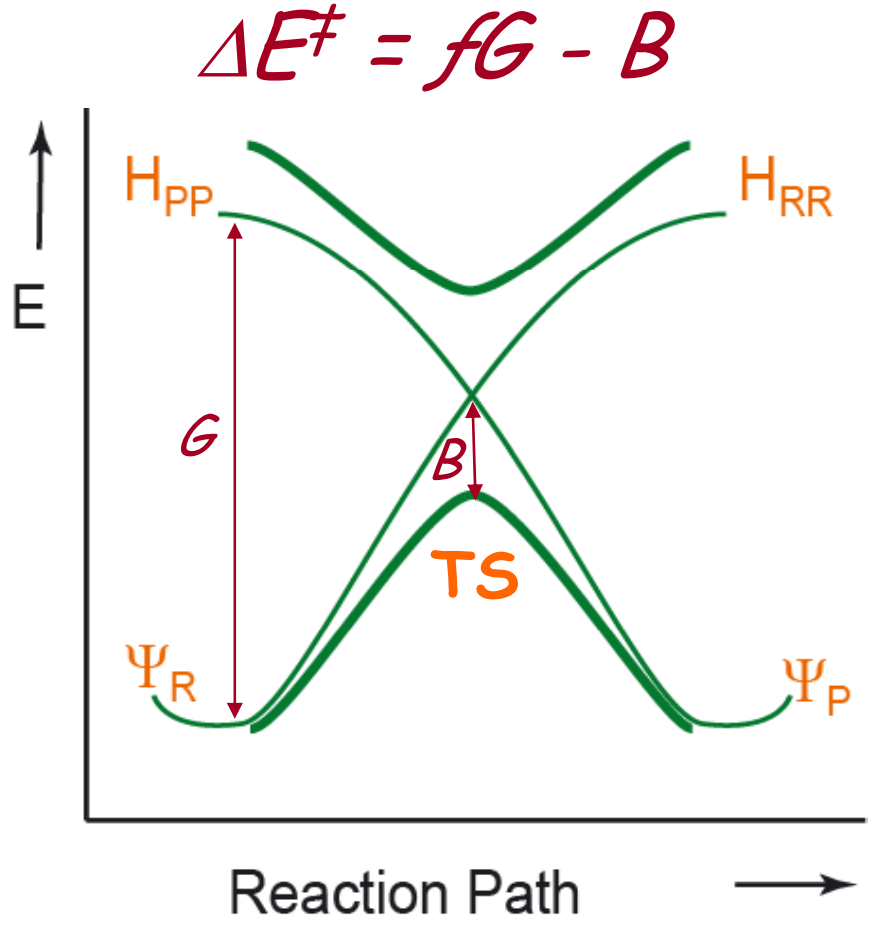
VB – Reactivity Tool



VB Structures

Ψ_R $Cl\cdot\cdot\cdot CH_3$ $:Cl^-$

Ψ_P $Cl:$ $CH_3\cdot\cdot\cdot Cl$



Empirical VB (EVB)

Advantages

- Simple picture of reactivity
- Relatively fast
- Comparative – reduces mistakes
- Calibration – reliable results
- Good & easy description of Reaction Coordinate

Disadvantages / Problems

- QM region - parameterization
- Difficult to handle more than two states
- Strong assumptions

ab initio VB/MM

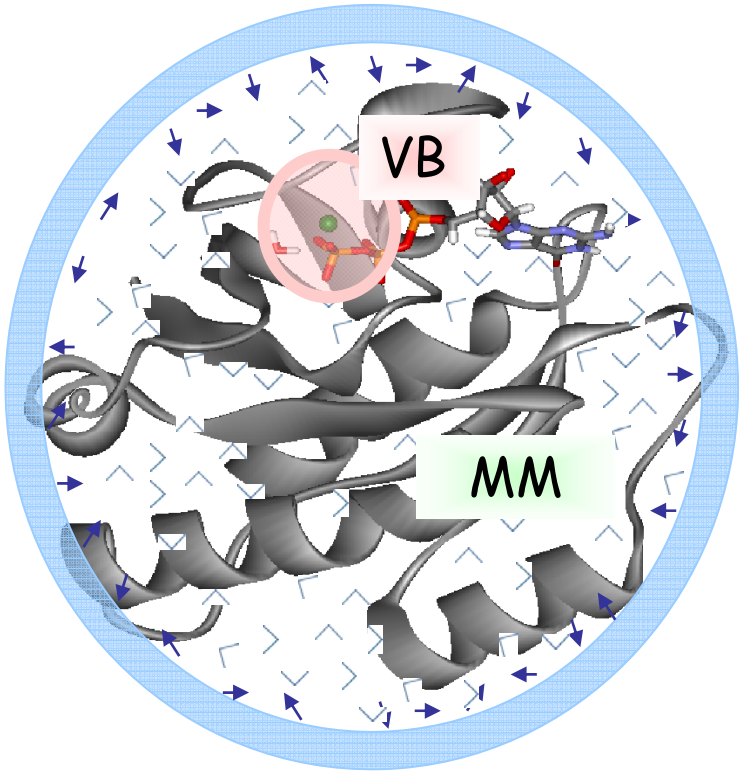
Ab-initio VB/MM

$$H_{VB/MM} = H(VB) + H(MM) + H(VB/MM)$$

Bonding

Electrostatic

✓VdW



HOW?

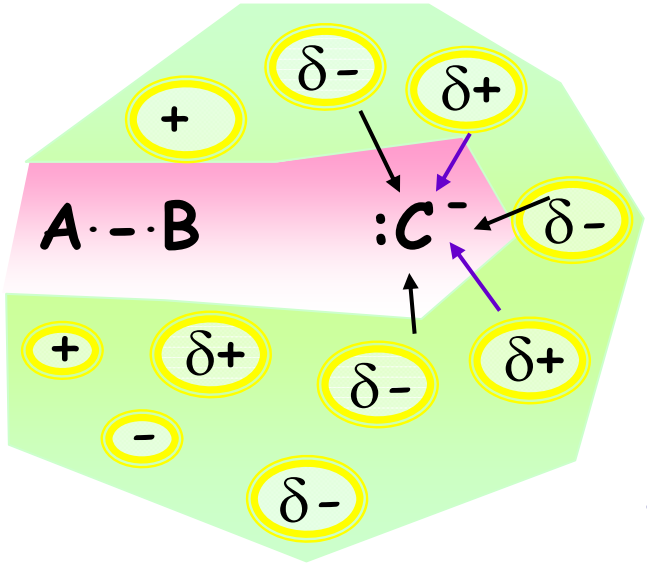
- **VdW** – classically
- **Electrostatic**:
  Mechanical embedding each VB structure
  → Wavefunction polarization (electrostatic embedding)
-

Shurki & Crown JPC B, 2005 109, 23638

ab initio VB/MM

VB structures – Electron localization

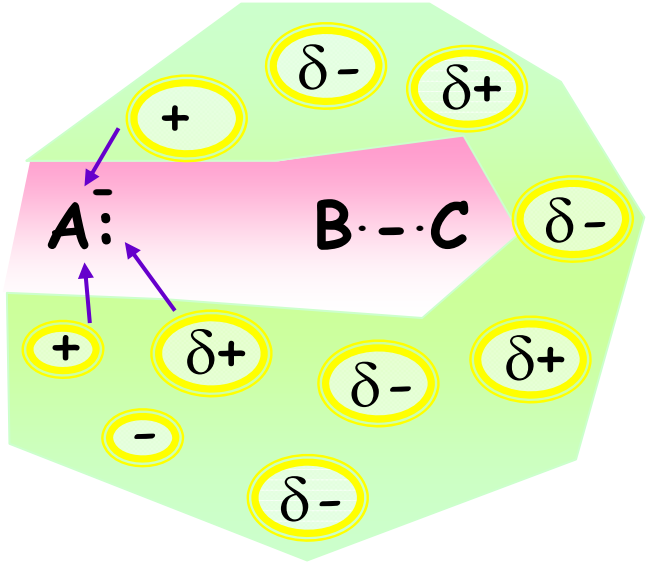
Ψ_R **A·–·B :C⁻**



Less

Stabilization

Ψ_P **A:⁻ B·–·C**

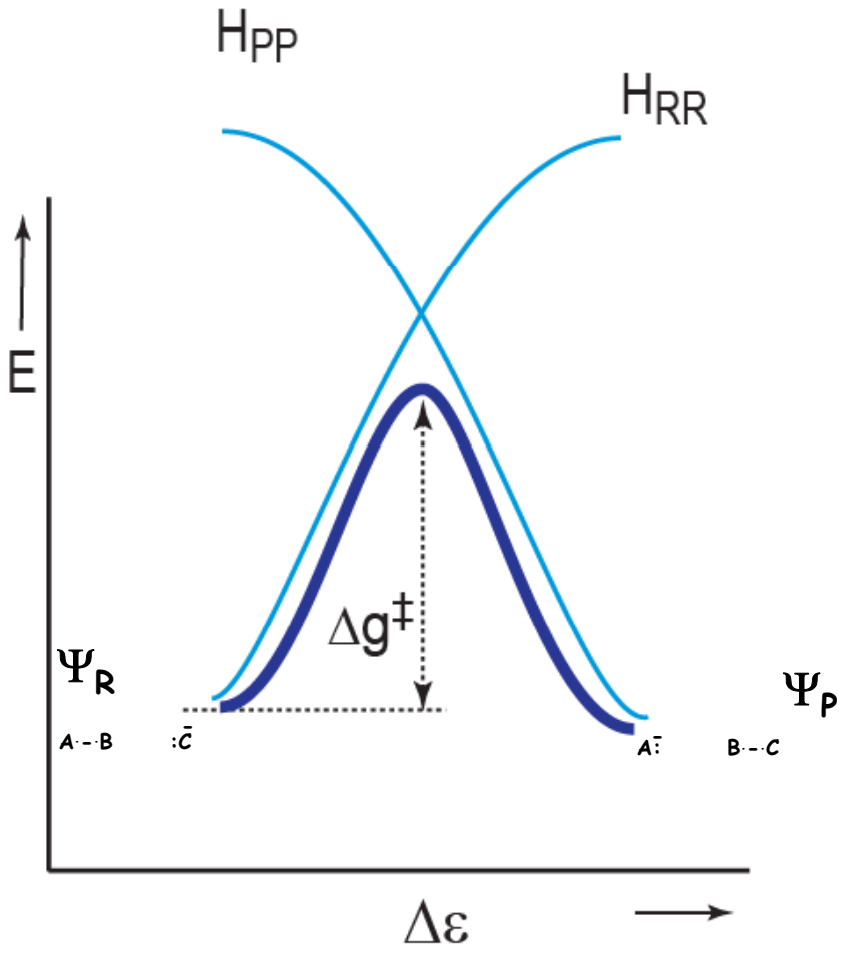


More

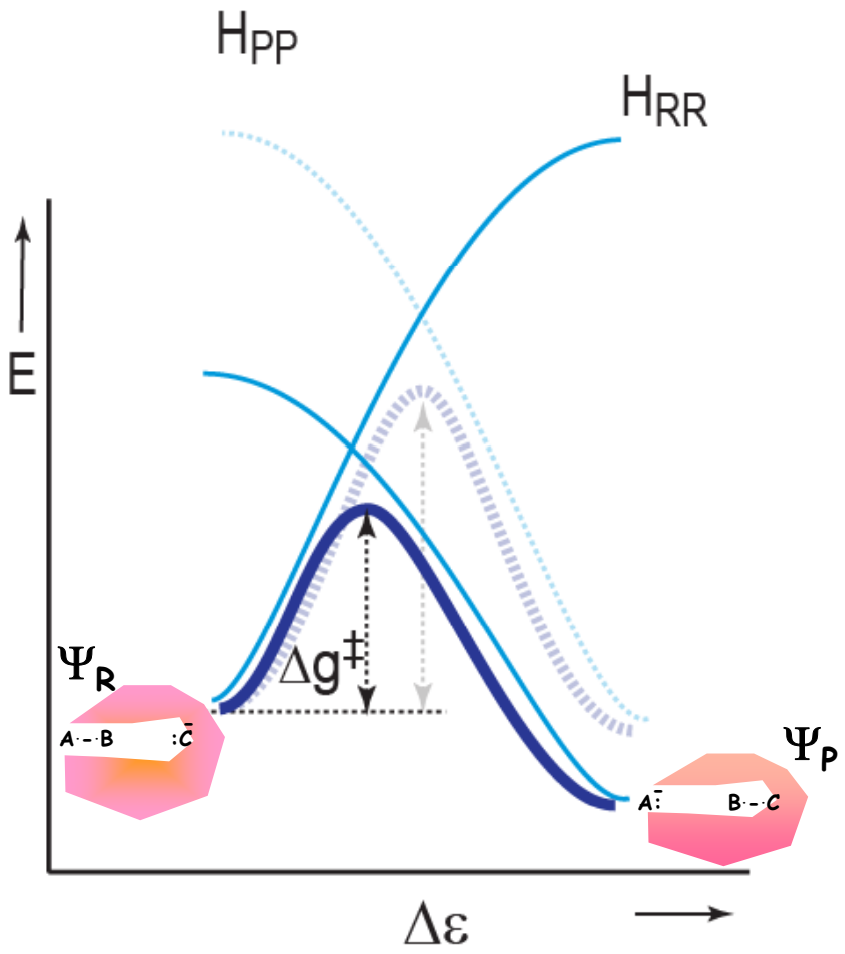
$$\Psi_{Total} = c_R\Psi_R + c_P\Psi_P$$

Mechanical Embedding with each VB structure separately should include most of the wavefunction polarization.

Gas



Protein



ab initio VB/MM

$$H_{VB/MM} = H(VB) + H(MM) + H(VB/MM)$$

Hii is the diabatic state energy:

$$H_{ii} = H_{ii}(VB) + H_{ii}^{\text{int}} + H(MM)$$

H_{ii}^{int} is calculated classically

How to calculate Hij ?

Assumption: Both overlap S_{ij} and reduced resonance integral, β_{ij} , are invariant to the environment.

$$\beta_{ij}^{gas} = \beta_{ij}^{env} \qquad S_{ij}^{gas} = S_{ij}^{env}$$

$$\beta_{ij} = H_{ij} - \tfrac{1}{2}\left(H_{ii} + H_{jj}\right)S_{ij}$$

$$H_{ij} = H_{ij}^{0}(VB) + \tfrac{1}{2}\left(H_{ii}^{\text{int}} + H_{jj}^{\text{int}}\right)S_{ij}$$

Solve new matrix,
Get new wavefuncetion

This formula will serve also in the general case

Shurki & Crown JPC B, 2005 109, 23638

ab initio VB/MM

New matrix is solved:

$$\begin{pmatrix} H_{11}^{0} + H_{11}^{\text{int}} & H_{12}^{0} + \frac{1}{2}\left(H_{11}^{\text{int}} + H_{22}^{\text{int}}\right)S_{12} \\ H_{21}^{0} + \frac{1}{2}\left(H_{11}^{\text{int}} + H_{22}^{\text{int}}\right)S_{21} & H_{22}^{0} + H_{22}^{\text{int}} \end{pmatrix}$$

New wavefunction, and energy are obtained:

$$E_{total} = E + H^{O}(MM)$$

Relax the environment accordingly and repeat

Finally, for the reaction profile:
use potential of mean force (PMF) combined with FEP/US

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ab initio VB/MM

Finally …

The ab –initio VB calculations of the reactive fragments utilized the program **XMVB**:

Lingchun Song, Wei Wu, Yirong Mo, Qianer Zhang, **XMVB** – an ab initio Non-orthogonal Valence Bond Program, Center of Theoretical Chemistry, Department of Chemistry, and State Key Laboratory for Physical Chemistry of Solid Surfaces, Xiamen University, Xiamen Fujain 36005, China.

The MM calculations as well as dynamics utilized the MOLARIS program with the ENZYMIX force-field:

Microscopic and Semimicroscopic Calculations of Electrostatic Energies in Proteins by the POLARIS and ENZYMIX Programs, F. S. Lee, Z. T. Chu, and A. Warshel, J. Comp. Chem. 14, 161 (1993).

Results: Li-F

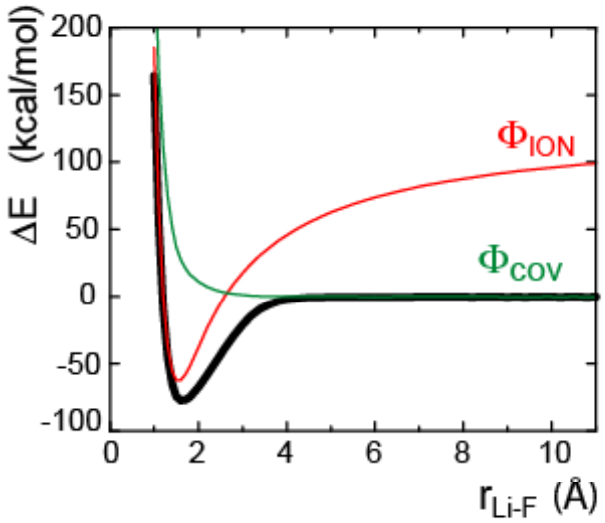
VB Structures:

Φ_{COV} Li·—·F ; Φ_{ION} Li^+ $:F^-$; ~~Φ_{ION} $Li:^-$ F^+~~

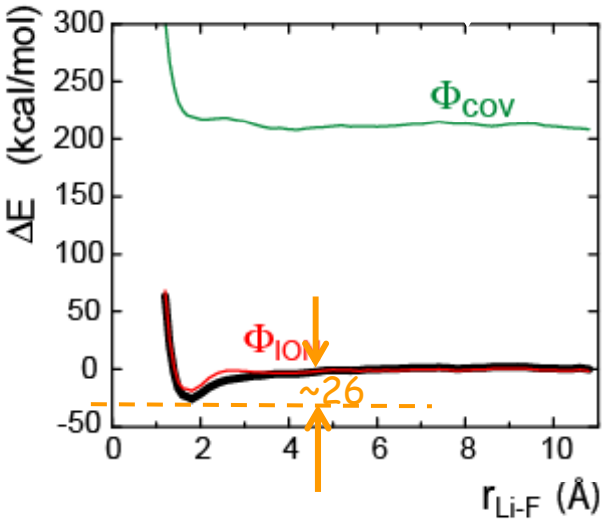
Energy Curves

6-31G* basis set
1S electrons frozen

Gas Phase



Solution



- correct description of dissociation into ions in solution
- Predicted dissociation of barrier ~26 kcal/mol (exp. ~5 kcal/mol)

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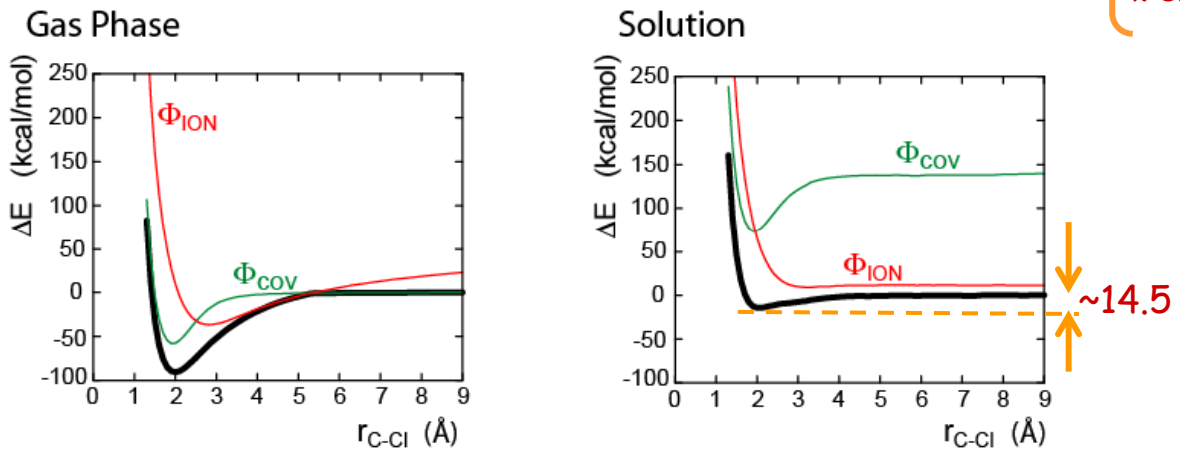
Results: Tertiary-Butyl Chloride (t-BuCl)

6-31G basis set
π electrons frozen

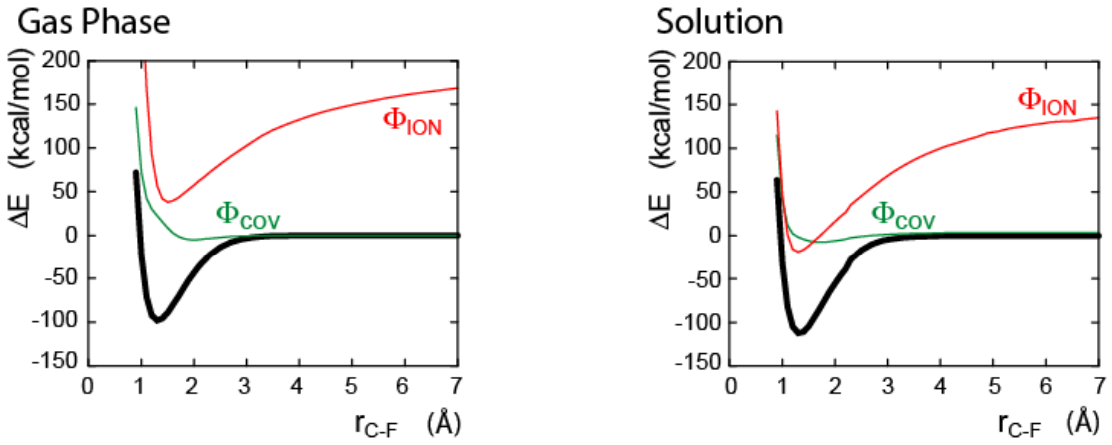
Energy Curves



- Dissociation into: radicals – vacuum vs ions - solution
- Predicted dissociation barrier of ~14.5 kcal/mol (Exp. ~19.5 kcal/mol)

Results: CH_3-F

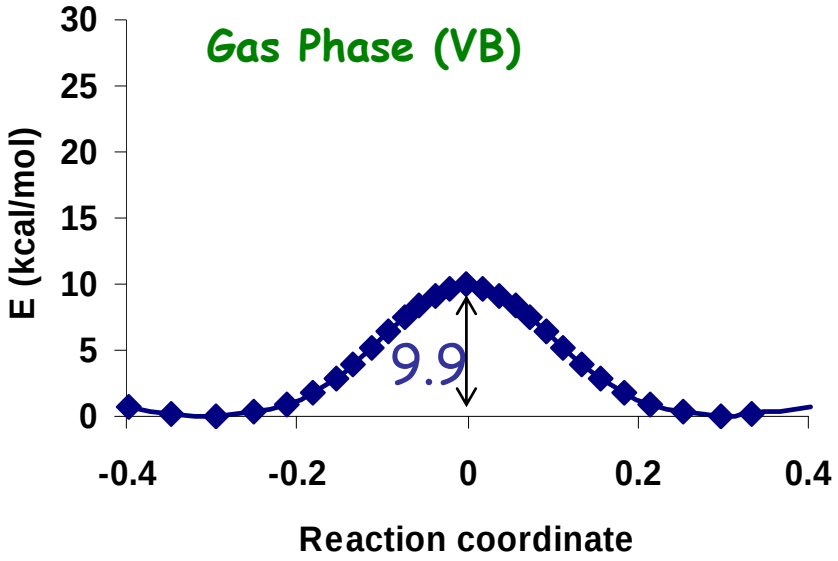
Energy Curves



- Homolytic dissociation in both vacuum and solution
- Most of the bond energy comes from resonance

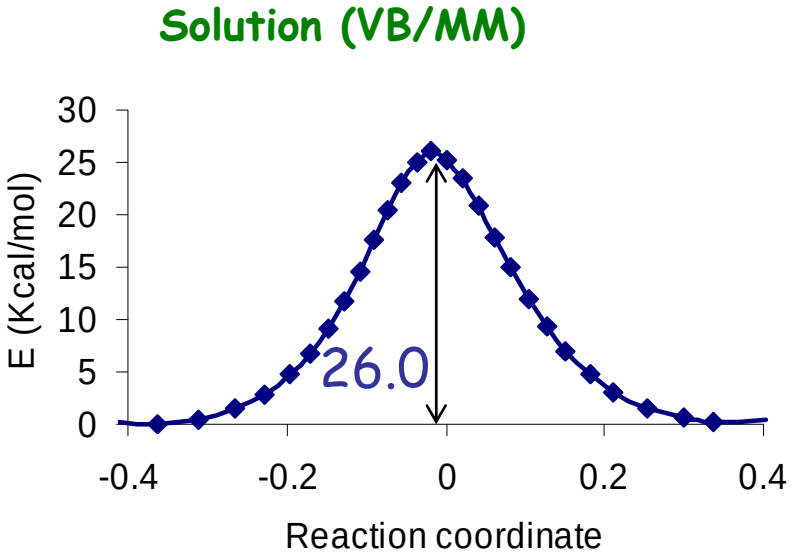
6-31G* basis set
Core electrons frozen

BOVB
6-31G* basis set
Core+π electrons frozen



Experimental
Gas ~10.2
Solution ~26.6

VB/MM predicts correctly the energetics



Sharir-Ivry & Shurki JPC A, 2008, 112, 2489

ab initio VB/MM

Mechanical Embedding

H_{ii}^{int} is calculated classically

$$\begin{pmatrix} H_{11}^{0} + H_{11}^{\text{int}} & H_{12}^{0} + \frac{1}{2}\left(H_{11}^{\text{int}} + H_{22}^{\text{int}}\right)S_{12} \\ H_{21}^{0} + \frac{1}{2}\left(H_{11}^{\text{int}} + H_{22}^{\text{int}}\right)S_{21} & H_{22}^{0} + H_{22}^{\text{int}} \end{pmatrix}$$

Requires the approximations: $\beta_{ij}^{gas} = \beta_{ij}^{env}$ $S_{ij}^{gas} = S_{ij}^{env}$

ab initio DE-VB/MM

Wavefunction Polarization

Environment partial charges are included in the quantum Hamiltonian:

H_{ii}^{int} is included in the quantum Hamiltonian

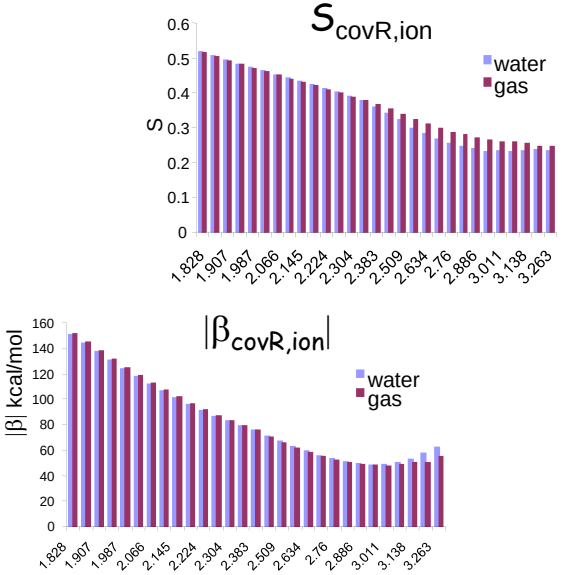
$$\begin{pmatrix} \left(H_{11}^{0}\right)' & \left(H_{12}^{0}\right)' \\ \left(H_{21}^{0}\right)' & \left(H_{22}^{0}\right)' \end{pmatrix}$$

in case of an electrostatic environment:

$\beta_{ij}^{gas} = \beta_{ij}^{env}$ $S_{ij}^{gas} = S_{ij}^{env}$ **No Need!**

Sharir-Ivry, Shurki, JPC B 2008 112, 12491

Examination of approximations regarding S_{ij} and β_{ij}



Sharir-Ivry, Shurki,
JPC B 2008, 112, 12491

TS geometry (2.38Å)

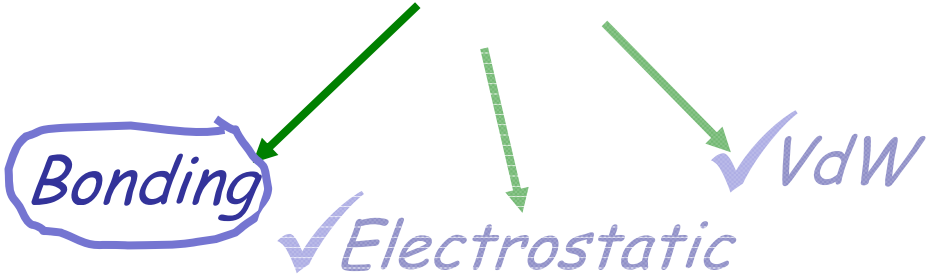
	Gas	VB/MM	DE-VB/MM
overlap			
$S_{covR,covP}$	0.124	Same as gas	0.118
$S_{covR,ion}$	0.376		0.359
$S_{covP,ion}$	0.349		0.359
Reduced Resonance Integral			
$\beta_{covR,covP}$	-45.9	Same as gas	-45.1
$\beta_{covR,ion}$	-75.4		-75.6
$\beta_{covP,ion}$	-75.4		-75.4
weights			
φ_{covR}	0.268	0.216	0.217
φ_{covP}	0.268	0.219	0.222
φ_{ion}	0.462	0.565	0.560

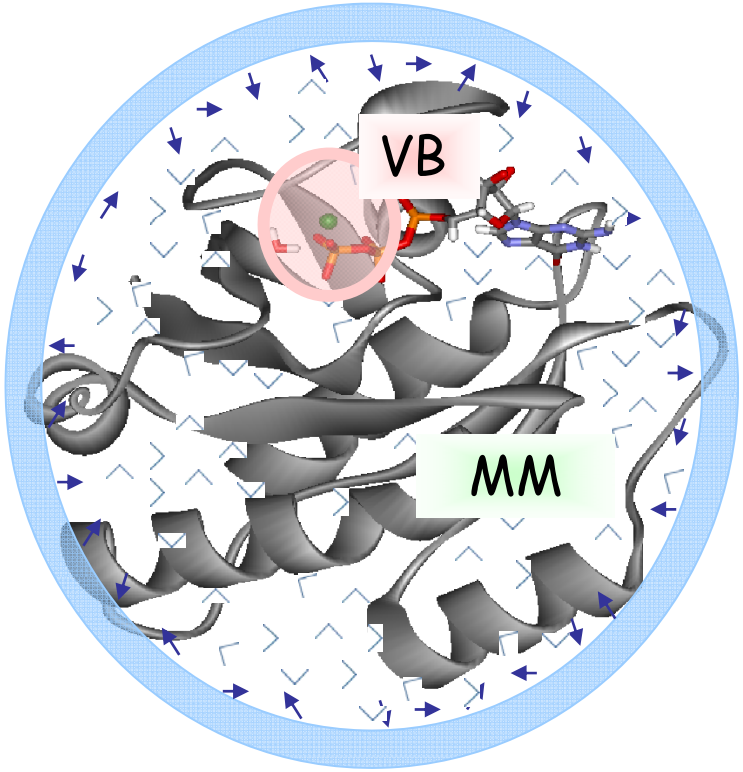
- *Changes in overlap and reduced resonance are negligible*
- *The trends in the weights are kept ,VB/MM sufficient for wavefunction polarization*

The approximations in VB/MM seem reasonable

ab initio VB/MM

$$H_{VB/MM} = H(VB) + H(MM) + H(VB/MM)$$



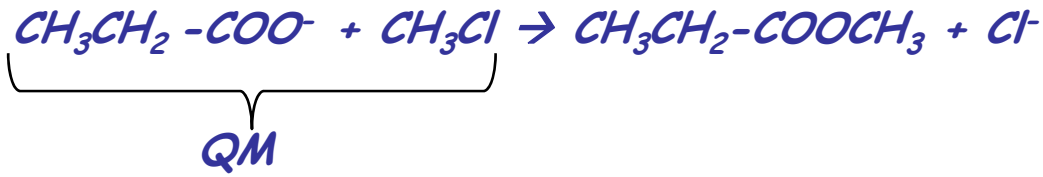


HOW?

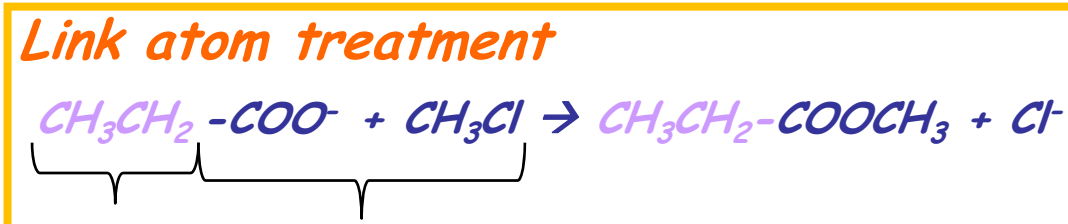
- **VdW** – classically
- **Electrostatic**:
  Mechanical embedding each VB structure
  → Wavefunction polarization (electrostatic embedding)
- **Bonding** – link atom scheme

Link Atom Scheme

Full treatment



Link atom treatment



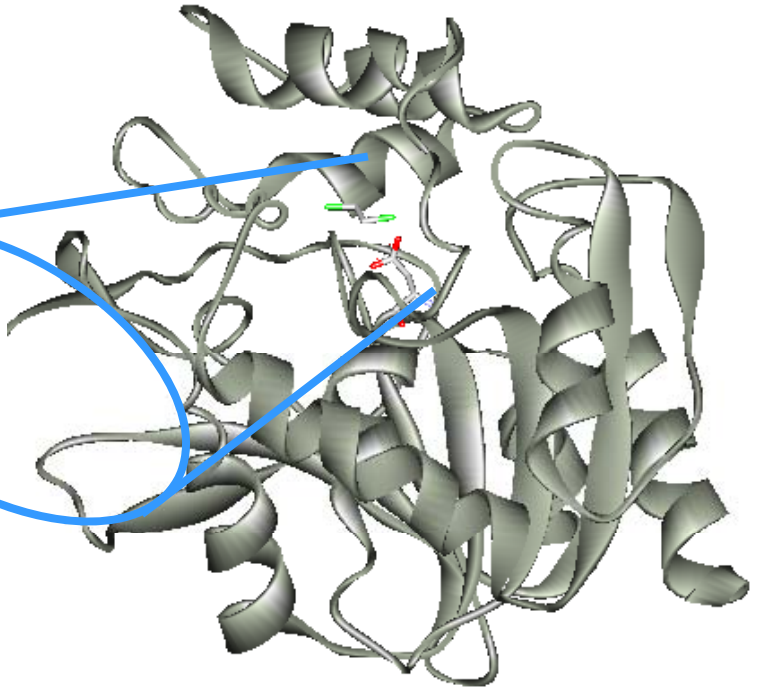
Reaction barriers (kcal/mol)

	$\Delta G_g^{\ddagger}$	$\Delta G_w^{\ddagger}$
Full treatment	11.9	18.2
Link atom treatment	11.5	18.7

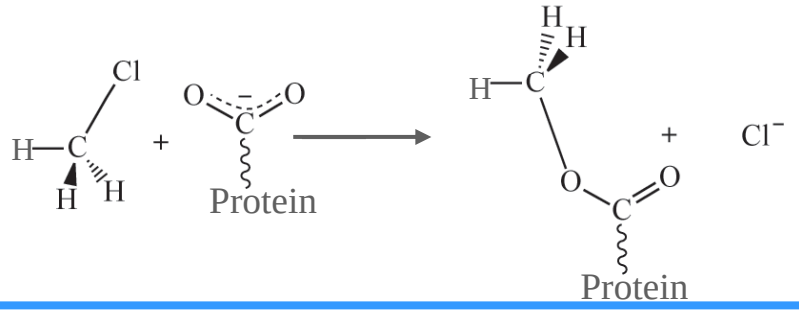
Barriers are similar for the two treatments
Link atom treatment is suitable

Sharir-Ivry, et al. JPC B 2010, 114, 2212

haloalkane dehalogenase (DhlA)



Our Model System of the Reactive Part



L-VBSCF
6-31G* basis set
Core+π electrons frozen

	Gas	Water	Protein
Exp	(18-28) ~7	(<26) ~-12	(<15)
VBSCF	13 7.1	20.1 -8.9	11.2

Low barriers (different experimental system and insufficient description of gas phase), yet the overall trend is correct

Solvation Energies (weighted)

		Reactants	TS	$\Delta_{(TS-R)}$	$\Delta\Delta_{(P-W)}$
water	CovR	-54	-17	37	
	Ion	-26	-49	-23	
protein	CovR	-54	-23	31	-6
	Ion	-37	-61	-24	-1
	Tot				**-8**

* Results based on one run and include VdW and intra electrostatic interaction.

- The stabilization in the protein is consistently larger than in water
- Water stabilize CovR in the reactants geometry much more than in the TS - leading to the increased barrier
- This differential stabilization considerably decreases in the protein

Sharir-Ivry, et al. JPC B 2010, 114, 2212

Conclusions

- Two methods were presented: VB/MM and DE-VB/MM
- The approximations made for VB/MM were shown to be reasonable
- Mechanical embedding of each VB structure separately captures most of the environmental effect of wave-function polarization
- The method allows studies of reactions in solvents as well as enzymes and enables understanding of the effect of mutations on the reaction.