QM/MM in MOLCAS

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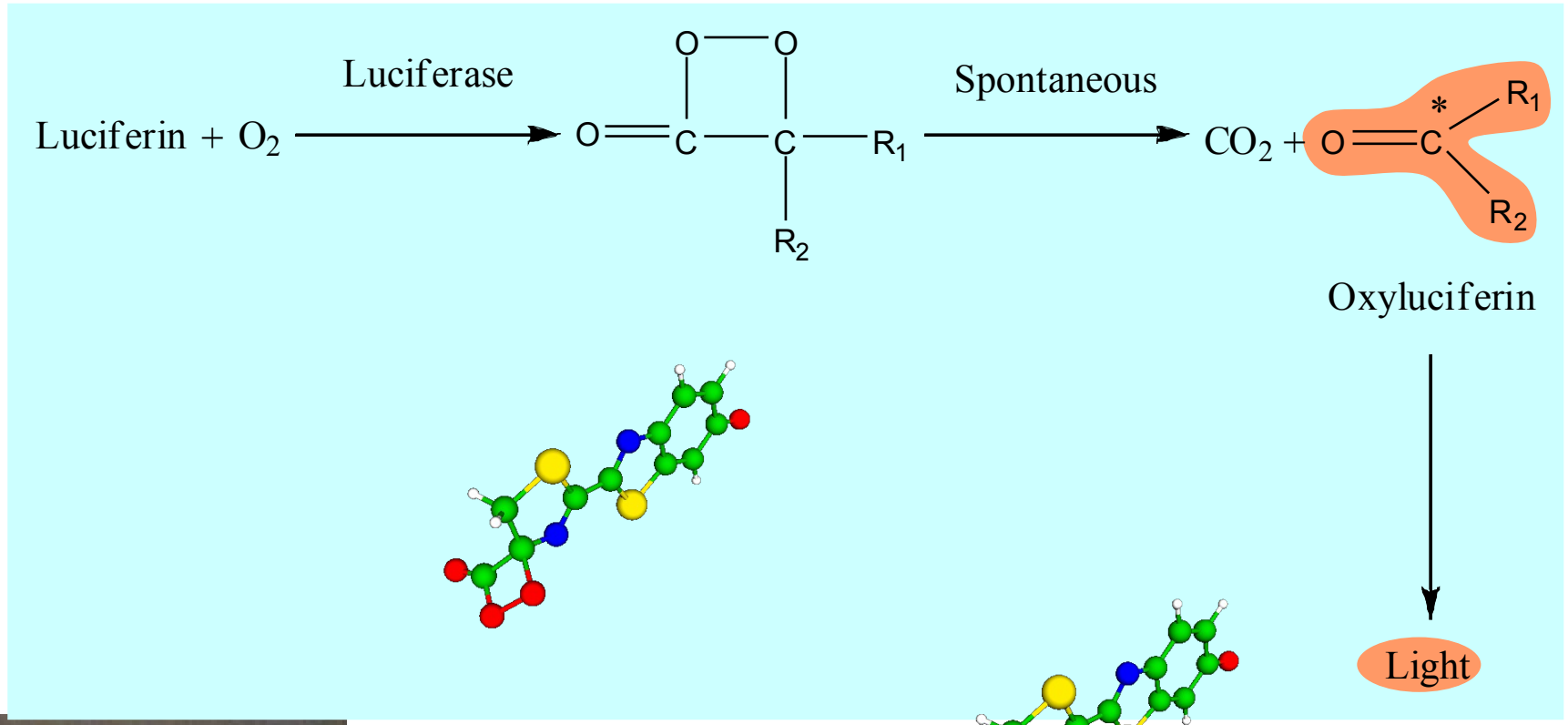
- Introduction: Luciferin chemistry
- QM/MM principles
- Recent QM/MM developments
- The ESPF method
- Current Model developments
- Luciferin chemistry: results
- Conclusions

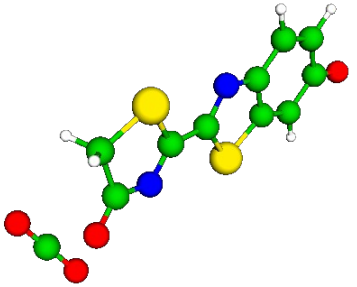
Introduction

QM/MM methods is today used as a tool to study chemistry at action in large systems. I will give you here a brief example of what can be done.

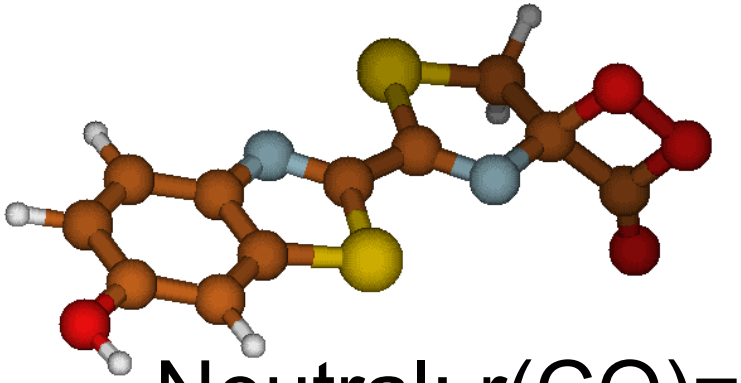
This workshop will not include any exercises using QM/MM, however, a workshop addressing the practical parts of the technique is scheduled for the spring 2010 in Lund.

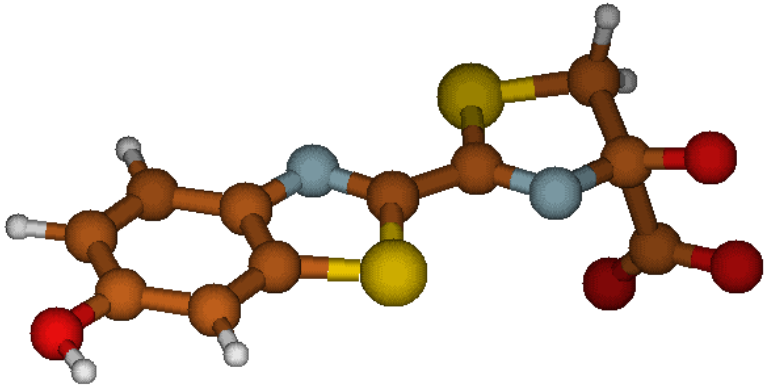
Luciferin chemistry by MOLCAS



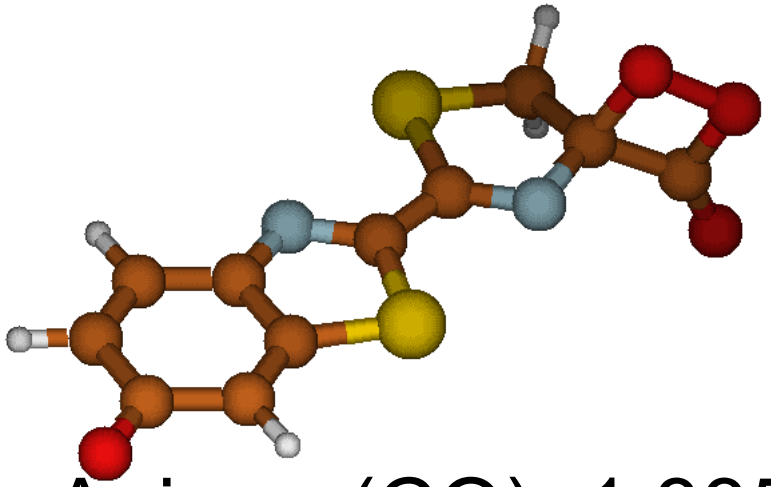


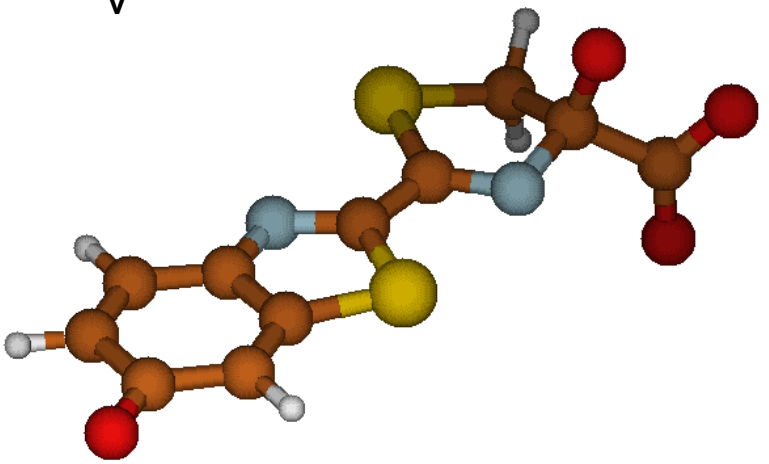
Neutral or anion form of keto-L?





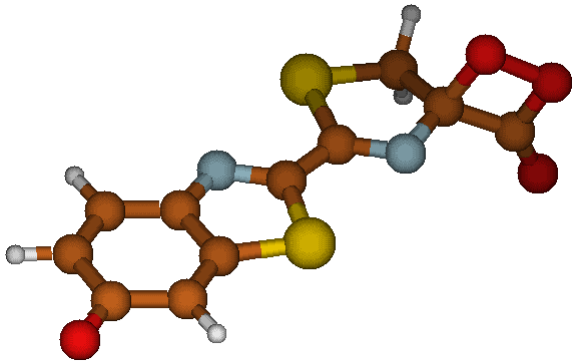
Neutral: r(CO)=1.324 Å, E_a=23.4 kcal/mol, concerted dissociation. T_v=3.32 eV

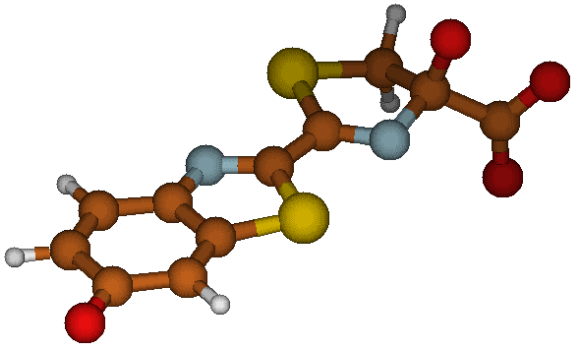




Anion: r(CO)=1.335 Å, E_a=7.3 kcal/mol, biradical dissociation. T_v=2.54 eV

Neutral or anion form of keto-L?





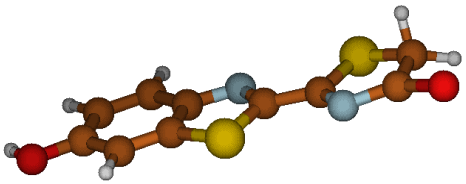
Oxy-LH2(-1): r(CO)=1.335 Å, E_a=7.3 kcal/mol, biradical dissociation. T_v=2.54 eV

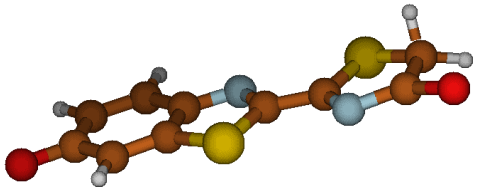
- Activation energy consistent with a biochemical process.
- a long r(CO) bond closer to that of excited formaldehyd (1.362 Å)
- dissociation process has the expected character
- emission in the right energy range
- Note the sp^2 vs. sp^3 hybridization of the oxygen anchor carbon at the TS for the concerted and biradical mechanism, respectively.

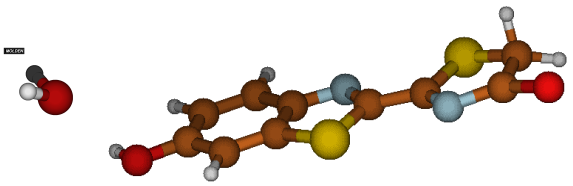
Polarization in the micro environment

TD-DFT calculated T_v values in eV.

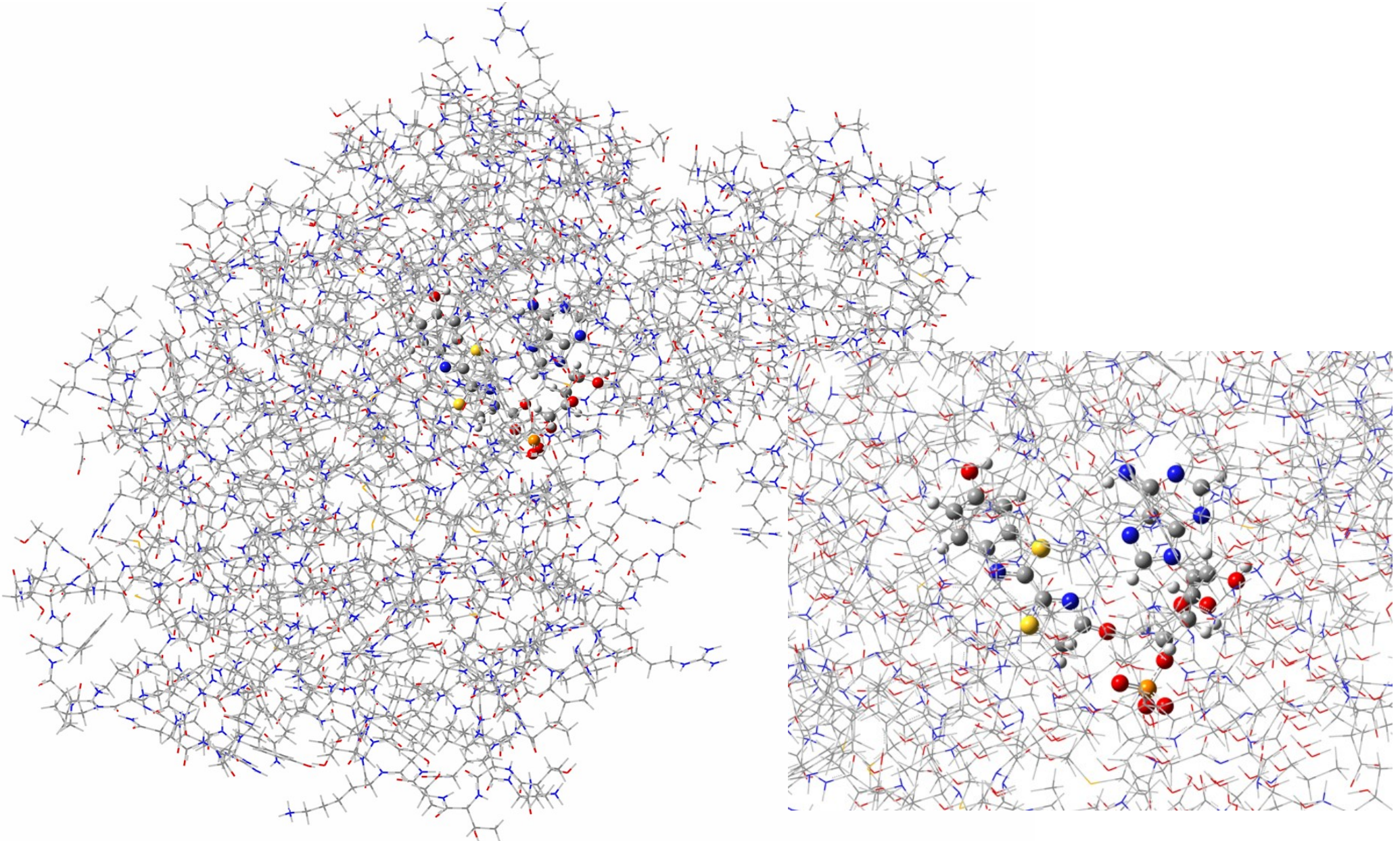
keto-trans	keto-trans + CH_2Cl_2	keto-trans + H_2O	keto-trans(-1)
٣.٣٢ (٣.٣٥)	٣.٢٧	٣.١٩	٢.٥٤ (٢.٩٩,٢.٨٧)



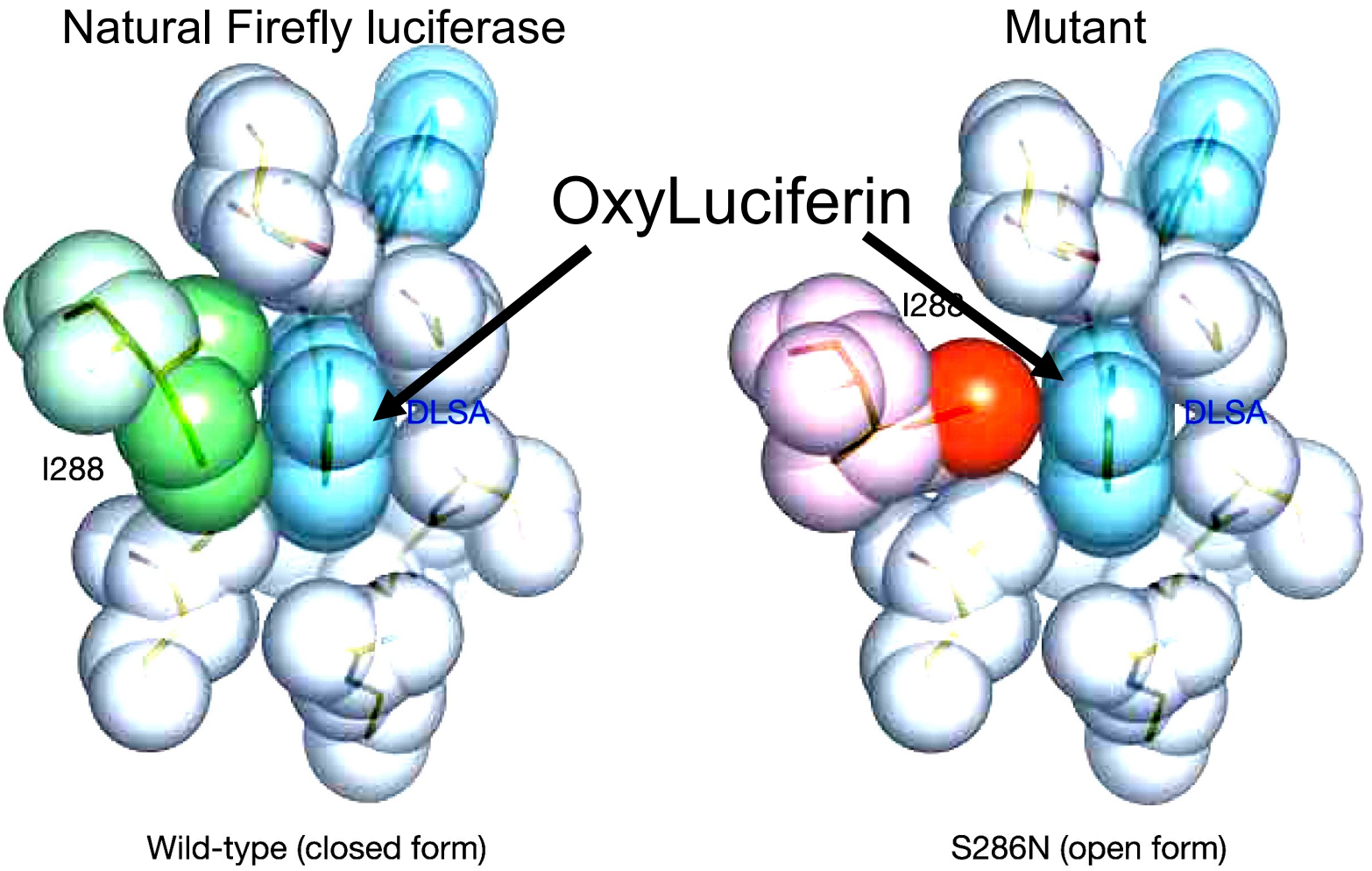




Luciferin-Luciferase Complex:
CASPT2/Tinker QM/MM



What's the origin of the variation of the bioluminescence colour?



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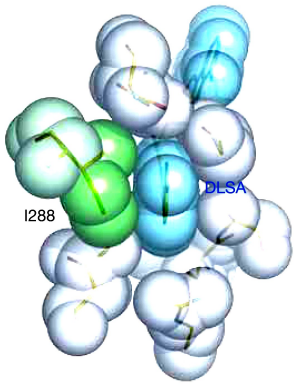
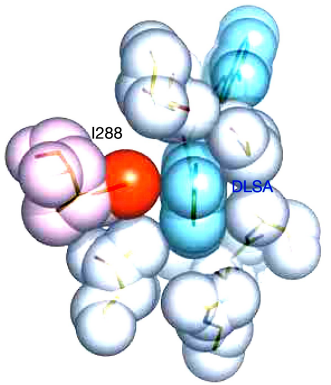


Wild-type (closed form)

- **The tight pocket of the wild-type luciferase should not allow too much structural relaxation of the oxyluciferin before it emits light and decade to its ground state.**

- **Most of the chemical energy is then transformed into light with a short wavelength.**

What's the origin of the variation of the bioluminescence colour?



S286N (open form)

- **The loose pocket of the mutant, on the other hand, should let the oxyluciferin structure to relax a bit before the decay on the ground state.**

- **Part of the chemical energy is "wasted", and the emitted light wavelength is longer.**

The QM/MM principles (1)

$$E = \left\langle \Psi \left| \hat{H} \right| \Psi \right\rangle = \left\langle \Psi \left| \hat{H}_{QM} + \hat{H}_{MM} + \hat{H}_{QM/MM} \right| \Psi \right\rangle$$

- $\left\langle \Psi \left| \hat{H}_{QM} \right| \Psi \right\rangle = E_{QM}$: total energy of the isolated QM subsystem
- First approximation: the major part of the interactions are independant of the electronic coordinates
  $\left\langle \Psi \left| \hat{H}_{MM} \right| \Psi \right\rangle = E_{MM} \langle \Psi | \Psi \rangle = E_{MM}$: molecular mechanics force-field energy of the isolated MM part
- Second approximation 'a la MM': only the QM/MM electrostatic interactions depend on the electronic coordinates
  $\left\langle \Psi \left| \hat{H}_{QM/MM} \right| \Psi \right\rangle = \left\langle \Psi \left| \hat{H}^{elect}_{QM/MM} \right| \Psi \right\rangle + E^{other}_{QM/MM}$

The QM/MM principles (2)

$$E = \left\langle \Psi \left| \hat{H}_{QM} + \hat{H}^{elect}_{QM/MM} \right| \Psi \right\rangle + E^{nuc}_{QM} + E^{other}_{QM/MM} + E_{MM}$$

- The wavefunction is (almost always) polarized by its electrostatic surroundings
- Usually, the one-electron effective hamiltonian is modified

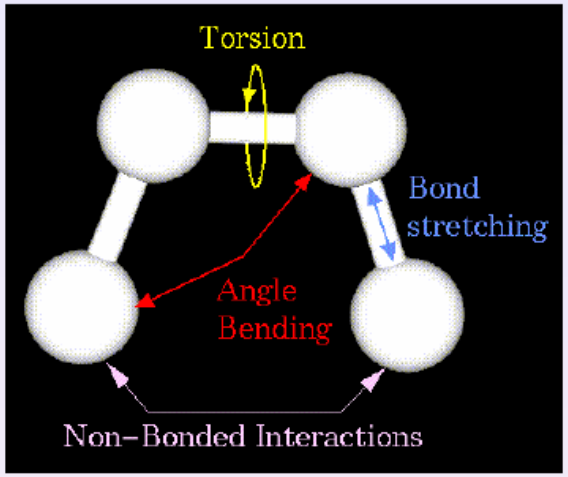
$$h^{QM/MM}_{\mu\nu} = \left\langle \chi_\mu \left| \sum_a \frac{q_a}{r_a} \right| \chi_\nu \right\rangle$$

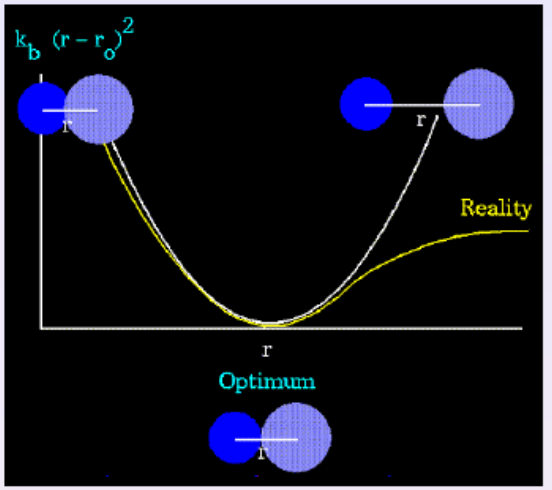
- The QM/MM and MM 'classical' interactions usually share the same functional form

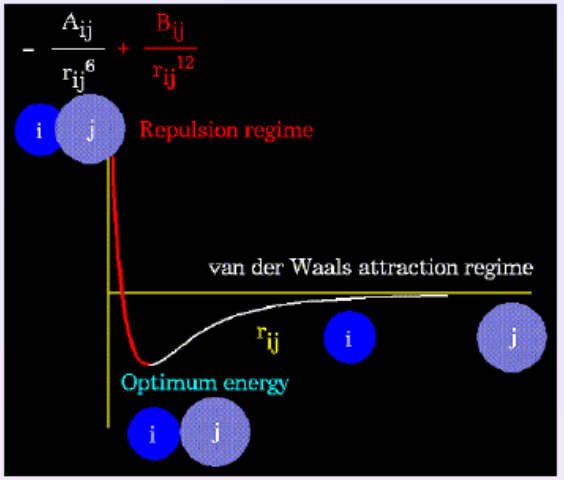
$$\begin{aligned} E^{other}_{QM/MM} &= E_{bonded} + E_{non-bonded} \\ &= E\,(\text{strech}) + E\,(\text{bend}) + E\,(\text{torsion}) + \cdots \\ &\quad + E\,(\text{van der Waals}) \\ &\quad + E\,(\text{QM nuclei} - \text{MM electrostatic potential}) \end{aligned}$$

The QM/MM principles (3)

What about the MM part ?







- Any MM forcefield is highly parametrized, for reproducing:
  - experimental data
  - QM results

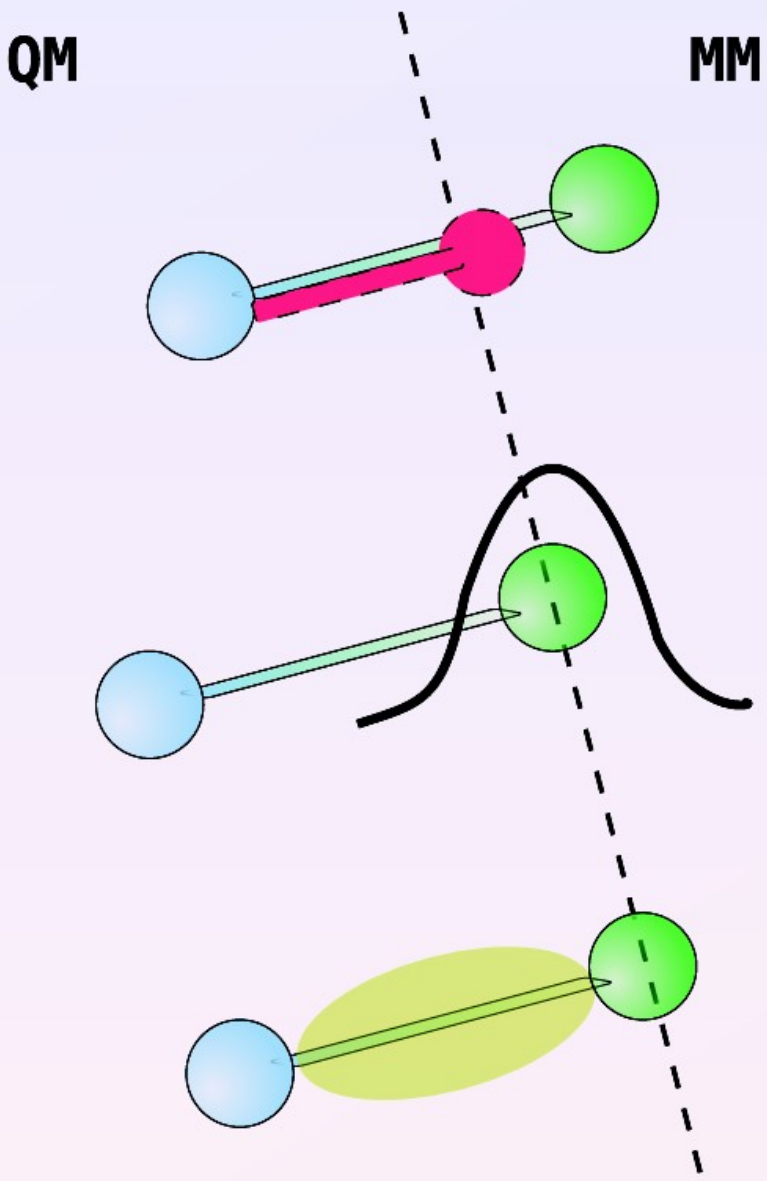
Caution for a QM/MM hybrid scheme ! One must be careful when using the standard parameters

The QM/MM principles (4)

QM/MM frontier ?

- Nothing if no bonds
- Link atom or link group
- Effective atomic or group pseudo-potentials
- Frozen orbitals

In principle, this requires (re-)parametrization of the MM force-field



Recent QM/MM developments

1. The ESPF scheme for sophisticated QM/MM electrostatics
2. The integrated ESPF QM/MM MD algorithm
3. The ESPF QM/MM scheme including a polarizable force-field

All these developments are now part of the Molcas package (version 7.0 and above), including the coupling to a modified Tinker program

The ESPF method[4]

- Direct method:
  - $V_{\mu\nu}^{MM} = \left\langle \mu \left| \frac{q^{MM}}{r^{MM}} \right| \nu \right\rangle \propto N_{MM}$
  - no multipoles (MM2 ...)
  - $E^{elec}\left(\mathrm{A}=\mathrm{QM};\mathrm{B}=\mathrm{MM}\right) \neq E^{elec}\left(\mathrm{A}=\mathrm{MM};\mathrm{B}=\mathrm{QM}\right)$
  - all the MM multipoles usually polarize the wavefunction, the closest ones may overpolarize !
- Approximate method: multipolar atomic operators $\mathbf{Q}^A$ fitted to the electrostatic potential (ESPF)
  - $\Delta H_{\mu\nu} = \sum_A Q_{\mu\nu}^A \phi_{MM}^A = \sum_A \sum_K \left(\left(\mathbf{T}^\dagger \mathbf{T}\right)^{-1} \mathbf{T}^\dagger \right)^{AK} V_{\mu\nu}^K \phi_{MM}^A$
  - $\phi_{MM}^A = \sum_i^{MM} \frac{q_i}{R_{iA}} + \cdots + \mathrm{PBC} + \ldots$
  - $V_{\mu\nu}^K = \left\langle \mu \left| \frac{1}{r_K} \right| \nu \right\rangle \propto N_K \ll N_{MM}$

[4] Ferré & Ángyán, *Chem. Phys. Lett.* **356** (2002)

The ESPF method features

- Geometries / relative energies in good agreement with the 'direct' method

$$\Delta\Delta E(S_0 \rightarrow S_1 \text{ or } S_2) < 1 \text{ kcal mol}^{-1}$$

- Atomic multipoles: $\mathbf{q}^A = \sum_{\mu\nu} P_{\mu\nu} Q^A_{\mu\nu}$
- QM/MM electrostatic interaction energy can be partitionned: $E^A_{QM/MM} = q^A \times V^A \Rightarrow$ unicity of the QM/MM electrostatic energy
- Easy implementation of a QM/MM MD algorithm

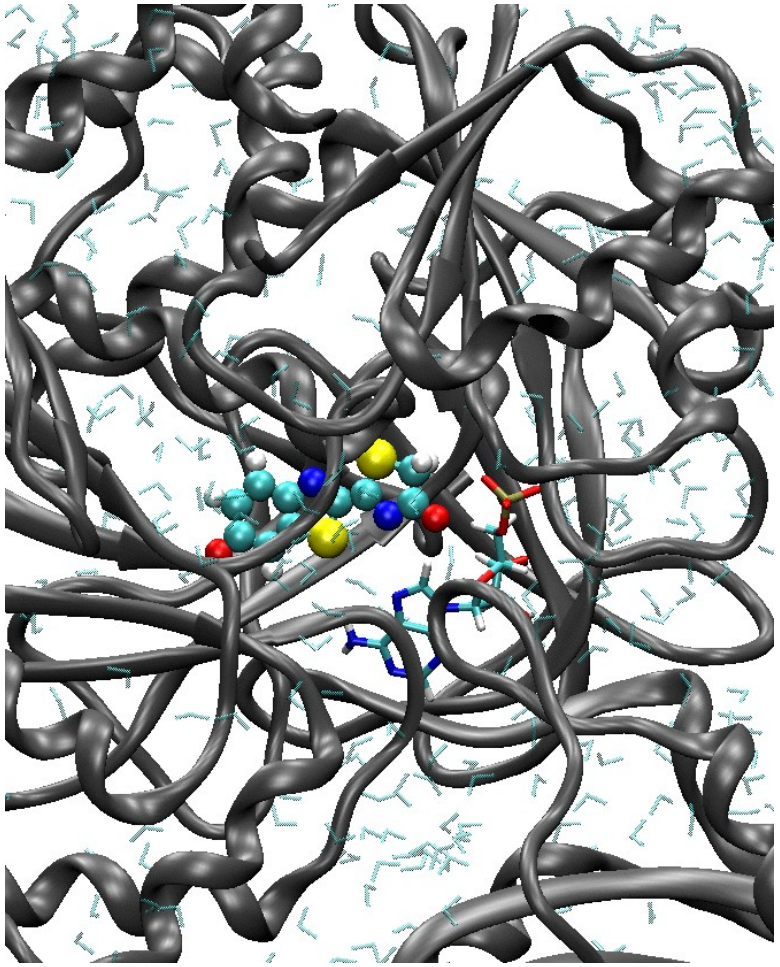
Problems $\longrightarrow$ improvements

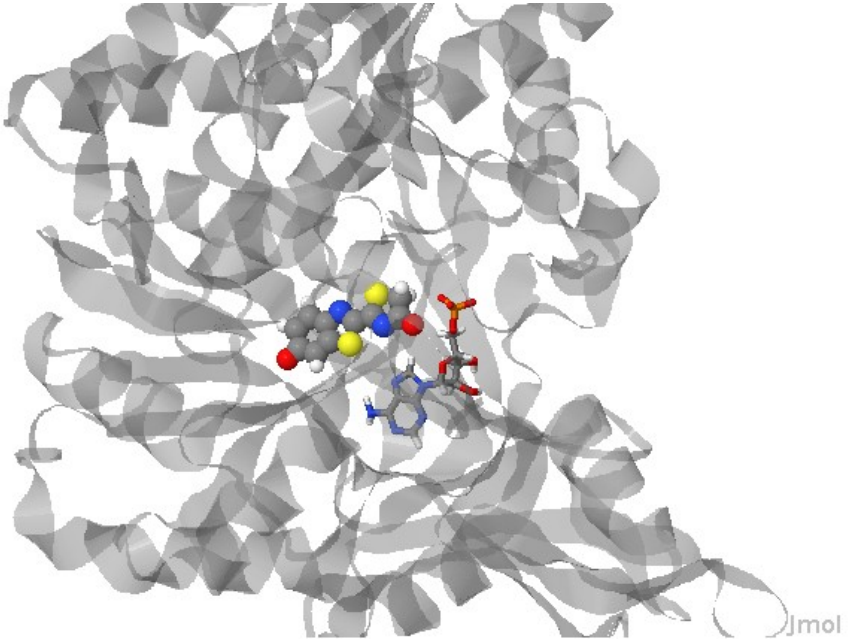
- Usual fitting problems (overdetermination) $\longrightarrow$ SVD decomposition. But complicates the gradient formulation
- The fit depends heavily on the grid around the QM subsystem $\longrightarrow$ constraints. But complicates the gradient formulation
- Which density matrix must be used when SA-CASSCF wavefunctions are computed ?
- A lot of other problems: still to be analyzed

Current model developments

- On-the-fly CASPT2 scaling of the CASSCF gradient for QM/MM MD trajectories
- Polarizable MM: ϕ^A_{MM} depends on the QM electronic state $\longrightarrow$ induced dipoles on the MM side
- (On-the-fly) QM-parametrized MM/MD trajectories $\longrightarrow$ statistical sampling

Luciferin-Luciferase Complex:
CASPT2/Tinker QM/MM





QM/MM model: Solvated protein, 10329 atoms (626 water molecules),
QM system : OxyLH2(-1)

Results

- The same substrate in native and mutated enzyme exhibits the same emission spectra.That is the observed red-shift is not due to a structural difference of the active site/substrate upon mutation of the enzyme.

Conclusions

QM/MM for photochemistry available at

- http://www.teokem.lu.se/molcas
- http://sites.univ-provence.fr/lcp-ct/ferre/nf_tinker_qmmm.html