

## Theoretical Molecular Modelling and Quantum Theory Calculations of macromolecules and their practical applications

### Abstract

By performing Molecular Mechanic calculations and Quantum Theory calculations (semi-empirical and *ab initio*) on different molecules, it is found that the semi-empirical Quantum Theory method and the *ab initio* method can predict experiment. Semi-empirical methods (MNDO, AM1 and PM3) are theoretically less accurate than *ab initio* but they are orders-of-magnitude faster, allowing larger molecules to be studied. The practical application of Quantum Theory on macromolecules shows that quantum mechanics is becoming more able to give understanding of material properties and allow the design of novel electronic devices based on the understanding of the delocalized molecular orbitals. The theoretical approach is very useful to investigate and characterize the reaction mechanisms of inter-molecular bonds and intra-molecular bonding.

### Keywords:

Molecular Mechanics / Quantum Theory, Theoretical and molecular modelling methods, Practical application

### 1. Introduction

By the late 1920s, several formulations of Quantum Theory had been put forward. Schrödinger <sup>[1]</sup> and Heisenberg <sup>[2]</sup> developed two mathematically distinct representations of quantum mechanics. The Schrödinger equation is the basis for one of the widely used representations of quantum theory, including the time-dependent Schrödinger equation and the time-independent Schrödinger equation. The wave packet problem provided physical insight into the origin of the uncertainty relation, i.e. the Heisenberg uncertainty relation: large uncertainty in momentum results in small uncertainty in position, and conversely. This is a direct consequence of the superposition principle and the probability wave nature of the eigenkets. Schrödinger's method involves partial differential equations, whereas Heisenberg's method employs matrices. By 1928, Dirac <sup>[3]</sup> advanced a general approach to Quantum Theory, in which his developments were based on two fundamental concepts: absolute size and the superposition principle. These two ideas are at the heart of the differences between classical physics and quantum theory. Dirac demonstrated <sup>[4]</sup> that both the Schrödinger and the Heisenberg methods were subsets of this general theory which cleared up many disagreements about the form of the correct theory. Quantum Theory Methods describe observables and provide the methods to generate probability distributions to compare with experimental observations <sup>[4]</sup>.

In past decades, quantum mechanics has been developed to perform quantum mechanical calculation for a variety of molecules ranging from the smallest atom, H to very large molecules, such as DNA <sup>[5-8]</sup>. With the assistance of powerful computers, more Quantum Theory calculations have been developed to understand the shape and size of single macromolecules, the intermolecular association of molecules, and the solvent effects on the configuration and reactivity of molecules <sup>[9]</sup>. Because

determination of the 3-dimensional structure of molecules is important to predict their conformation in typical media, the chemical and physical properties of molecules given by theoretical and molecular modelling allow exploration of their potential application in catalysis, photonics<sup>[10]</sup>, pharmaceutical application<sup>[11, 12]</sup>, semi-conducting materials<sup>[13]</sup>, surfactant design<sup>[14]</sup>. To deal with macromolecules, the idea is to build the molecule by adding each optimized group part by part and re-optimizing the new unit to deal with large molecules, e.g. polymers chains<sup>[15]</sup>. By saving time and using less computer space, will cut costs and give more accurate results from the calculations.

In the article, the theoretical and molecular modelling methods and recent development of quantum mechanics on practical applications will be summarized.

## 2. Theoretical and Molecular modelling methods

*ab initio* and semi-empirical quantum mechanical methods have been used extensively to study ground state structures, energies and relativities of a wide variety of molecules<sup>[16]</sup>. The most extensive *ab initio* studies are 6-31G\*\* calculations<sup>[17]</sup>. Such calculations can yield excellent results, for instance, *ab initio* studies on the calculation of Isocyanate cycloaddition to olefins to form blactams<sup>[18, 19]</sup>. However, it is costly of time and money when the large molecules studied. Semi-empirical methods (MNDO, AM1 and PM3) are theoretically less accurate but they are much faster, allowing a larger number of molecules to be studied<sup>[20]</sup>.

C. I. Williams and M. A. Whitehead compared the two methods with experimental results by studying isocyanate geometries and  $\beta$ -lactam formation<sup>[20]</sup>. When the semi-empirical and *ab initio* geometries were compared with experimental values even though the time required to perform the complete optimization with an *ab initio*, or density functional methods is orders of magnitude greater than required for the semi-empirical method, the semi-empirical transition state geometries were markedly more asynchronous than the corresponding *ab initio* or DFT transition states. The PM3 method gave transition states geometries and activation barriers comparable to very high-level *ab initio* calculations. They concluded that semi-empirical methods (especially PM3) would be ideal for this type of calculations. Adam J. Dickie et al.<sup>[13]</sup> reached the similar conclusion that PM3 is robust and parallels experiment and is even more useful when such parallelism fails because it alerts the researcher to use larger basis set.

## 3. Practical application of quantum mechanics

### 3.1 Quantum mechanical study on self-assembled monolayers

As molecules become increasingly integrated into modern electronic technologies, it becomes essential to understand the molecular orbital (MO) distribution of these novel devices. Self-assembled monolayer of electron-rich molecules on solid semiconductor surface is one of potential devices, because of the ability to tune the surface electronic properties by modifying the molecular monolayer.

Adam J. Dickie *et al.*<sup>[13]</sup> performed PM3 and *ab initio* methods to calculate heats of formation, band gap energies and geometries of monomer and dimer structure of  $\text{H-C}\equiv\text{C}-(\text{CH}_2)_6\text{-C}\equiv\text{C-Sn}$ , and  $\text{H-C}\equiv\text{C-}p\text{-C}_6\text{H}_4\text{-C}\equiv\text{C-Sn}$ . Delocalized Molecular Orbitals, DLMO analysis of the self-assembled monolayer showed the Sn-O

head-groups extend  $\pi$ -conjugation of the monolayer chains to allow infinite thin films to act as semi-conducting materials. Meanwhile, a potential barrier exists between the surface-localized DLMO HOMOs and the Organotin-centred DLMO LUMOs. The above results allowed the theoretical design of spacers between the alkynyl or phenyl repeat units to generate surface adsorbed molecule whose chain are at the optimum separation to form good crystals and good conductors.

Adam J. Dickie *et al.* <sup>[21]</sup> reported a serial templating methodology using linked aminosilane/stannane units and simple beaker chemistry yielded thin film nanoassemblies on semiconductor surfaces that provide nucleating sites for crystallization of octadecanola.

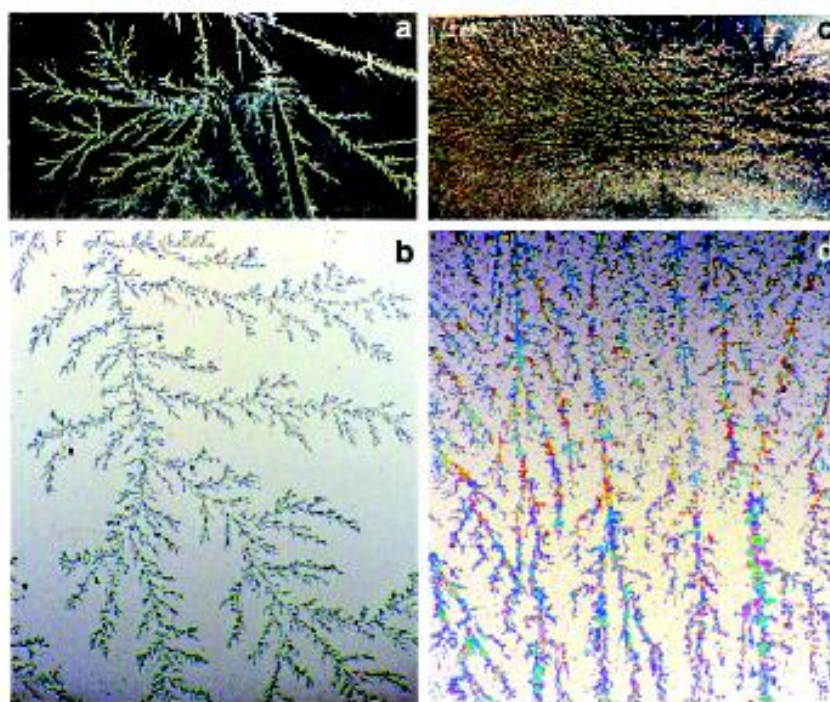


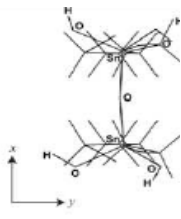
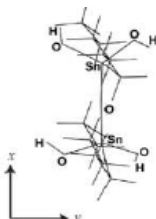
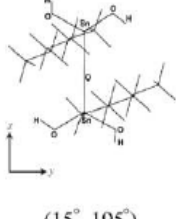
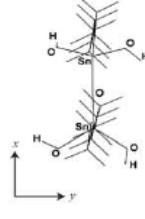
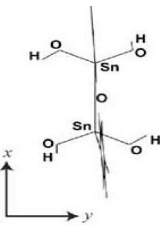
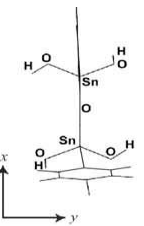
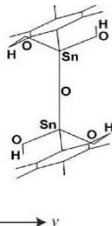
Figure 1. Crystal growth from  $(\text{NMe}_2)_3\text{Si-O-R-C}\equiv\text{C-Sn}(\text{NEt}_2)_3$ /phenylacetylene/octadecanol on a silicon wafer [ $\text{R}=(\text{CH}_2)_3$ , a,b;  $\text{R}=\text{CH}_2$ , c,d]. (a,c) 5 cm; (b,d) 5 mm <sup>[21]</sup>.

As shown in Fig 1a., the highly conjugated and organometallic tionalkynyl molecules form highly ordered and densely packed thin film on  $\text{SiO}_2/\text{Si}$  (100) substrates. Obviously, crystalline assemblies obtained using  $(\text{NMe}_2)_3\text{Si-O-CH}_2\text{-C}\equiv\text{C-Sn}(\text{NEt}_2)_3$  were densely packed and highly branched (Fig. 1c,d), while using  $(\text{NMe}_2)_3\text{Si-O-(CH}_2)_3\text{-C}\equiv\text{C-Sn}(\text{NEt}_2)_3$  as the surface activation unit produced linear octadecanol crystalline assemblies with perpendicular branch growth (Fig.1a,b). Crystals obtained using the rigid  $(\text{NMe}_2)_3\text{Si-O-(C}_6\text{H}_4\text{)-C}\equiv\text{C-Sn}(\text{NEt}_2)_3$  surface activator were predominantly thick and linear, with short side branches.

According to the experimental observation, it is found the crystallization patterns were dependent on the surface activation unit employed. The quantum mechanical calculation on the geometries provided the theoretical support for the shape difference of self-assembled thin layer. For instance, Adam J. Dickie *et al.* <sup>[13]</sup> calculated geometries of  $[(\text{H-C}\equiv\text{C-(CH}_2)_6\text{-C}\equiv\text{C})(\text{HO})_2\text{Sn}]_2\text{-O}$  dimmer,

$[(\text{H}-\text{C}\equiv\text{C}-p\text{-C}_6\text{H}_4\text{-C}\equiv\text{C})(\text{HO})_2\text{-Sn}]_2\text{-O}$  dimer using the semi-empirical PM3 method , and the results are listed in Table 1.

Table1. Geometries of  $[(\text{H}-\text{C}\equiv\text{C}-(\text{CH}_2)_6\text{-C}\equiv\text{C})(\text{HO})_2\text{Sn}]_2\text{-O}$  dimer and  $[(\text{H}-\text{C}\equiv\text{C}-p\text{-C}_6\text{H}_4\text{-C}\equiv\text{C})(\text{HO})_2\text{-Sn}]_2\text{-O}$  calculated using the semi-empirical PM3 method <sup>[13]</sup>

Calculated dimer	Dimer Geometry, $xy$ plane ( $\theta_1 \theta_2$ )			
$[(\text{H}-\text{C}\equiv\text{C}-(\text{CH}_2)_6\text{-C}\equiv\text{C})(\text{HO})_2\text{Sn}]_2\text{-O}$ dimer				
	$(0^\circ, 0^\circ)$	$(-55^\circ, -53^\circ)$	$(15^\circ, 195^\circ)$	$(78^\circ, 78^\circ)$
	$\angle\text{O-Sn-O}=158.3^\circ$	$\angle\text{O-Sn-O}=161.6^\circ$	$\angle\text{O-Sn-O}=156.6^\circ$	$\angle\text{O-Sn-O}=163.8^\circ$
	<hr/>			
$[(\text{H}-\text{C}\equiv\text{C}-p\text{-C}_6\text{H}_4\text{-C}\equiv\text{C})(\text{HO})_2\text{-Sn}]_2\text{-O}$ dimer				
	$(90^\circ, 90^\circ)$	$(0^\circ, 90^\circ)$	$(23^\circ, -23^\circ)$	
	$\angle\text{O-Sn-O}=169.1^\circ$	$\angle\text{O-Sn-O}=171.6^\circ$	$\angle\text{O-Sn-O}=168.6^\circ$	

For  $[(\text{H}-\text{C}\equiv\text{C}-(\text{CH}_2)_6\text{-C}\equiv\text{C})(\text{HO})_2\text{Sn}]_2\text{-O}$ , the most favorable PM3 dimers of are found when the z-axis rotation of the carbon backbones are at  $(\theta_1, \theta_2)$  angles of  $(0^\circ, 0^\circ)$  and  $(-55^\circ, -53^\circ)$ . The  $(0^\circ, 0^\circ)$  structure is most favored because this orientation places minimal stress upon the Sn–O–Sn cross-link, and weak out-of-plane –CH<sub>2</sub>– packing is allowed. The  $(15^\circ, 195^\circ)$  has low Sn–O–Sn angle stress, but is not favored because no out-of-plane packing exists. The  $(-55^\circ, -53^\circ)$  orientation is also a highly favored, low-energy structure, because strong in-plane –CH<sub>2</sub>– packing, offsets the Sn–O–Sn bond strain: the  $(78^\circ, 78^\circ)$  has the highest amount of in-plane packing, but also the most Sn–O–Sn strain. Trends in band gaps follow the energy trends, and again, are decreased with respect to the monomer structures.

In three types of  $[(\text{H}-\text{C}\equiv\text{C}-p\text{-C}_6\text{H}_4\text{-C}\equiv\text{C})(\text{HO})_2\text{Sn}]_2\text{-O}$  dimers, the edge-on dimer,  $(\theta_1, \theta_2)=(90^\circ, 90^\circ)$  is favoured over the herringbone,  $(\theta_1, \theta_2)=(0^\circ, 90^\circ)$ , and face-packed,  $(\theta_1, \theta_2)=(23^\circ, -23^\circ)$  dimer structures for reasons of symmetry . The edge-on structure, with C<sub>2</sub> symmetry, allows constructive, in-phase, and nodeless overlap between orbitals centred on separate H–C≡C–p–C<sub>6</sub>H<sub>4</sub>–C≡C chains. This symmetric overlap lowers the orbital energies, producing the most stable dimer. The herringbone dimer is slightly favoured over the face-packing dimer, because of electrostatic  $\pi$ - $\sigma$  interactions between the more negatively charged phenyl ring face and the more positively charged ring edge.

### 3.2 Quantum mechanical study on dendrimer generations

Dendrimers <sup>[22]</sup> constitute a fascinating area in nanotechnology, because their distinct structure and properties can be manipulated in various ways to make use of such nanostructures in a variety of applications. To develop synthetic techniques for these interesting macromolecules in a controlled fashion, it is required to understand their actual shape and size, the environment in their cavities, and their intermolecular association. Theoretical and molecular modelling investigations of dendrimers have given more details about their chemical and physical properties to allow for their practical applications. For instance, pharmaceutical applications of dendrimers require knowledge of the size of the internal cavities of the dendrimers to allow a guest (drug) molecule to fit in, and molecular modelling provides information about the overall size of a dendrimer, its three dimensional orientation in space, and the relativities of the peripheral chemical groups <sup>[23]</sup>.

Rami Hourani *et al.* <sup>[10]</sup> theoretically investigated 3, 5-dihydroxybenzylalcohol based dendrimer generations 1–5 using Molecular Mechanics (MM+) method and the PM3 Semi-Empirical Molecular Orbital Theory. The calculations gave information about the development of the three dimensional structure of these dendrimers from generation 1 to 5. Generations 4 and 5 are globular in shape with well-defined internal cavities that can be used as a guest-host system. Beyond DG5, the area for additional bonding is constricted; they can form more hydrogen bonds, but the reactive molecules cannot reach the hydrogen because the system is closed up. The optimizations revealed the overall sizes of these dendrimers, which ranged between 16–75 Å for generations 1–5, respectively. This was found experimentally because DG6 and above could not be synthesized. The dimensions of the internal cavities in DG4 and 5 are a suitable size for various small drugs and catalysts (Fig.2).

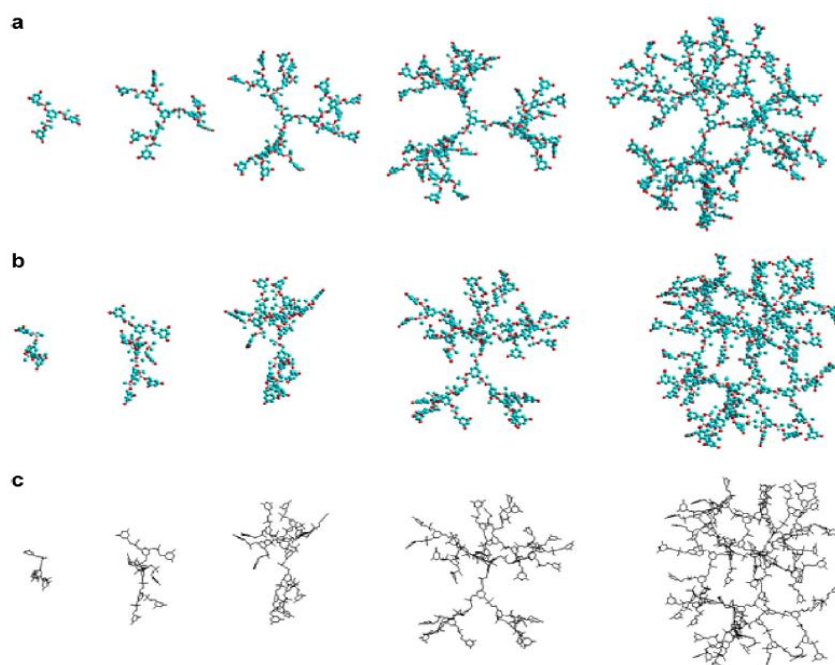


Fig. 2. The optimized structures of dendrimer generation 1–5 using the molecular modelling MM+ method shown as (a) sticks and balls of dendrimers (b) sticks and balls of side view of dendrimers (c) sticks of side view of dendrimers to show clearly the development of the globular shape as the

dendrimer generation increases.<sup>[10]</sup>

Molecular Orbital Theory has been shown very useful to obtain important information about the shape, size, energy, and Delocalized Molecular Orbitals for 3,5-dihydroxybenzylalcohol (DHBA) based dendrimers and also to explain the inability to make higher dendrimer generations after a certain limit. This useful information can be applied to other types of dendrimers and macromolecules.

### 3.3 *Quantum mechanical study on the self-assembly of poly(styrene-alt-maleic anhydride, SMA)*

The association of block copolymers in solution has been extensively studied and the methods used to investigate the mechanisms of association are macroscopic characterization methods such as dynamic light scattering (DLS), viscosity analysis, etc., to define the size and the macroscopic properties of the association, and more precise micro-level characterization methods such as TEM, AFM, etc., to understand the interaction between the molecules and the shape of the association. Quantum mechanical studies of the interactions between the polymer chains are theoretically more demanding due to the large size of the two blocks (A,,,AB,,,B) and are therefore rare in the literature. In comparison, the association between alternating copolymer chains has not been widely studied.

Alternating copolymers are repetitive copolymers, and the global behaviour of the association can be modelled using a few repetitive conformational units; therefore, quantum chemistry is an excellent method to study alternating copolymers. The repetitive unit will be defined by studying the conformation of the molecule by adding each group composing the polymer part by part.

Poly(styrene-maleic anhydride) is a water-soluble polymer, and its structure is pH-dependent because of the maleic anhydride ring. C. Malardier-Jugroot et al.<sup>[24]</sup> chose the theoretical approach to investigate and characterize the association mechanism behavior of SMA chains by performing precise scan around all the dihedral angles of the molecule and considering all possible chiralities of the polymer at different pH values. The conformations of the monomer and the dimer at pH 3, 7, 12, and the trimer at pH 7, the quadrimer, pentamer, hexamer at pH 3, 7 have been studied, respectively.

As shown in Fig.3., structure of the isolated SMA chains at pH 7, caused by Na<sup>+</sup>, is linear because of strong H-bond makes the structure independent of chirality. At pH 7 the chains are very close to the optimal structure needed to associate in solution and will be stabilized by the interaction between the benzene rings along the chain; therefore, this association will be favored at pH 7. Fig.4. shows the strong interaction between SMA-Na<sup>+</sup> chains at pH7 from  $\pi$  stacking interactions between benzene rings in two chains. Further, the molecular orbital calculations predicted the tubular association of SMA-Na<sup>+</sup> at pH 7 to give nanotubes.

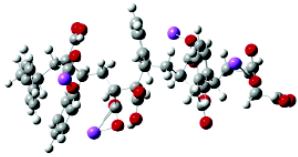

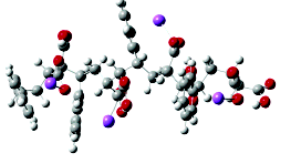

<i>Chirality</i>	<i>Optimised structure</i>	<i>Backbone representation</i>
SR RR SR		
SR SR SR		

Fig.3. Two different conformations of the quadrimers of SMA at pH 7 corresponding to two chiralities (SR-RR-SR and SR-SR-SR). The structures are very linear, and the orientations of the benzene groups are similar.<sup>[15]</sup>

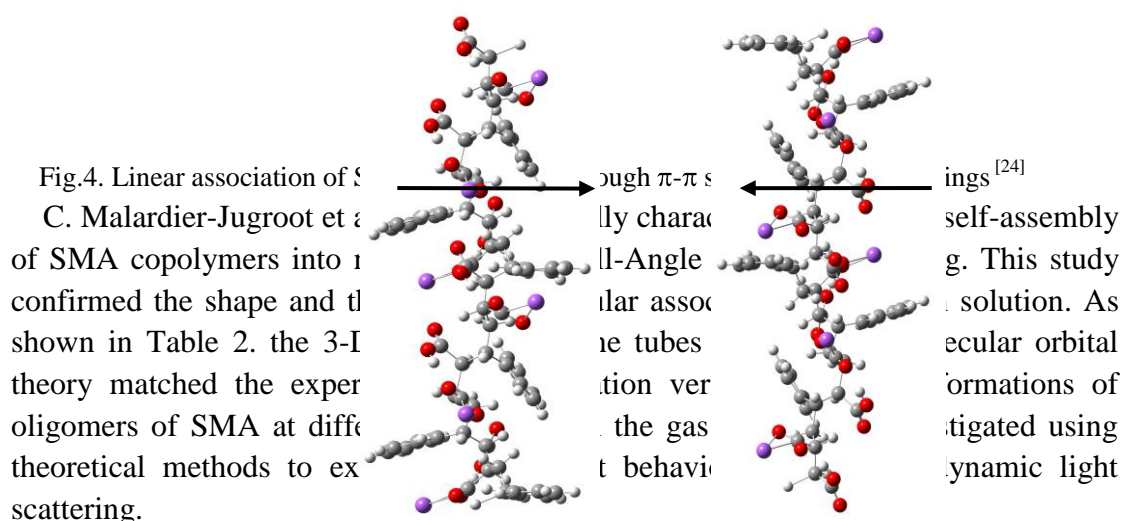


Table 2. Parameters of associated SMA- $\text{Na}^+$  nanotubes in solution

Parameters	Associated SAM	Methods used
Shape	Tubular structure (square)	Theoretical/SANS,cryo-TEM
Inner radius	14.0 / 13.0 $\pm$ 0.8 Å	Theoretical / SANS
Outer radius	20.5 / 19.5 $\pm$ 1.5 Å	Theoretical / SANS

It is a good example of theoretical calculations explaining experimental observation. Therefore, the quantum mechanical study of alternating polymers at different pH values is essential to understand the association mechanism of the polymer chains.

### 3.4 Mixed quantum mechanics/ molecular mechanics study on Cytochrome P450CAM Enzymatic Catalysis Cycle<sup>[26]</sup>

The cytochrome P450 monooxygenase family plays a vital role in the metabolism of xenobiotic substances in plants, fungi, bacteria, insects, and mammals. The complex pathway from the inactive resting species to the putative catalytically active

ferryl species (compound I) is believed to be common across different P450 members and involves sequential changes in oxidation state, ligand composition, and spin state of the heme.

Victor Guallar *et al.* [26] studied the catalytic pathway of cytochrome P450cam by means of a hybrid quantum mechanics/molecular mechanics method. The results revealed an active role of the enzyme in the different catalytic steps: i) The protein initially controlled the energy gap between the high- and low-spin states in the substrate binding process, allowing thermodynamic reduction by putidaredoxin reductase and molecular oxygen addition; ii) A second electron reduction activated the delivery of protons to the active site through a selective interaction of Thr252 and the distal oxygen causing the O-O cleavage; iii) Finally, the protein environment catalyzed the substrate hydrogen atom abstraction step with a remarkably low free energy barrier (~8 kcal/mol).

The QM/MM calculation results were consistent with the effect of mutations on the enzymatic efficacy and provided a satisfactory explanation for the experimental failure to trap the proposed catalytically competent species.

#### 4 Conclusions

Though performing theoretical calculation and molecular modelling on ground state structures, energies and relativities of macromolecules, it is concluded that both semi-empirical quantum mechanical method and *ab initio* method are comparable with experimental results while semi-empirical methods (especially PM3) is robust and would be ideal for this type of calculations. So far, Prof. Whitehead's group has preformed quantum mechanical studies on self-assembled monolayer on spacers, dendrimer generations and self-assembly of polymer in solution, which turns out theoretical calculations are in great agreement with experimental observations. Therefore, quantum mechanical approach is becoming more and more powerful to provide theoretical support for structure and chemical / physical properties of various molecules, and also very useful to investigate and characterize the reaction mechanism of inter-molecules and intra-molecules. Based on the understanding of molecular orbital, it allows exploring potential applications of macromolecules in industry fields, developing synthetic techniques for interesting macromolecules in a controlled fashion, and designing novel electronic devices *etc.*

#### References

1. Muller-Kirsten; Harald J. W. *Introduction to Quantum Mechanics: Schrodinger Equation and Path Integral*. Baker & Taylor Books. **2006**.
2. Lindley David. *Uncertainty: Einstein, Heisenberg, Bohr, and the struggle for the soul of science*. Doubleday Press. **2007**.
3. Pais Abraham; Pais Abraham; Jacob Maurice; Olive David I.; Atiyah Michael Francis; Goddard Peter. *Paul Dirac: The Man and his Work*. Cambridge University Press. **1998**.
4. Michael D. Fayer. *Elements of quantum mechanics*. Oxford University Press. **2001**.
5. T. Clark. *A Handbook of Computational Chemistry*. Wiley, New York. **1985**.
6. Jursic B. *J. Mol. Struct. (Theochem)*. **1994**, 309, 241.



7. Yarligan, S.; Oretir C. *J. Mol. Struct.(Theochem)*.**1996**, 366, 227.
8. Xi H. Chen; John Z. H. Zhang. *J. Phys. Chem.* **2004**, 120, 11386.
9. C. Malardier-Jugroot; T.G.M. van de Ven; M.A. Whitehead. *J. Mol. Struct. (Theochem)*. **2004**, 679, 171.
10. Rami Hourani; Ashok Kakkar; M.A. Whitehead. *J. Mol. Struct. (Theochem)*. **2007**, 807, 101.
11. Patrick Charbonneau; Bertrand Jean-Claude; M.A. Whitehead. *J. Mol. Struct. (Theochem)*. **2001**, 574, 85.
12. C. Karvellas; C.I. Williams; M.A. Whitehead; B.J. Jean-Claude. *J. Mol. Struct. (Theochem)*. **2001**, 535, 199.
13. Adam J. Dickie; Ashok K. Kakkar; M.A. Whitehead. *J. Mol. Struct. (Theochem)*. **2005**, 723, 111.
14. F. Villamagna; M.A. Whitehead,;AK. Chattopadyay. *J. Mol. Struct. (Theochem)*. **1995**, 343, 77.
15. C. Malardier-Jugroot; T. G. M. van de Ven; M. A. Whitehead. *J. Phys. Chem. B*. **2005**, 109, 7022.
16. T. Clark. *A Handbook of Computational Chemistry*. Wiley, New York, **1985**.
17. H.G. Mack; H. Oberhammer. *Chem. Phys. Lett.* **1989**, 157 (5), 436.
18. F.P. Cossio; B. Lecea; X. Lopez; G. Roa; A. Arrieta; J.M. Uglade. *J. Chem. Soc., Chem. Commun.* **1993**, 1450.
19. D. Fang; Z.F. Xu; X.Y. Fu. *J. Mol. Struct. (Theochem)*. **1995**, 333, 159.
20. C.I. Williams; M.A. Whitehead. *J. Mol. Struct. (Theochem)*. **1999**, 49, 93.
21. Adam J. Dickie; Florence Quist; M. A. Whitehead; Ashok K. Kakkar. *Langmuir*. **2004**, 20, 4315.
22. Mitsu Kotera; Jean-Marie Lehn; Jean-Pierre Vigneron. *Tetrahedron*. **1995**, 51, 1953.
23. C.N. Likos; S. Rosenfeldt; N. Dingenouts; M. Ballau; P. Lindner; N. Werner; F. Vogtle. *J. Chem. Phys.* **2002**, 117 (4), 1869.
24. Malardier-Jugroot C. *Ph.D.Thesis, Department of Chemistry, McGill, Montreal, Canada*. 2004.
25. C. Malardier-Jugroot; T. G. M. van de Ven; T. Cosgrove; R. M. Richardson; M. A. Whitehead. *Langmuir* . **2005**, 21, 10179.
26. Victor Guallar; Richard A. Friesner. *J. Am. Chem. Soc.* **2004**, 126, 8501.