

## Index

### General index

Abbreviations and Glossary	XV
Resumen (spanish summary)	XVIII
Résumé (french summary)	XX
Chapter 1- Introduction	1
References	5
Chapter 2- Background	6
2.1- Biological background	6
2.1.1- Protein tyrosine phosphorylation	6
2.1.2- Protein tyrosine phosphatase 1B and type 2 diabetes mellitus	7
2.1.3- Structure of the enzyme	9

## Index

---

2.1.4- Mechanism of catalysis	12
2.1.5- Ions in biological macromolecules	14
<b>2.2- Experimental background</b>	<b>15</b>
2.2.1- Protein crystals	16
2.2.1.1- Principles of protein crystallization	17
2.2.1.2- Crystallization of protein-ligand complexes	21
2.2.2- The solution to the phase problem: Molecular Replacement	22
2.2.3- The interpretation of the electron density	25
2.2.4- Refinement	26
2.3- Theoretical background	31
2.3.1- The Born-Oppenheimer and the fix nuclei approximations	34
2.3.2- The Hartree-Fock method	36
2.3.2.1- The variational principle	36
2.3.2.2- Slater determinants	37
2.3.2.3- The energy of a Slater determinant	38
2.3.2.4- The Self-Consistent Field method	41
2.3.3- The basis set approximation	41
2.3.3.1- The Roothan-Hall equations	42
2.3.3.2- Orbital types	44
2.3.3.3- Improving the basis sets	45
2.3.3.4- Commonly used basis sets	47

---

## Index

---

2.3.3.5- Basis Set Superposition Error (BSSE)	48
2.3.4- Møller-Plesset perturbation theory	49
2.3.5- Density Functional Theory (DFT)	54
2.3.5.1- The Hohenberg-Kohn theorems	55
2.3.5.2- The Kohn-Sham method	57
2.3.5.3- The exchange-correlation potentials	58
2.3.5.4- The exchange-correlation functionals	61
2.3.5.5- The Local Density Approximation (LDA) and the Local Spin Density Approximation (LSDA)	62
2.3.5.6- Gradient corrected methods	64
2.3.5.7- Higher order gradient or <i>meta</i> -GGA methods	65
2.3.5.8- Hybrid or <i>hyper</i> -GGA methods	66
2.3.5.9- DFT pros and cons	66
2.3.6- Molecular Mechanics	67
2.3.6.1- The force field energy	69
2.3.6.2- Existing force fields	75
2.3.7- Combined Quantum Mechanical/Molecular Mechanical approaches:	
the ONIOM method	76
2.3.8- Potential Energy Surfaces (PES)	81
2.3.9- Geometry optimization techniques	83
2.3.9.1- Steepest Descent	83

---

## Index

---

2.3.9.2- Conjugate Gradient methods	84
2.3.9.3- The Berny algorithm	85
2.3.10- Molecular Dynamics simulations	86
2.3.10.1- Solving the classical equations	86
2.3.10.2- Temperature in Molecular Dynamics	87
2.3.10.3- Molecular Dynamics Methods	88
2.3.10.3a- The velocity Verlet algorithm	89
2.3.10.3b- The leap-frog algorithm	89
2.4- Current state of the field	91
References	92
 <b>Chapter 3-Objectives and Strategies</b>	 98
3.1- General objective	99
3.2- Specific objectives	99
3.2.1- Crystallographic objectives	99
3.2.2- Molecular modeling objectives	100
 <b>Chapter 4-Results and Discussion</b>	 101
4.1- Experimental results	101
4.1.1- Crystallization of PTP1B-ion complexes and measurement of X-ray diffraction data	101
4.1.2- Crystal structure determination	103

Study of the movement of the WPD helical loop of human protein tyrosine phosphatase PTP1B and the factors that influence it.

## Index

---

4.1.3- Refinement of the flexible WPD loop occupation in each crystal	104
4.1.3.1- Analysis of case 1	106
4.1.3.2- Analysis of case 2	106
4.1.3.3- Analysis of case 3	107
4.1.3.4- Analysis of case 4	107
4.1.3.5- Analysis of case 5	107
4.1.3.6- Analysis of case 6	107
4.1.3.7- Analysis of case 7	108
4.1.3.8- Analysis of case 8	108
4.1.3.9- Analysis of case 9	108
4.1.3.10- Analysis of case 10	109
4.1.3.11- Analysis of case 11	109
4.1.3.12- Correlation of B-factors of the flexible loop and the ions	110
4.1.3.13- Bromide complexes	110
4.1.3.14- Iodine complexes	112
4.1.3.15- Effects of concentration	114
4.1.3.16- Occupation refinement	115
4.1.4- Discussion on crystallographic results	117
4.2- Theoretical results	118
4.2.1- Parameter determination, force fields and Molecular Mechanics	119
4.2.1.1- Determination of chloride, bromide and iodide ions	

---

## Index

---

parameters for use in molecular simulations of TIP3P	
compatible solvated systems with CHARMM27 force field	120
4.2.1.2- Validation of the optimized parameters	126
4.2.1.2a- Systems with a single water molecule	127
4.2.1.2b- Systems with multiple water molecules	128
4.2.1.3- Further validation of the new parameters:MD simulation	131
4.2.2- Combined Quantum Mechanical/Molecular Mechanical calculations	136
4.2.2.1- Determination of the QM region	137
4.2.2.1.1- Working with the CHARMM27 force field	137
4.2.2.1.1.1- 4 Å radius	139
4.2.2.1.1.2- 6 Å radius	143
4.2.2.1.2- Changing the force field: the AMBER FF	147
4.2.2.1.2.1- 4 Å radius	149
4.2.2.1.2.2- 6 Å radius	153
4.2.2.1.2.3- 8 Å radius	156
4.2.2.1.2.4- Interaction energies	161
4.2.2.1.3- Taking the charge into account: models with	
total charge -2	163
4.2.2.1.3.1- 4 Å radius, total charge -2	164
4.2.2.1.3.2- 6 Å radius, total charge -2	167
4.2.2.1.3.3- Interaction energies	170

---

## Index

4.2.2.1.4- Final model for the QM region	172
4.2.2.2- Ongoing hybrid ONIOM calculations	175
4.2.3- Molecular Dynamics simulations for the protein-halidecomplexes - Production run	176
References	186
 <b>Chapter 5-Conclusions and Perspectives</b>	189
5.1- Conclusions	189
5.2- Perspectives	191
 <b>Chapter 6-Experimental Details</b>	192
6.1- Expression and purification of the protein	192
6.2- Co-crystallization	192
6.3- X-ray diffraction data collection	193
6.4- X-ray data processing	193
6.5- Determination of an initial model and subsequent refinement	193
References	194
 <b>Appendix</b>	195