QM/MM modelling of enzyme reactions
Wrap-up

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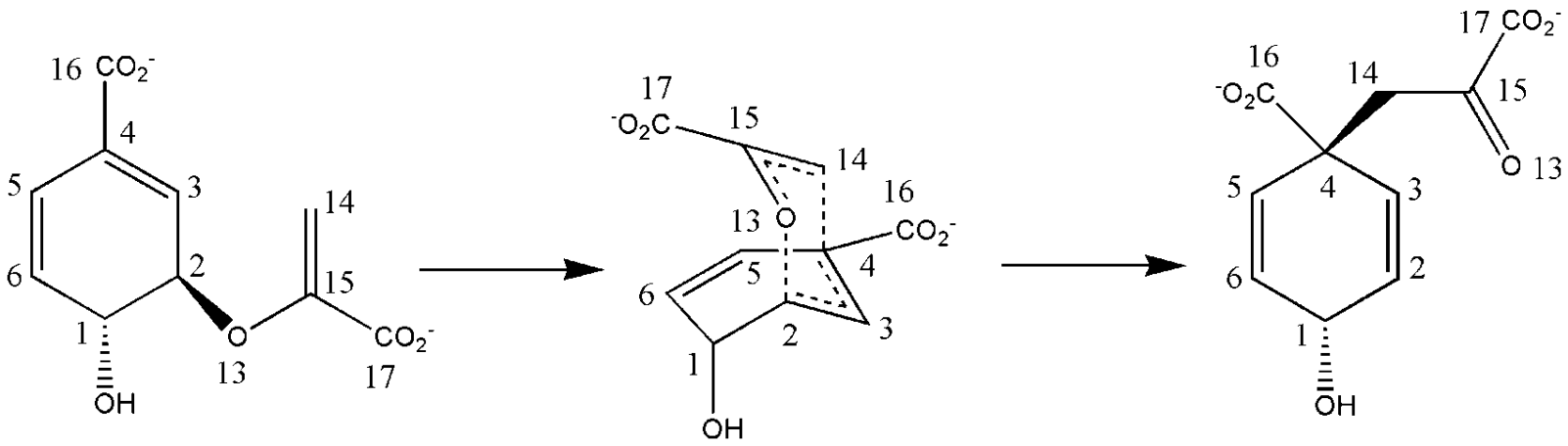
CCPBioSim tutorial workshop, Bristol, 24 May 2019

Chorismate mutase reaction

- Claisen rearrangement reaction, modelled by following *R*

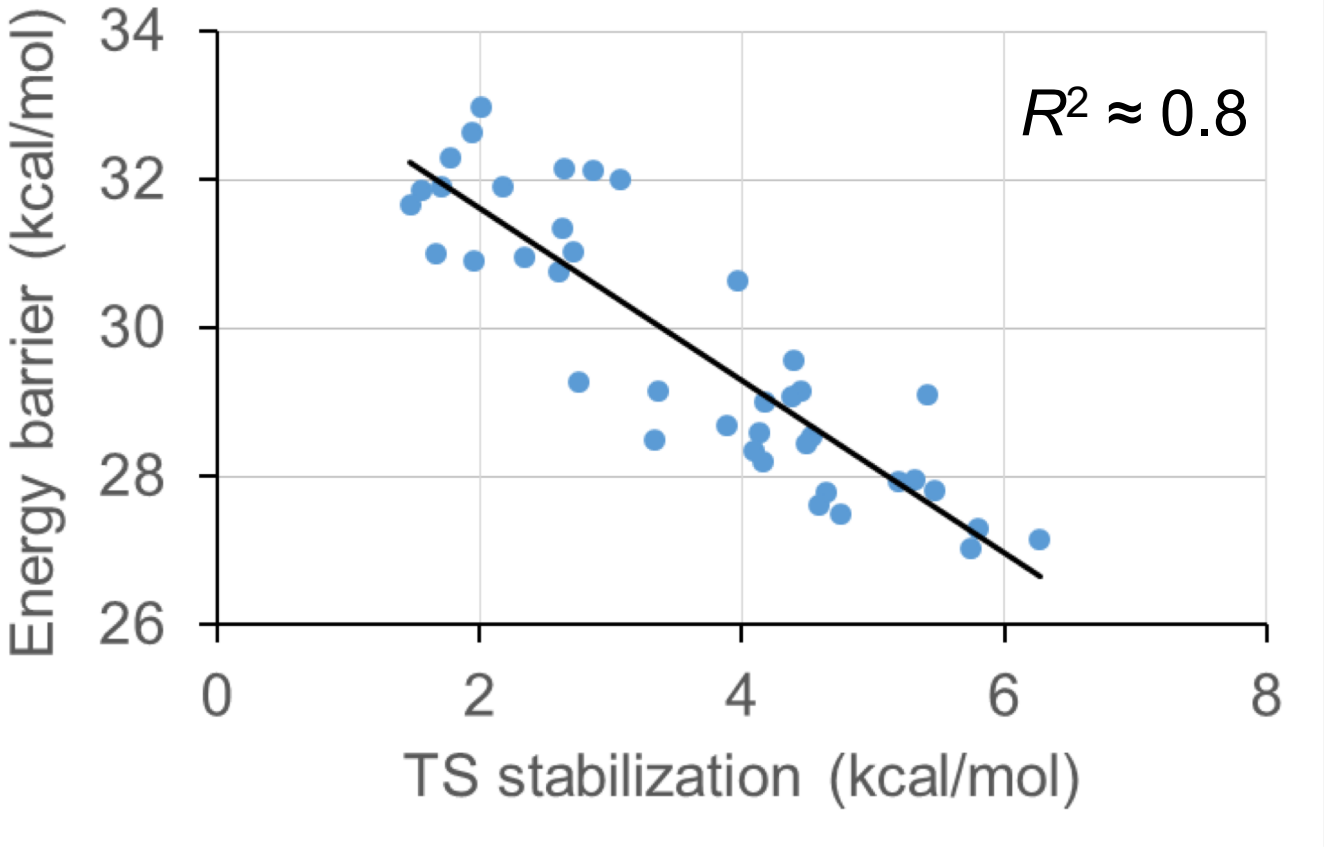


chorismate

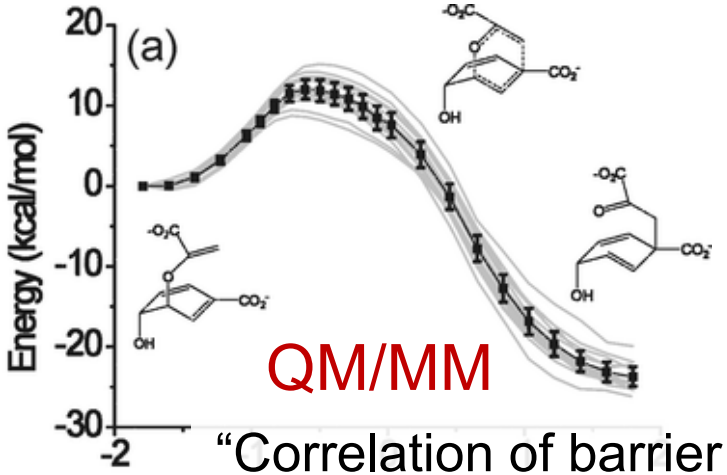
reaction coordinate ***R***:
d(C2-O13) − *d*(C4-C14)

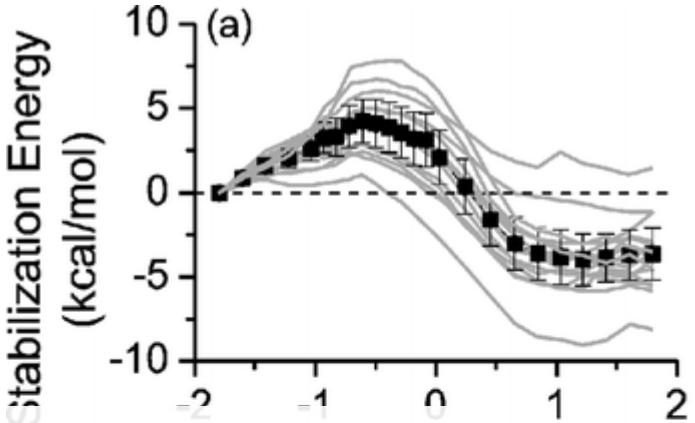
prephanate

Transition state stabilisation – AM1

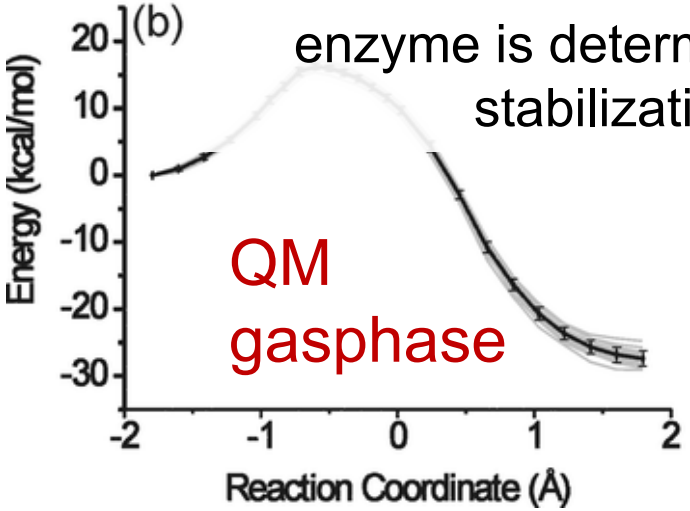


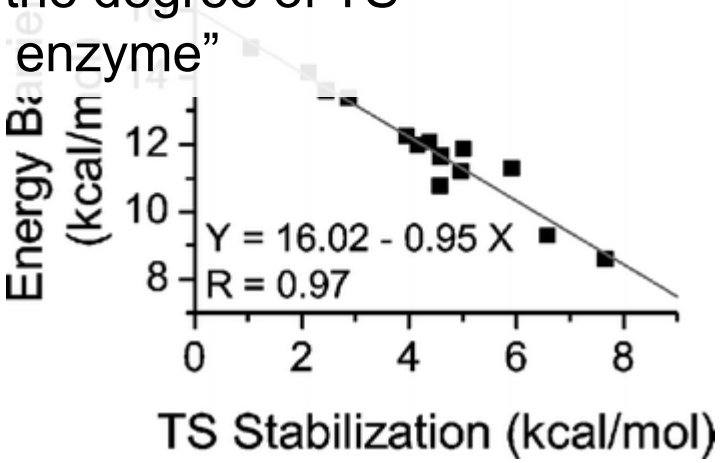
Transition state stabilisation – B3LYP





"Correlation of barrier height with TS stabilization shows that the efficiency of reaction in the enzyme is determined by the degree of TS stabilization in the enzyme"



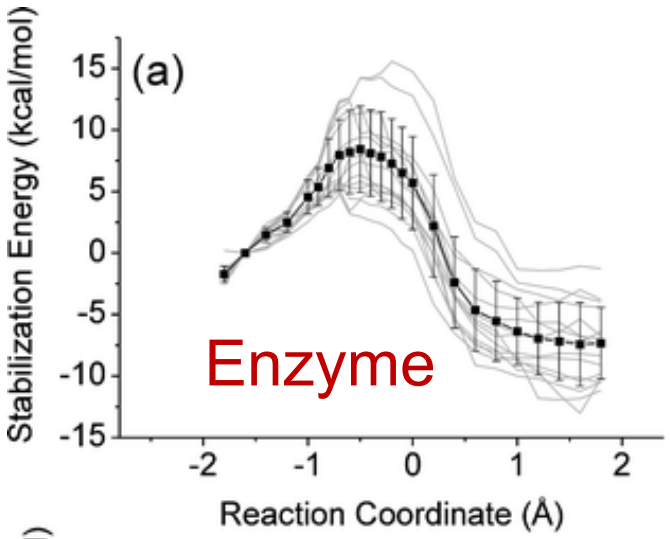


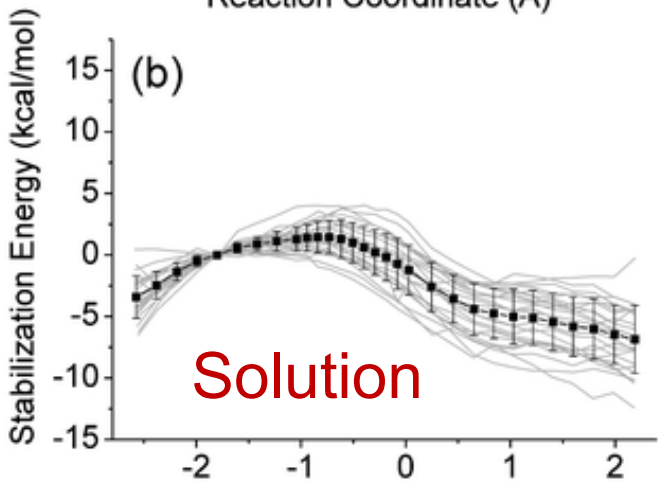
F. Claeyssens, K.E. Ranaghan, F.R. Manby, J.N. Harvey & A.J. Mulholland, ***Chem. Commun.*** 5068-5070 (2005)

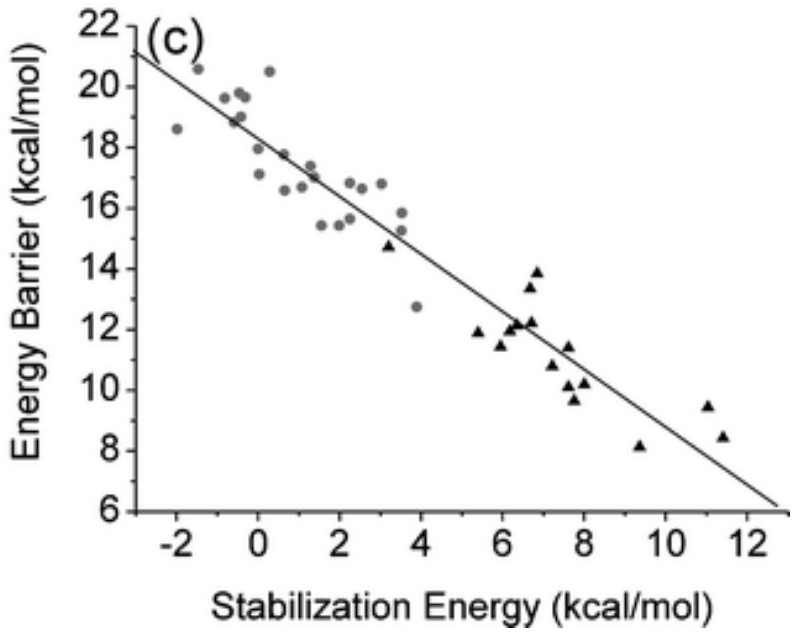
Enzyme *vs.* solution

$$k_{TST} = \kappa \left(\frac{kT}{h} \right) e^{-\Delta^{\ddagger}G/RT}$$

	Exp	B3LYP/MM
Solution	20.7 ± 0.4	17.4 ± 1.9
Enzyme	12.7 ± 0.4	11.3 ± 1.8



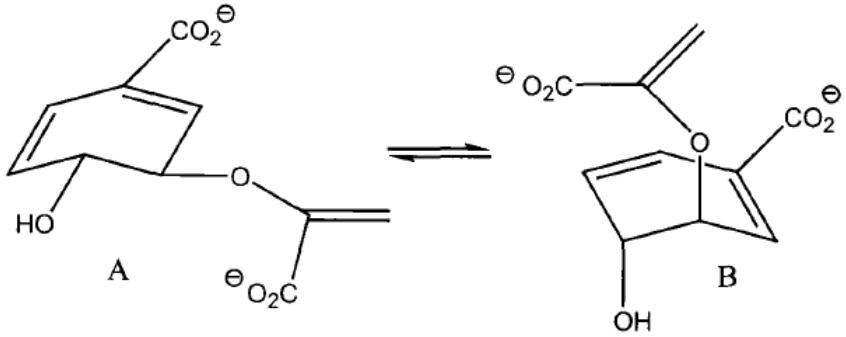




Claeyssens et al. (Mulholland) Org. Biomol. Chem., (2011) 9, 1578-90

TS stabilisation *vs.* conformational effects

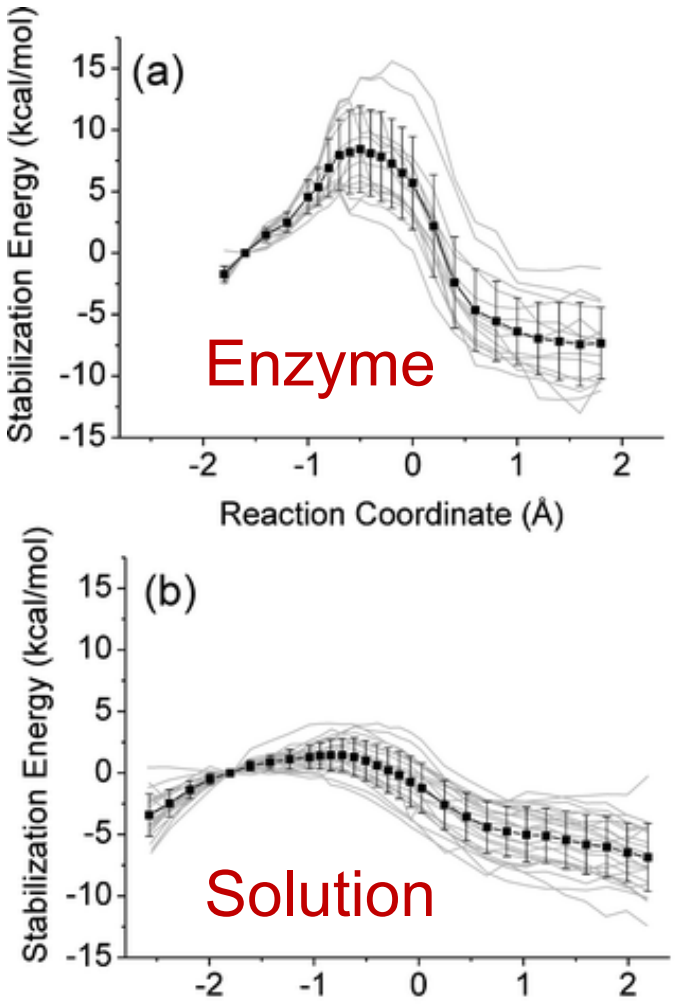
- Chorismate is bound in conformation B ('TS like'), whereas A is global minimum in solution



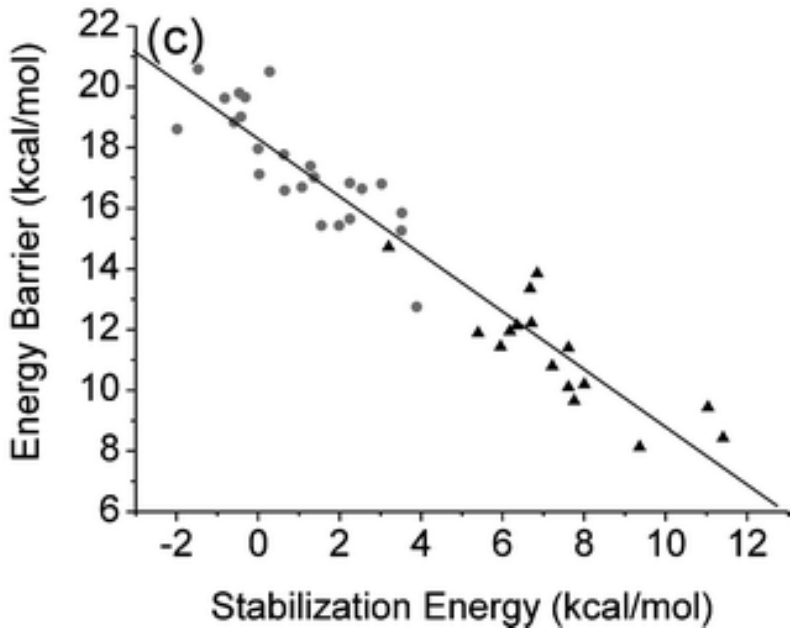
- *Catalysis is due to a <u>combination</u> of TS stabilization and conformational effects*
  - Better TS stabilization in enzyme than in water (4.2 kcal/mol vs 1.3 kcal/mol) = 2.9 kcal/mol
  - Substrate compression/strain contributes 2.2 kcal/mol (positioning of carboxylates); + 0.6 kcal/mol (shorter C-C distance)
  - Binding of reactive pseudo-diaxial conf. contributes ~1.5-3 kcal/mol
- **All these effects are probably due to TS complementarity**

[1] Strajbl et al. (Warshel) *JACS*, 2003, **125**, 10228
[2] Ranaghan & Mulholland, *Chem. Comm.*, 2004, 1238

Enzyme *vs.* solution



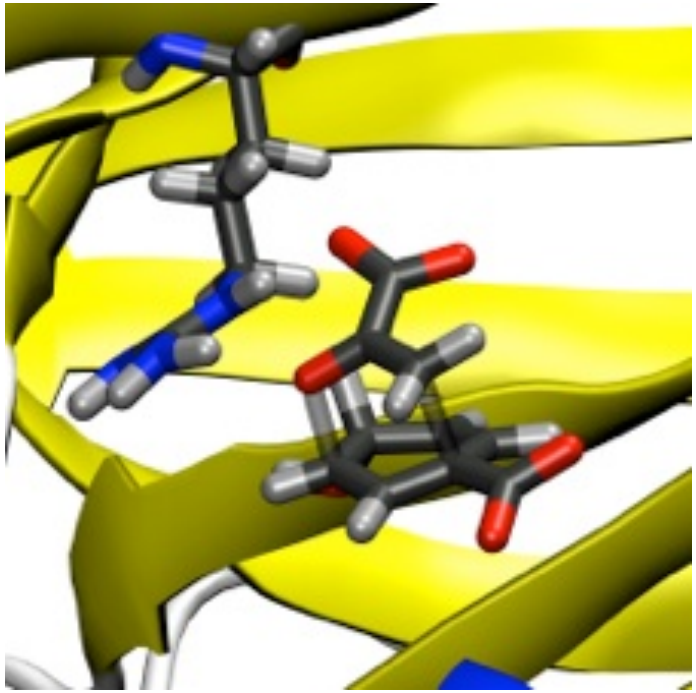
	Exp	B3LYP/MM	
Solution	20.7 ± 0.4	17.4 ± 1.9	***18.3-21.1***
Enzyme	12.7 ± 0.4	11.3 ± 1.8	



Claeyssens et al. (Mulholland) Org. Biomol. Chem., (2011) 9, 1578-90

Role of active site residues (incl. Arg90)

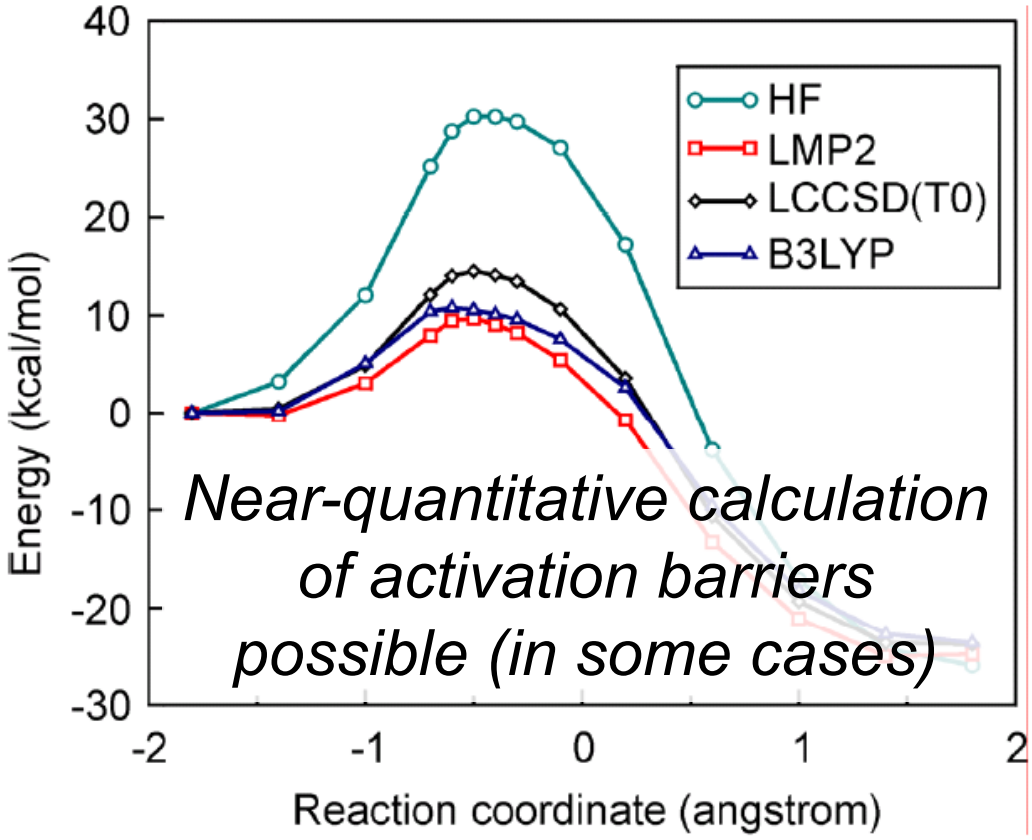
Electrostatic stabilization energy (kcal mol^{-1})*	
Full enzyme	9.9 (2.4)
Arg90	6.0 (0.8)
Arg7	3.1 (0.5)
Glu78	2.1 (0.3)
Cys75	1.3 (0.3)
Tyr108	1.1 (0.2)
Arg116	1.0 (0.9)
Phe57	0.8 (0.3)
Arg63	−0.6 (0.5)



*From B3LYP/6-31(d)//MM calculations

Claeyssens et al. (Mulholland) Org. Biomol. Chem., (2011) 9, 1578-90

Chorismate mutase: high-level QM



QM method	$\Delta^{\ddagger}H$ (300K)	
Hartree-Fock	28.3	(2.1)
B3LYP	10.2	(1.8)
LMP2	9.5	(1.0)
LCCSD(T0)	13.1	(1.1)
Experiment	12.7	

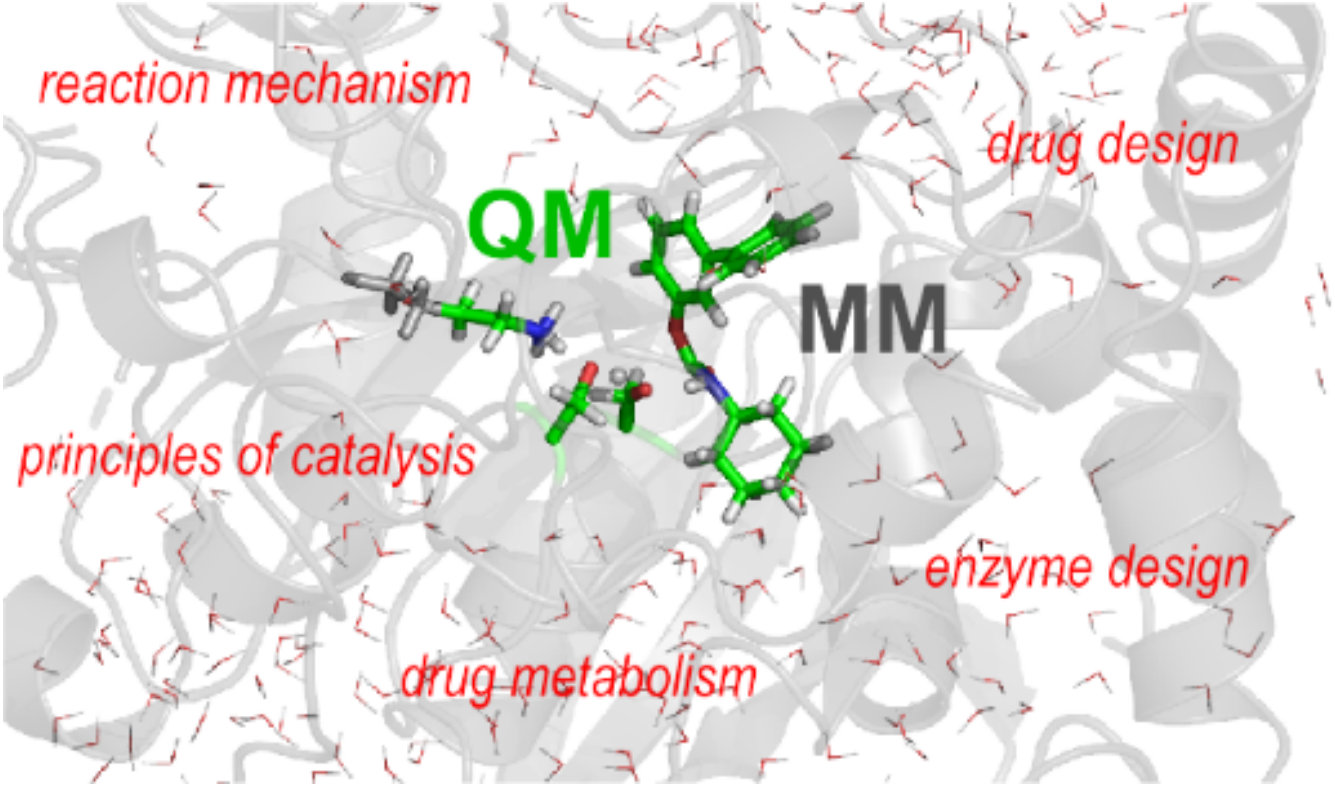
Entropic contribution
(compare AM1 PES vs. FES)

Calc.	2.5
Exp.	2.7

Claeyssens *et al.*, *Angewandte Chemie*, 2006

QM/MM reaction modelling in enzymes

- Van der Kamp, Mulholland (2013) *Biochem 52: 2708*



Planning a QM/MM study

- Choice of QM method
- Choice of MM force field (incl. MM parameters for QM atoms)
- Partitioning into QM and MM regions (covalent boundaries?)
- Type of simulation (QM/MM MD, QM/MM minimization)
- Testing against model system / higher level QM
- Choice of software…

Software for MM & QM/MM

	Free	Fast	Flexible	User friendly (for QM/MM)	QM/MM	QM interfaces
• CHARMM	?	–	✓	–	✓	GAMESS, Turbomole, Q-Chem
• AMBER	✓*	✓*	–	✓	✓	Gaussian, **Orca**, TeraChem, Q-Chem
• NAMD	✓	✓		-	✓[1]	**MOPAC**, **Orca**
• Gromacs	✓	✓		?	✗?	
• Tinker-HP (polarizable MM)	✓	?		–	✓[2]	Gaussian, PSI4, **NWChem**
• Others…						

- **ChemShell** (esp. for DFT & high-level QM/MM)

material: https://sites.google.com/site/qmmmworkshop2017/

[1]Melo *et al.* Nature Methods 2018, doi: 10.1038/nmeth.4638
[2]Lagardère *et al.* Chem Sci 2018, doi: 10.1039/C7SC04531J