ab initio VB/MM & Interpretation

Performance of classical VB Calculations

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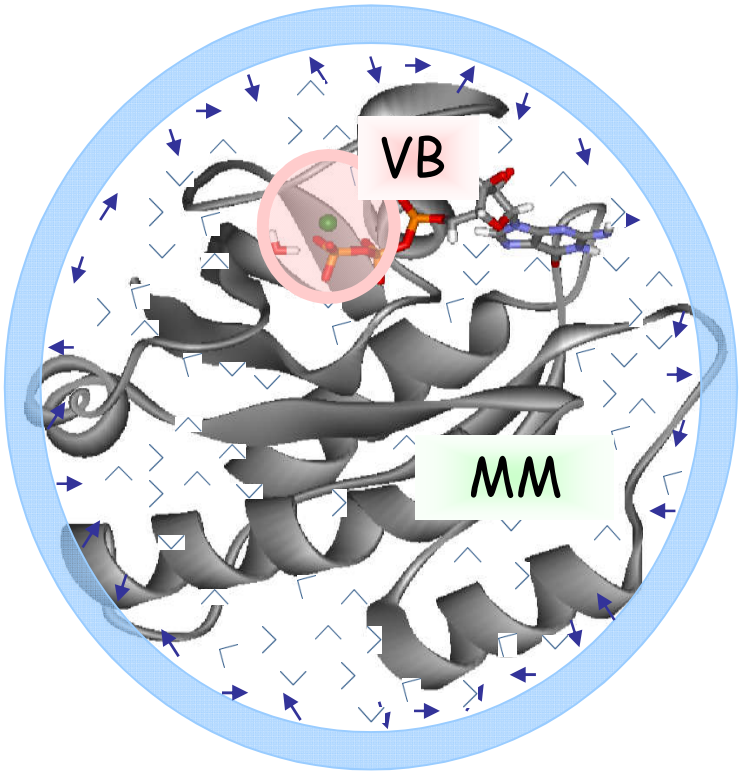
Method Development - ab initio VB/MM

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



Bonding

Electrostatic

VdW

Electrostatic:
- ❖Mechanical Embedding
- ❖Electrostatic Embedding
- ❖Environment polarization

HOW?

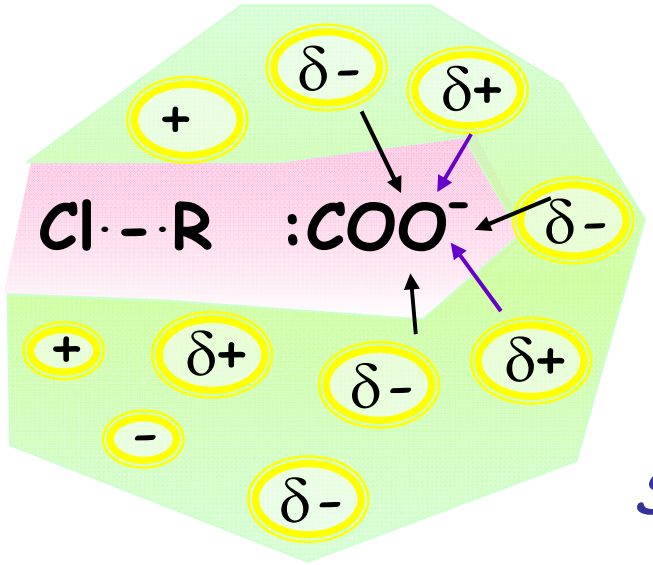
- **Bonding** – link atom scheme
- **VdW** – classically
- **Electrostatic**:
  Mechanical embedding each VB structure
  → Wavefunction polarization (electrostatic embedding)

JPC B, 2005, 109:23638;
JPC. B 2010, 114, 2212

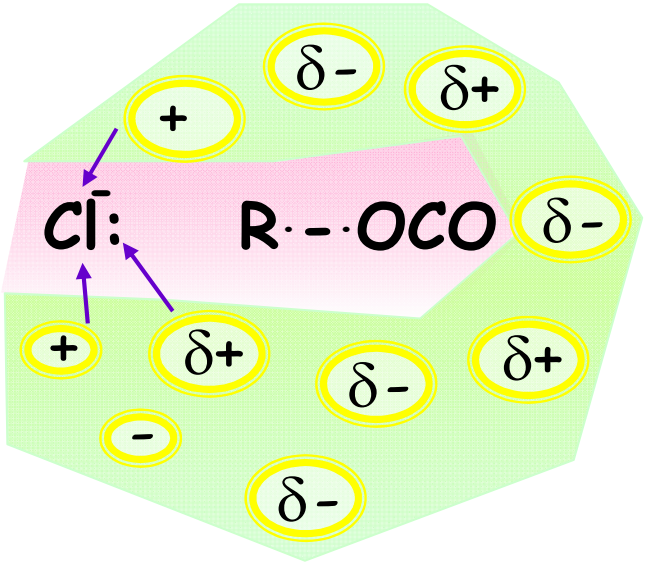
ab initio VB/MM

VB structures – Electron localization

Ψ_R **Cl··–·R :COO⁻** Ψ_P **Cl⁻:** **R·–·OCO**



Stabilization



Less *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.

JPC B, 2005, 109:23638;
JPC A, 2008, 112:2489;
JPC. B 2010, 114, 2212

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

JPC B, 2005, 109:23638;
JPC A, 2008, 112:2489;
JPC. B 2010, 114, 2212

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

Anti-catalytic effect of known mutants

	Calculated $\Delta\Delta g^{\ddagger(\mathrm{FEP})}_{wt\rightarrow mut}$	Calculated $\Delta\Delta g^{\ddagger(\mathrm{LRA})}_{wt\rightarrow mut}$	Observed $\Delta\Delta g^{\ddagger(obs)}_{wt\rightarrow mut}$
wt	0.0	0.0	0.0
W125F	2.4	4.7	≤ 2.3
W175Y	5.4	4.7	≤ 3.0
W175F	0.9	3.2	< 3.0
F172W	0.4	1.6	1.4

ε=4

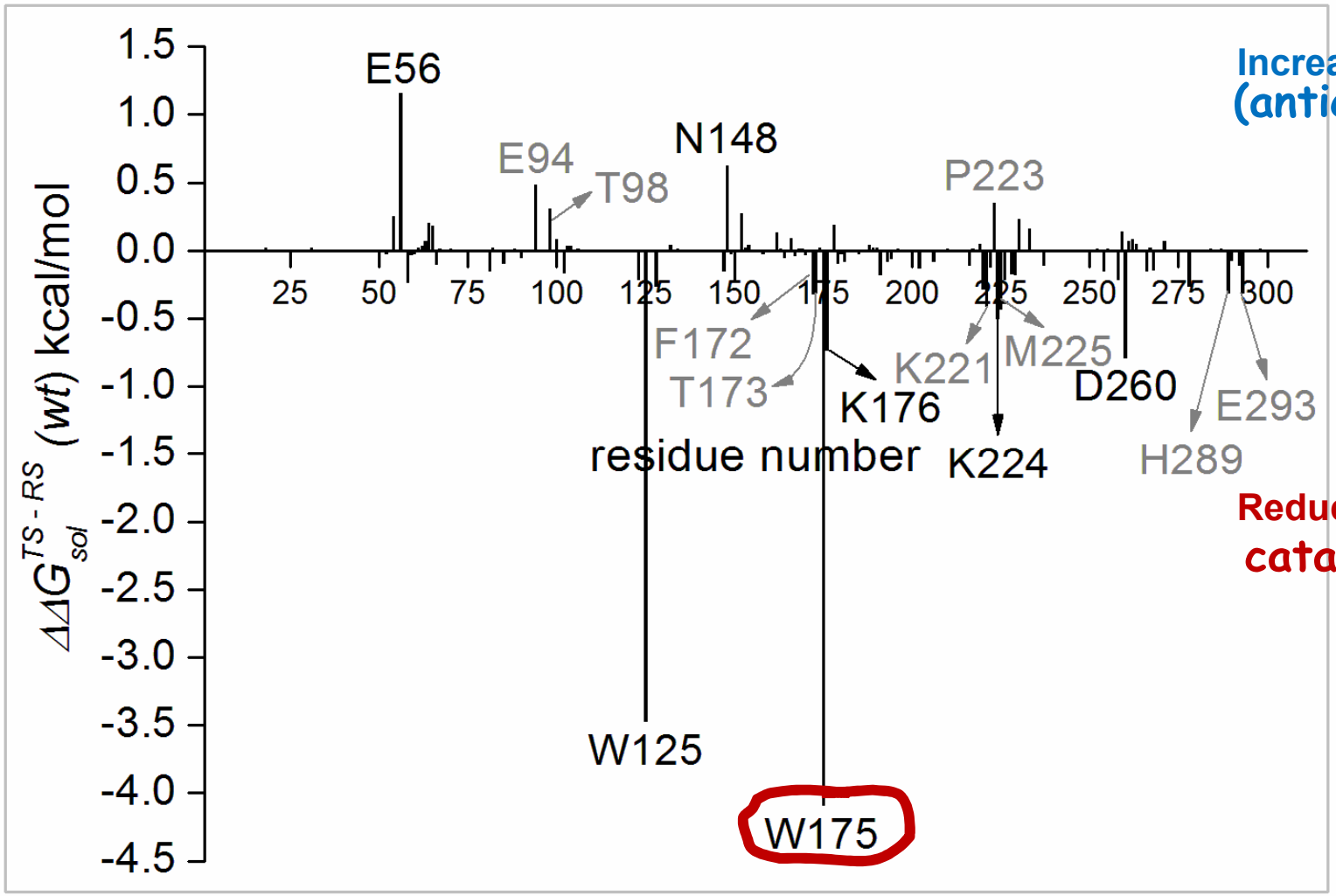
LRA – Agreement of LRA with experimental trends suggest that electrostatics has a major role in catalysis.

The advantage of LRA is its additivity

JCTC 2015 11:293

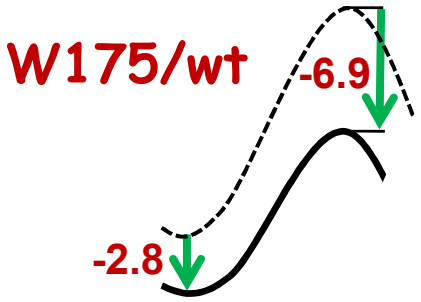
Hot Spots Identification

Contribution of particular residues to differential solvation



Chem. Eur. J. 2015, 21, 7159-7169

VB Interpretation



- Trp 175 is catalytic due to better solvation in the TS

total catalysis = **-4.1** kcal/mol

"catalytic"

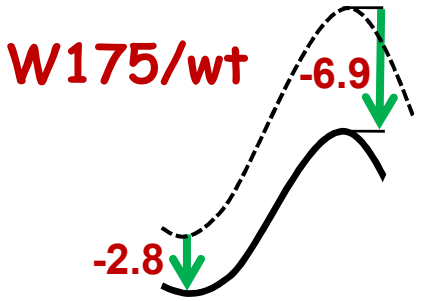
Contribution of particular VB structure.

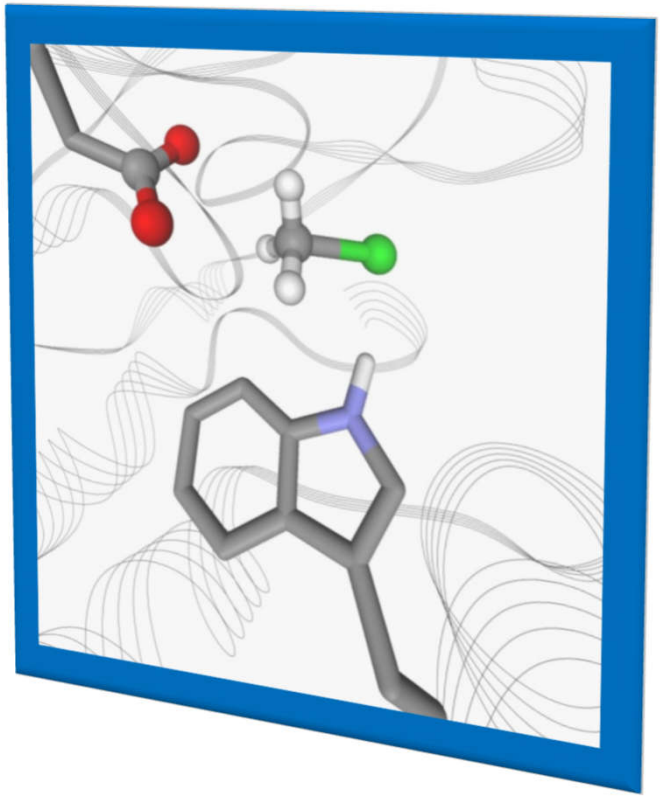
Total solvation is approximated as sum of weighted VB solvations.

$$\Delta G_{RS,sol} \approx W_{\Phi covR} * \Delta G_{RS,sol,\Phi covR} + W_{\Phi covP} * G_{RS,sol,\Phi covP} + \ldots$$

VB Interpretation

- The main contribution to this effect comes from the higher TS stabilization of both Φ_{ion} and Φ_{cov}





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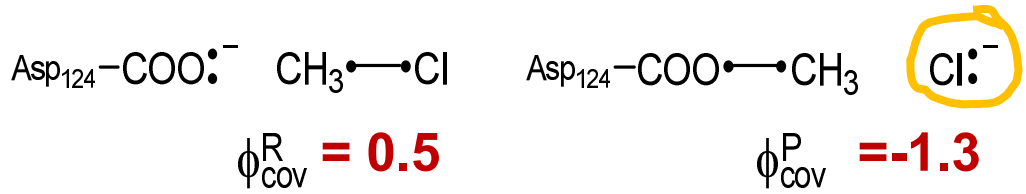
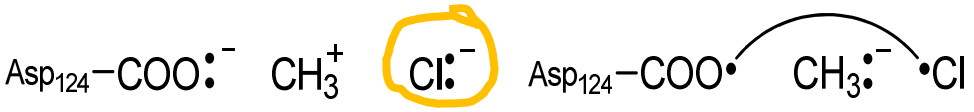


ϕ^{R}_{cov} = 0.5 ϕ^{P}_{cov} =-1.3



ϕ_{ion} =-3.3 ϕ_{lb} = 0.0

Trp175 is indeed known to stabilize the leaving chloride

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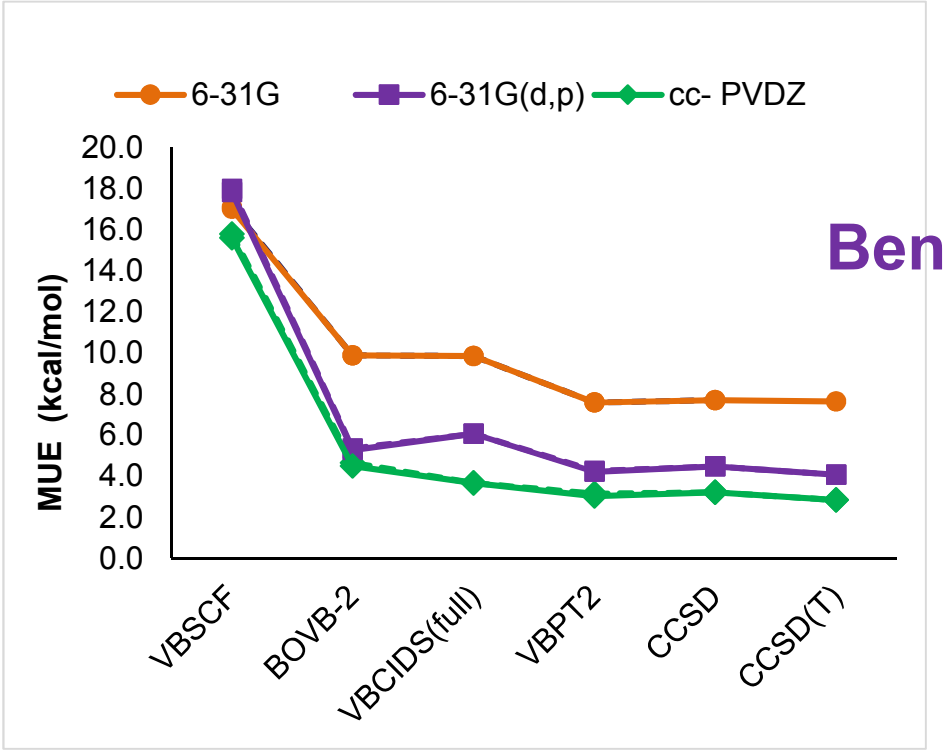
Performance of VB calculations



Benchmark of reaction barriers

Hydrogen Transfer Reactions

$OH + CH_4 \rightleftharpoons CH_3 + H_2O$

$H + OH \rightleftharpoons O + H_2$

$H + H_2S \rightleftharpoons H_2 + HS$

Truhlar's HTBH6 set of diverse reactions for benchmark calculations of barrier heights for hydrogen transfer reactions

Unpublished results

Maybe create a benchmark for strongly correlated systems that includes e.g. molecules people in this workshop have been testing – or something else…?