

# Introduction

## What is QM/MM?

- Hybrid method that QM (Quantum mechanics) and MM (molecular mechanics) calculation schemes
- The system is divided into two regions
  - ◆ QM and MM regions
  - ◆ Regions are designed based on compromise in calculation time and accuracy

## Why use QM/MM?

- The system is too large to use *ab initio* calculations
- MM calculations do not give the "correct" answer
- Processes involving change in electronic structure

## How QM/MM methods differ?<sup>[1]</sup>

### Treatment of the junction between QM and MM regions

#### Use of link atoms

- Hydrogen is ?inserted? along the bond contained in the QM/MM junction
  - ◆ Placed closed to the MM atom
  - ◆ Behavior is changed based on the identity of the MM atom

#### Localized orbitals

- Specially designed local orbitals assigned to boundary QM and MM atoms<sup>[2]</sup>
  - ◆ maintain closure of QM system
  - ◆ local orbitals are designed and tested based on empirical data
  - ◆ no need for extra atoms

#### Pseudopotential methods

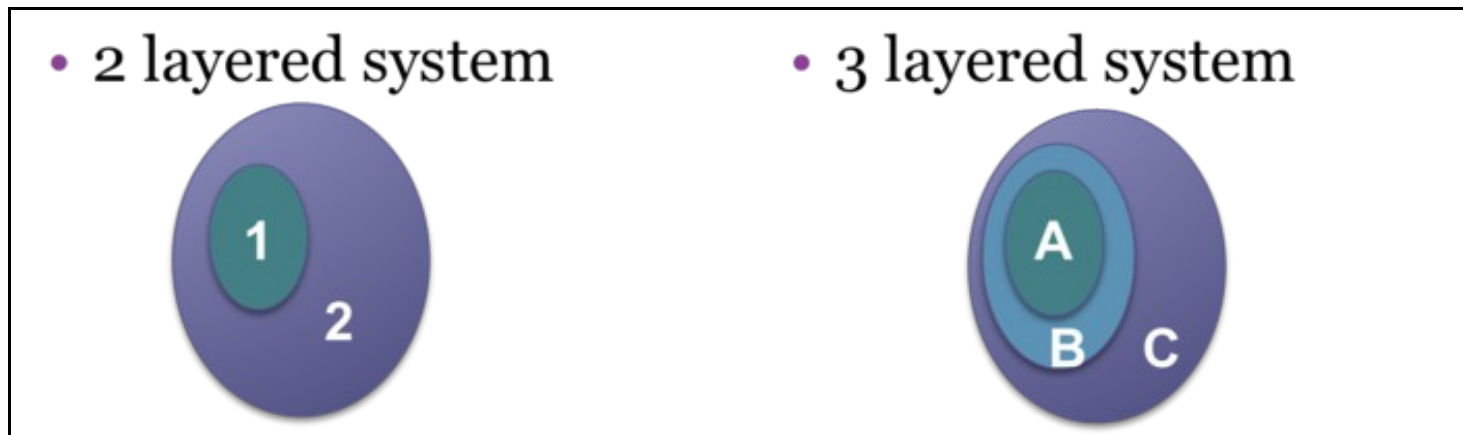
- MM-bounded boundary QM atoms are assigned a special basis set and potential<sup>[2]</sup>
  - ◆ mimic correct covalent bonding scheme
  - ◆ designed from small system models
  - ◆ no need for extra atoms

## Methods of energy calculations

## Subtraction Scheme

**ONIOM** - (our own n-layered integrated molecular orbital and molecular mechanics)

Method developed by Morokuma and co-workers which allows for different regions of a system to be calculated at different levels of theory and combine to produce a consistent energy expression. <sup>[3]</sup>

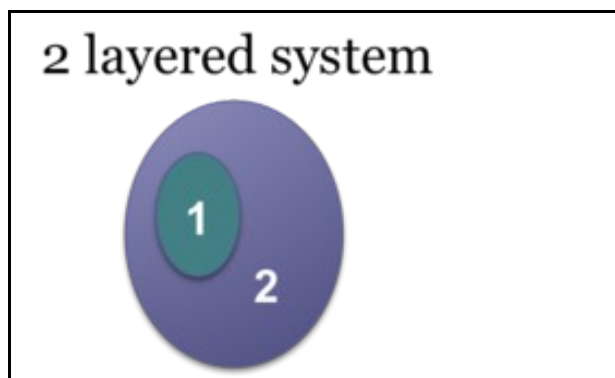


$E(\text{ONIOM2}) = E(\text{High, region 1}) + E(\text{low, regions 1 and 2}) - E(\text{low, region 1})$

$E(\text{ONIOM3}) = E(\text{High, region A}) + E(\text{Medium, regions A and B}) + E(\text{Low, regions A, B and C}) - E(\text{Medium, region A}) - E(\text{Low, region A and B})$  [www.gaussian.com/g\\_tech/g\\_ur/k\\_oniom.htm](http://www.gaussian.com/g_tech/g_ur/k_oniom.htm)

## Summation scheme

Example:



$$E_{\text{total}}(1 \text{ and } 2) = E_{\text{QM}}(1 \text{ and } 2) + E_{\text{QM/MM, ele}}(1 \text{ and } 2) + E_{\text{QM/MM, nucl}}(1 \text{ and } 2) + E_{\text{QM/MM, vdw}}(1 \text{ and } 2) + E_{\text{QM/MM, covalent}}(1 \text{ and } 2) + E_{\text{MM}}(2) \underline{\underline{[2]}}$$

**The way in which the electrostatic interaction between the QM and MM regions are described**

## Mechanical embedding

Polarization from MM electrostatics comes from interpolation scheme used to combine energy terms.

## Electronic embedding

QM polarization from MM electrostatics is explicitly considered.

## Linear-scaled Eward Method

Particle-mesh Eward technique with periodic boundary conditions<sup>[4]</sup>

## GSBP - generalized solvent boundary potential

Small region of the system surround QM region is treated explicitly. The remainder of the system is fixed and described in terms of solvent-shielded static field and a Poisson-Boltzmann reaction field.<sup>[4]</sup>

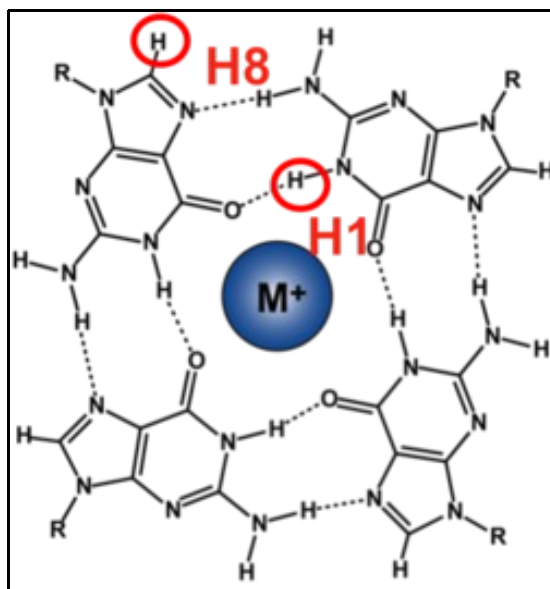
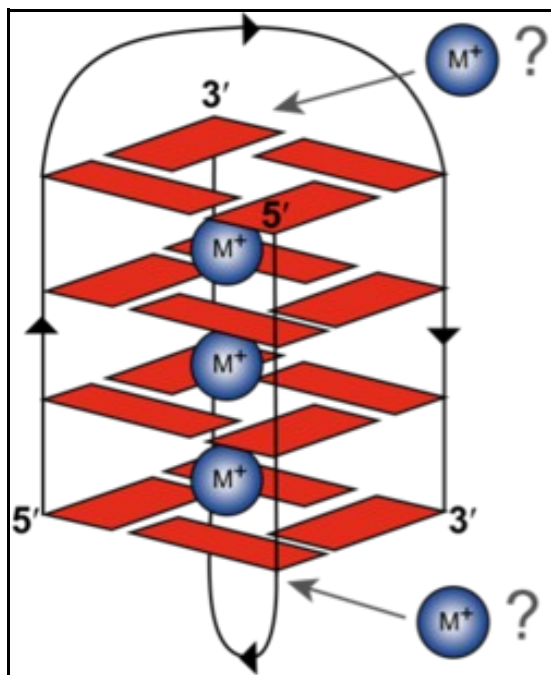
# Case study

## Project Introduction

### Goals

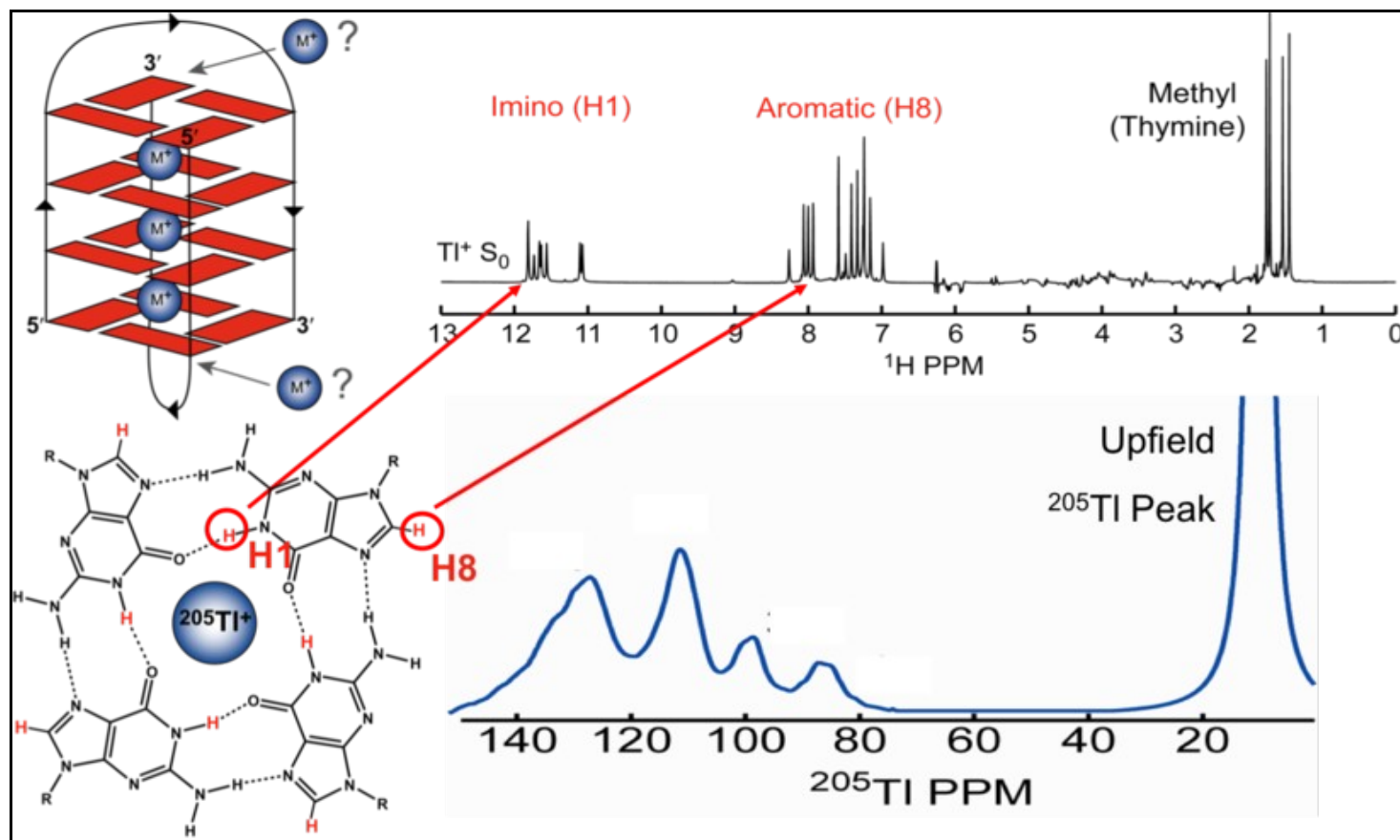
- Simulate the  $^1\text{H}$  and  $^{205}\text{Tl}$  NMR spectra based MM and QM/MM refined x-ray crystallographic and NMR structures
- Understand how differences in the structure lead to different chemical shifts
- Gain insight into molecular structural information directly from experimental chemical shifts

## The G-quadruplex Model System



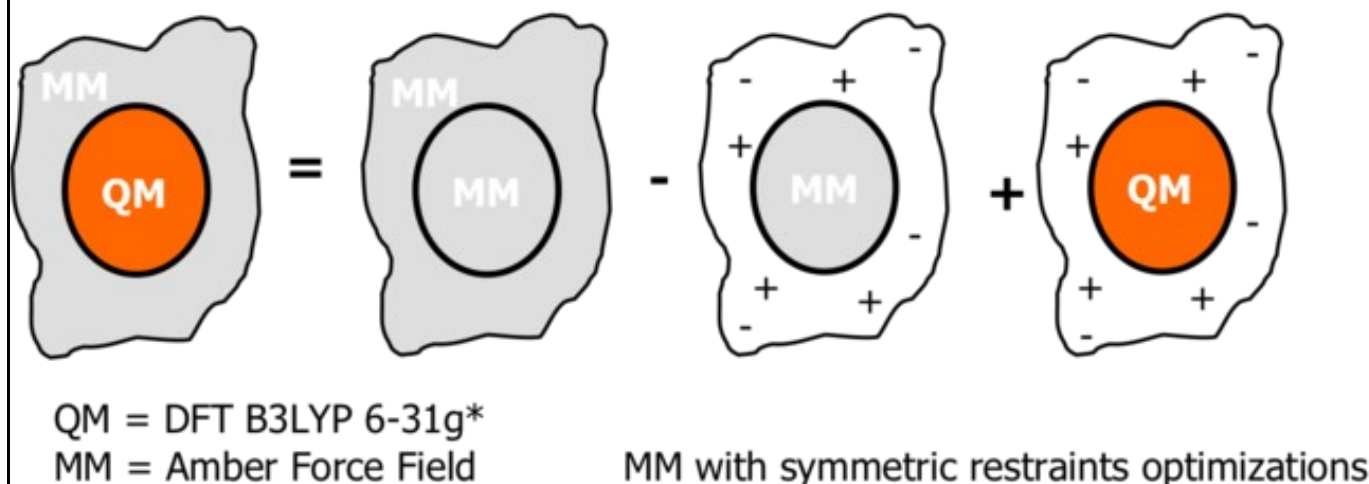
- Model System for the development of  $^{205}\text{Tl}$  NMR
  - ◆ All classes of biomacromolecules bind monovalent cations
  - ◆  $\text{Na}^+$  and  $\text{K}^+$  are poor spectroscopic nuclei
  - ◆  $\text{Tl}^+$  is an excellent mimic of  $\text{K}^+$
  - ◆  $^{205}\text{Tl}^+$  is a spin  $\alpha$  nucleus with a large gyromagnetic ratio  
 $\diamond ^1\text{H} > ^{19}\text{F} > ^{205}\text{Tl} > ^{31}\text{P}$
- $\text{G}_4\text{T}_4\text{G}_4$  is the telomeric sequence from the ciliate *Oxytricha Nova*
  - ◆ Homodimeric G-quadruplex with diagonal loops
  - ◆ Contains four G-quartets, each composed of four guanine bases
  - ◆ Exceptionally stable and structures have been solved by NMR and X-ray crystallography
  - ◆ Binds 3-5 monovalent cations

## Experimental NMR Spectra [5]



## Quantum Mechanics / Molecular Mechanics (QM/MM) Hybrid Methodology [6][7]

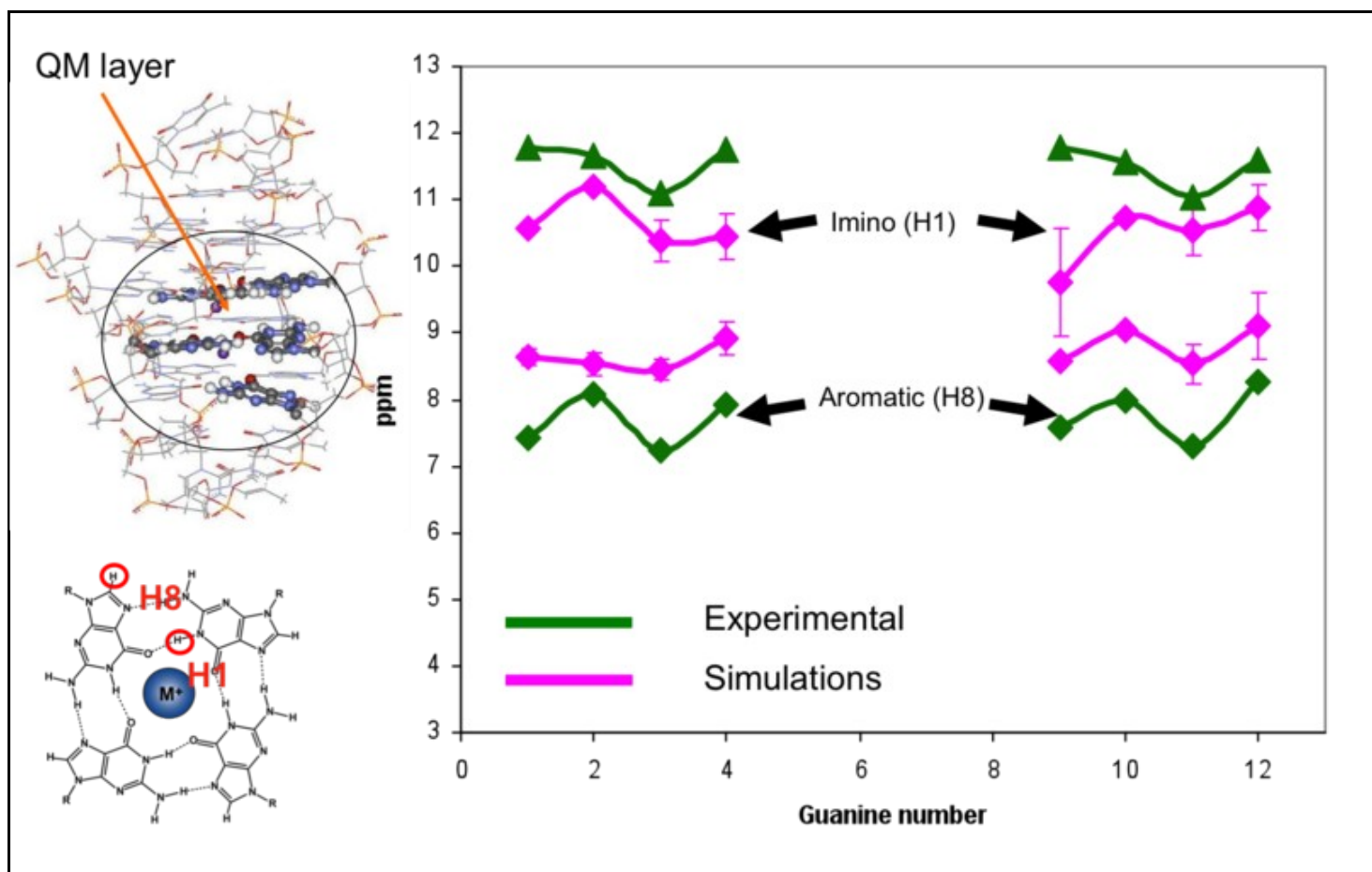
Two-layer ONIOM-Electronic Embedding (EE) (Morokuma), G03.  
in conjunction with gauge independent atomic orbital method  
(GIAO Method)



[www.gaussian.com/g\\_tech/g\\_ur/k\\_nmr.htm](http://www.gaussian.com/g_tech/g_ur/k_nmr.htm)

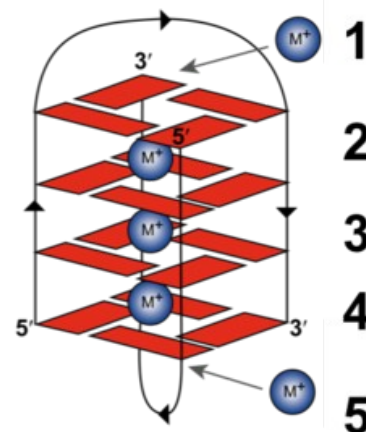
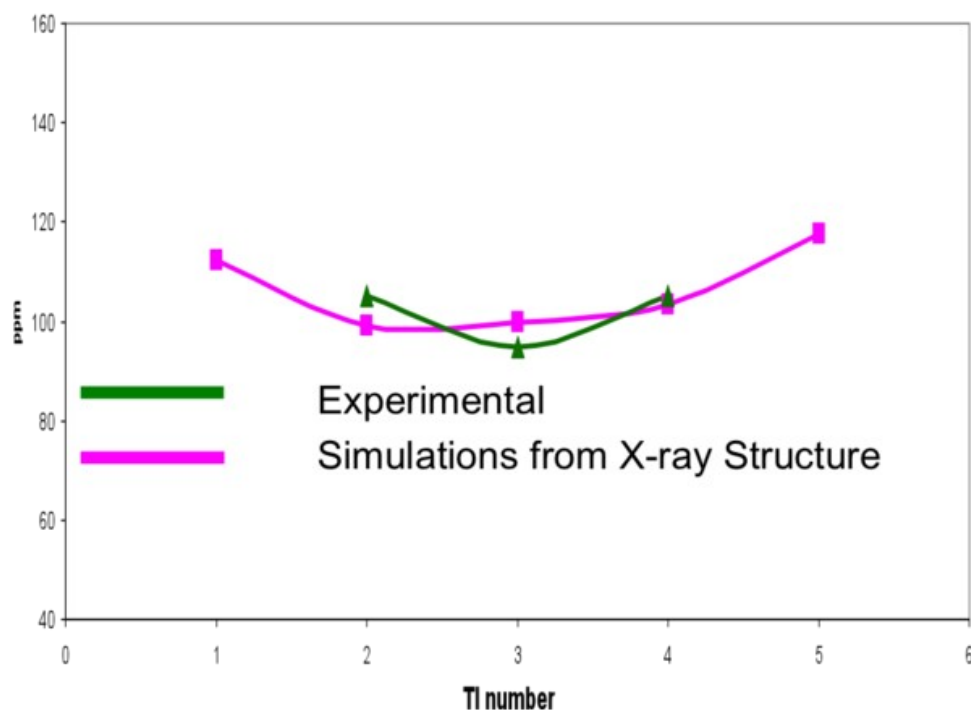
[www.gaussian.com/g\\_tech/g\\_ur/k\\_oniom.htm](http://www.gaussian.com/g_tech/g_ur/k_oniom.htm)

## **<sup>1</sup>H NMR simulations**

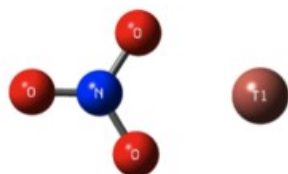
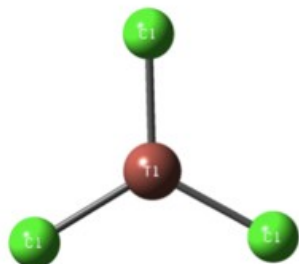


## $^{205}\text{Tl}$ simulations

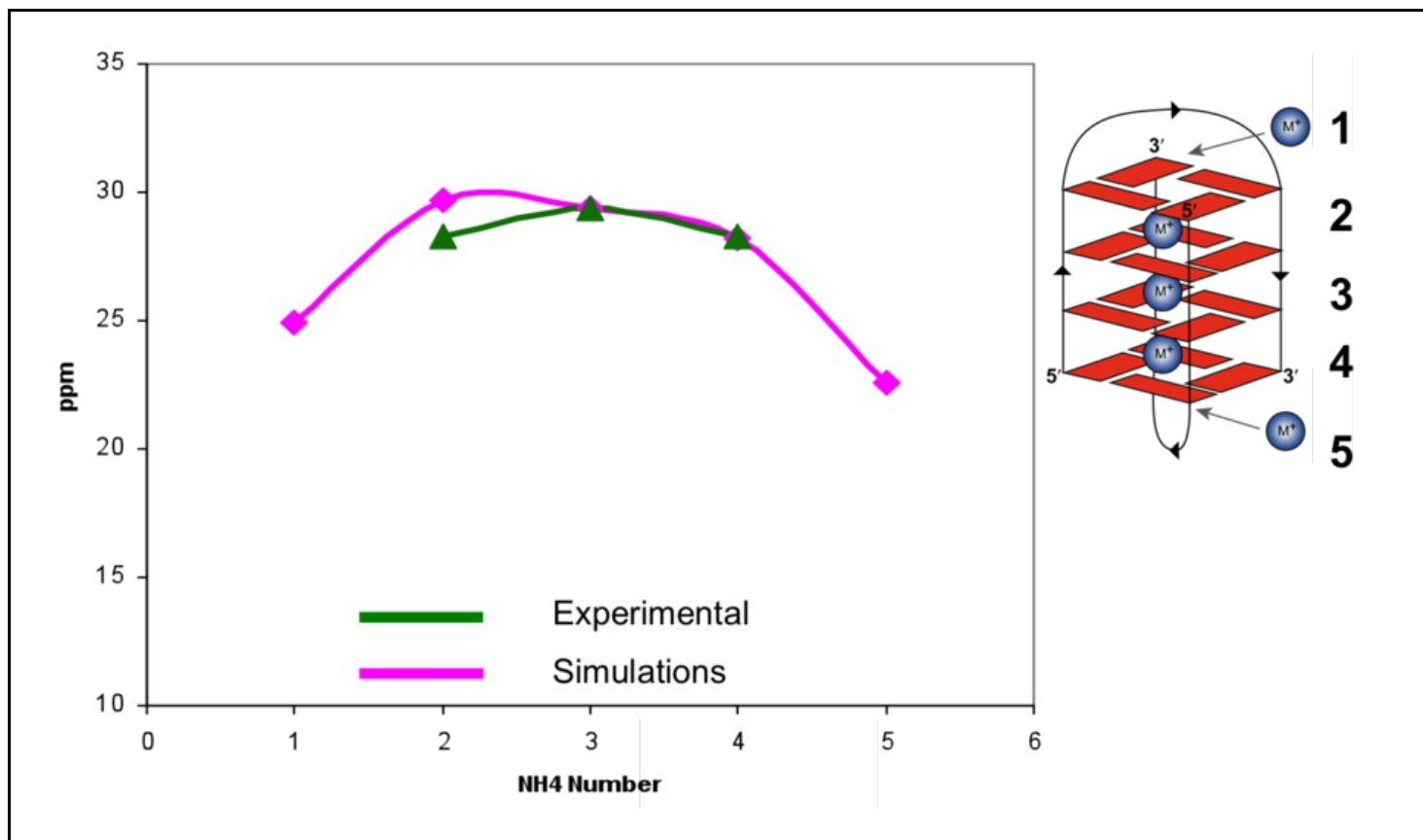
- All Electron Calculations  
Oniom-EE (B<sub>3</sub>LYP/UGBS:Amber Force Field)



## <sup>205</sup>Tl benchmarks<sup>[8]</sup>

TlNO<sub>3</sub>TlCl<sub>3</sub>

|                                  | ECP<br>(Electron<br>Core<br>Potential)<br>(Cep-EG) | All Electrons (UGBS) |
|----------------------------------|--|----------------------|
| TlNO <sub>3</sub>                | 301 ppm  | 8787 ppm             |
| TlCl <sub>3</sub>                | 271 ppm  | 7102 ppm             |
| Δδ                               | 30 ppm   | 1685 ppm             |
| Experimental Reference ~2300 ppm |  |                      |

**$^{15}\text{N}$  simulation of  $\text{NH}_4^+$  bound G-quadruplex<sup>[9]</sup>****Case study conclusions**

- We have completed NMR simulations of G-quadruplet at the QM/MM level where the influence of the surrounding environment is explicitly considered
- $^1\text{H}$ -NMR is found to be extremely sensitive to the configuration of the system, useful for gaining structural insight
- Stacking greatly impacts the  $^1\text{H}$  NMR Spectra
- The ions most exposed to the loops have different magnetic environments most likely due to structural disorder
- All-electron (UGBS) simulations of  $^{205}\text{Tl}$  NMR spectra provide valuable insight on the origin of chemical shifts

**Further Reading**

H. Hu, W. Yang / Journal of Molecular Structure: THEOCHEM 898 (2009) 17?30 [File:H Hu papper 2009.pdf](#)

H. M. Senn, W. Thiel. Current Opinion in Chemical Biology 2007, 11:182?187 [File:Senn paper.pdf](#)

M. Svensson, S. Humbel, R.D.J. Froese, T. Mastubara, S. Sieber, and K. Morokuma, J.Phys.Chem., 100, 19357 (1996). [File:Svensson paper.pdf](#)



R. A. Friesner and V. Guallar, *Annu. Rev. Phys. Chem.* 2005. 56:389-427 [File:Friesner.pdf](#)

## References

1. [2](#) Eduardo M. Sproviero et al. *Photosynth Res.* In Press.
2. [2.0](#) [2.1](#) [2.2](#) H. Hu, W. Yang / *Journal of Molecular Structure: THEOCHEM* 898 (2009) 17-30
3. [2](#) M. Svensson, S. Humbel, R.D.J. Froese, T. Mastubara, S. Sieber, and K. Morokuma, *J.Phys.Chem.*, 100, 19357 (1996).
4. [2](#) [4.0](#) [4.1](#) H. M. Senn, W. Thiel. *Current Opinion in Chemical Biology* 2007, 11:182-187
5. [2](#) Michelle L. Gill, Scott A. Strobel and J. Patrick Loria *Am. Chem. Soc.* 127, 16723-16732 (2005)
6. [2](#) J.A. Gascon and V.S. Batista, *Biophys. J.* 87, 2931-2941 (2004)
7. [2](#) J.A. Gascon, E.M. Sproviero and V.S. Batista, *J. Chem. Theor. Comput.* 2, 11-20 (2005)
8. [2](#) J. Hinton. (1992) *Ann Rep NMR Spectr* 13, 211
9. [2](#) Juli Feigen et al (2001) *Methods in Enzymology* Vol 338,400