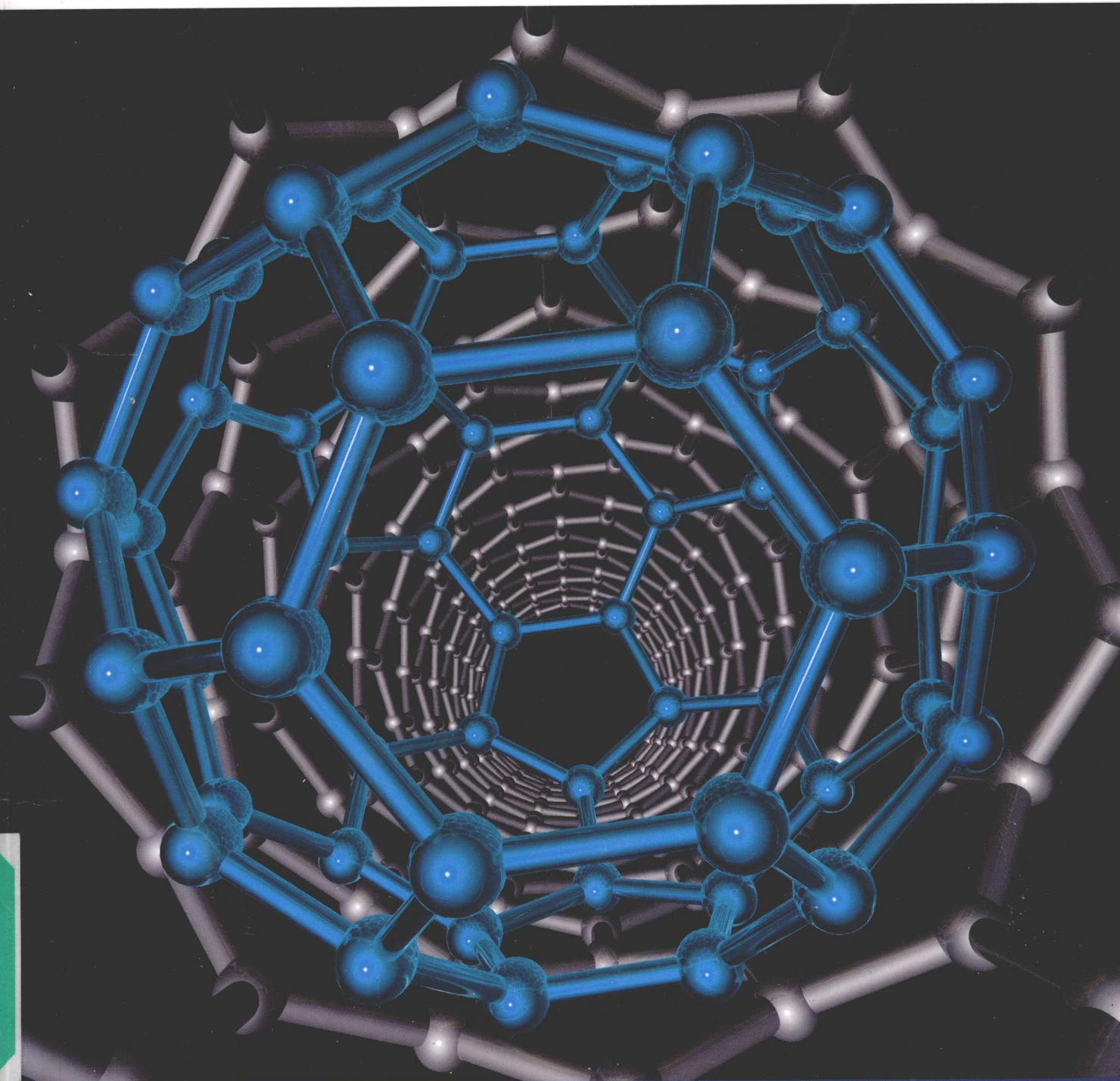


Molecular Modelling

Computational Chemistry Demystified

Peter Bladon, John Gorton and Robert B Hammond



RSC Publishing

Molecular Modelling ***Computational Chemistry Demystified***

Peter Bladon

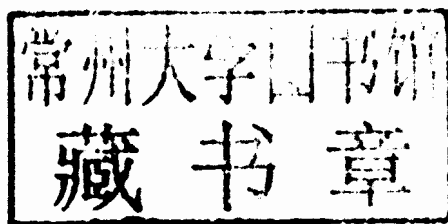
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Molecular Modelling
Computational Chemistry Demystified

Preface

'Molecular Modelling - Computational Chemistry Demystified'

While there are many books that deal with *Molecular Modelling* or *Computational Chemistry*, few of them meet the needs of someone who is just starting out, and wishes to set up their own system. Problems arise right at the beginning with the bewildering array of acronyms to do with both chemistry and computing.

A student studying chemistry at a well endowed university, and needing to fulfil requirements in computational chemistry, would find the necessary equipment and programs already set up. All (s)he has to do is to follow the prescribed parts of the course and pass the tests. The same student, having graduated, and now proceeding to a higher degree would be able to use the same or similar facilities when needed. But there are those who, for various reasons, choose to work alone, or are obliged to do so. Catering for these is what this book is all about. Molecular modelling can provide an entry into chemistry, that in former years was available by experimentation, now unfortunately, but understandably, frowned on by authority. For someone in this category who is impatient and wants to get started right away, we offer a first chapter that allows just this.

Demystification is one of our goals. But it does not require that Molecular Modelling be trivialized. So we have tried to provide a book that would be valuable to people at many stages of learning about Chemistry. Is this possible? We believe it is, since even the business of writing the book and the software has provided us with insights into aspects of chemistry that were new to us.

“First catch your hare...” This quotation is wrongly attributed to Mrs Beeton in her recipe for jugged hare. In the present context we can paraphrase it “First buy/acquire/beg/borrow... your computer”. We show in the second chapter how to use such a computer, that you maybe already have, and that is running a version of the Windows® Operating system, to run Molecular Modelling and Computational Chemistry programs. Not only that - the Interprobe programs (INTERCHEM, PRESTO, *etc.*) are included with this book, and sections are devoted to setting them up and using them!

The rest of the book is devoted to explaining the mystique and jargon that surrounds computational chemistry. There is a chapter devoted to modelling the crystalline state, a feature not catered for elsewhere. Other chapters deal with modelling biopolymers such as proteins that impinge on medicinal chemistry. There is an underlying heuristic aim throughout the book; problems for the reader to solve are provided.

The authors are conscious of the difficulties of explaining in detail how to perform tasks on a personal computer. The expectation of users today is that all the tasks will be started as the results of user - computer interaction. This means that *every* request from the computer and *every* response from the user shall be specified in detail. Such requirements can result in text that is difficult to read; we have done our best in this regard, and hope that the parts of the book that are not so circumscribed will make easier reading.

We have framed the instructional examples and the questions in the context of organic chemistry of recent decades, with an emphasis on structures. Modelling chemical *reactions* presents significant challenges and, it may be argued, can only be done in terms of starting, intermediate, and end *structures* and the stereochemistry and thermodynamics that relates them. To aid this we provide a chapter dealing with stereochemistry, and conformational analysis.

The book aims to be a practical guide to the use of computers in aiding structural chemistry, and when we have digressed into the chemistry itself, we have done so to explain the relevance of the modelling techniques or computations. The book is neither to be regarded as a textbook on crystallography nor a textbook on medicinal chemistry. However with these two topics, and the topic of protein structures, we hope to provide an introduction to fields of chemical science that are both challenging and worthy of serious study.

The reasons for issuing software with the book

In coupling the publication of this book with an offering of Open-Source software, we are making a bold statement. This comes from a belief that openness is the key to scientific progress. It is possible that a scientist in 2061, referring to one of the many papers concerning the docking of small molecule structures into protein cavities (a subject we touch upon in Chapter 9), would not be able to make any sense of the paper itself, and would have difficulty in reproducing the experiments. This would be in part due the complexity of the science, but a contributing factor would be the fact that the software being used is proprietary and secret. The case for software being open-source now largely rests on contemporary issues (who should own the software?), but we believe that this other aspect of future traceability is a more important reason for the algorithms and source code based on them to be completely disclosed. The present situation in computational chemistry is in stark contrast to that existing in conventional experimental work, where results obtained today can be (and regularly are) compared with results obtained in the last two centuries, if necessary by repeating the original experiments.

The ethical aspects of molecular modelling have been raised before. In a paper entitled *Guidelines for Publications in Molecular Modeling Related to Medicinal Chemistry*,¹ the members of Working Party on Computer Assisted Molecular Modeling, commissioned by IUPAC made several significant recommendations. In relation to proprietary algorithms they suggested that "... the commercializing companies have the obligation to submit for publication articles giving at least general descriptions of algorithms and databases used, with sample calculation results to aid calibration and evaluation."

The reasons why the Interprobe software came about

The straightforward answer is economic necessity. Twenty five years ago commercially available modelling packages were expensive and of limited scope. Subsequently mergers, takeovers, company failures, and 'rationalisations' have reduced the number of choices for purchasing software without reducing costs. What has resulted from twenty years of development is a set of programs that fills most of the needs of entry- level molecular modelling. We would be foolish to claim that it is the best, but we hope that what is provided may stimulate purchasers/users to

experiment. We would also welcome constructive comments aimed at its improvement.

The software owes its origin to earlier versions that were designed to work on Digital Equipment Vax computers and on SGI Irix systems. These versions were developed in the Department of Pure and Applied Chemistry at The University of Strathclyde where one of the authors was employed. The version of the software that is supplied with this book, and that works on systems running Microsoft Windows operating systems, derives from these programs. It is a reworking of these earlier systems and has been developed independently and without any outside financial aid.

We understand that in some circumstances complete openness of software has disadvantages; the chief being that ‘modified’ versions become available! In this connection, the Interprobe software is ‘protected’ by the fact that the compilers used are not open software; if you wish to modify the code for and distribute it, this is possible only if you acquire the Salford software currently licensed by the firm Silverfrost. This firm does provide, at no cost, a demonstration version of the compilers *etc.* that does allow you to make modifications to our programs for your own use, *but not redistribute them.* Furthermore, this enabling software only allows the production of versions for Microsoft Windows operating systems. We do not hide the fact that we would have preferred, in an ideal world, to have a system working under Linux. Maybe that will come.

Chemistry needs computing needs computers need chemistry!

That chemistry depends on computation and therefore on computers is not much in doubt. But let it not be forgotten that the reverse is also true. Two facts stand out:

(1) All modern computers depend on devices that require highly purified elemental silicon. The key to this is the chemistry of silanes, an area of chemistry opened up by the work of Alfred Stock in the first third of the 20th Century, and at the time considered of only academic interest.

(2) Any laptop computer that you own will rely on a *liquid crystal* screen for a display, and most desktop machines will also have screens of this type. In 1924 Daniel Vorländer wrote on page 89 of his monograph on liquid crystals:²

“Man hat mir wohl die Frage gestellt, ob sich die kristallin-flüssigen Substanzen technisch verwerten lassen? Ich sehe keine Möglichkeit dazu”

[“I have indeed asked myself whether liquid crystal substances are capable of technical application? I see no possibility of that.”]

He expressed his honest opinion, but how wrong he was!

These are just two examples, but what better testimony and reasons could we want, for the continued support of blue-sky research?

¹ P. Grund, D. C. Berry, J. M. Blaney, and N. C. Cohen, *J. Med. Chem.*, 1988. **31**, 2230.

² D. Vorländer, *Chemische Kristallographie der Flüssigkeiten.*, Akademische Verlagsgesellschaft, Leipzig, 1924.

Acknowledgements

J.G. acknowledges the help from many students and colleagues who have given great help and simplified his convoluted explanations.

P.B. acknowledges the help of many former colleagues at the University of Strathclyde; in particular, Dr. Mark Dufton for stimulating interest in protein chemistry, Dr. Robin Breckenridge for collaboration in the early days of Interprobe and for subsequently keeping him on track on drug design politics and economics, Dr. David Pugh for putting him right when dealing with crystal structures, and Professor Douglas McGregor for guidance on the humane treatment of computers. The molecular mechanics that is used in the Interprobe software is based on code that was generously supplied by Dr. Armin Widmer of Novartis, Basel and to whom a great debt is due.

R.B.H. acknowledges the help and support of colleagues at the University of Leeds in particular, Dr. Christopher Hammond for permission to reproduce a Table from his book. He also wishes to thank his parents Dorothy and Bryan for their steadfast support at all times.

We are also grateful to the Royal Society for permission to quote from Dirac's paper that is referred to in Chapter 1.

Formal permission has not been obtained for our quotation (in the Preface) from Vorländer's monograph; investigation has failed to reveal who is the current owner of the copyright.

We are grateful to the Cambridge Crystallographic Data Centre for permission to access, reproduce, and comment on selected files from that repository.

Typographical conventions used in this book

- (1) The fount that we use **generally** in the text is

Times New Roman 12 point

- (2) The fount that we use in the **endnotes** is

Times New Roman 11 point

- (3) When we wish to indicate that text is printed by a computer we show it in

Courier New 12 point

This fount is also used when we wish to indicate that you should type something in response to a computer.

- (4) When we want to show a complete line of text produced by a computer, without wrapping, we will use a fount as small as Courier New 8 point.

- (5) We use the convention of enclosing the **type** of response needed by the computer by enclosing the name describing the entity in chevron brackets thus:

<file name>

In this case your response should be an actual file name (**without** the brackets!).

- (6) In displaying SMILES strings in the text, we would have preferred to have used an equal spaced fount like Courier New. Unfortunately this had the effect of seeming to introduce spaces before and after brackets thus:

```
c2cc(-c1cccc1)ccc2CCC
1234567890123456789012
```

So we settled for Arial

```
c2cc(-c1cccc1)ccc2CCC
1234567890123456789012
```

This gets rid of the spaces but characters do not have equal widths.

- (7) In the instructions for using the Interprobe programs INTERCHEM and PRESTO that have graphical user interfaces (GUIs), we have adopted a convention of referring to the Menu Buttons by their Row and Column coordinates, usually following the wording on the button. The Menu Name may also be included, thus:

Dual Mode Menu, Invert Structure (R1/C6)

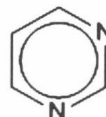
(8) In displaying line drawings of 6-membered aromatic rings the presence of the six pi-electrons is shown by a circle inscribed within the hexagon. We prefer this notation to that showing alternating double and single bonds (the Kekulé notation). We do not extend this notation to the 5-membered rings of heterocyclic compounds such as pyrrole, furan and thiophen, preferring in these cases to show the double bonds.



Benzene

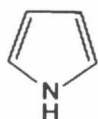


Pyridine

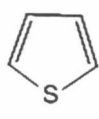


Pyrimidine

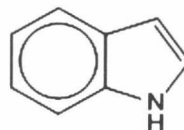
BUT



Pyrrole



Thiophene



Indole



Cyclopentadienyl

Contents

Chapter 1	Introduction	1
1.1	The Beginnings - Some History	1
1.2	About the Book	1
1.2.2	Some Caveats	3
1.3	Getting Started	3
1.4	Basics	6
1.5	Atoms and Bonds	6
1.6	Isomerism, Stereoisomerism, Configuration, and Conformation	6
1.7	Low Dimensional Structural Information	8
1.8	SMILES in INTERCHEM	8
1.9	Where now?	9
	References and Endnotes: Chapter 1	10
Chapter 2	Computers for Molecular Modelling	13
2.1	Caveats	13
2.1.1	Is Special Computer Equipment Needed?	13
2.1.3	Are there choices to be made?	13
2.2	Choice of Operating System	13
2.3	Choice of Hardware - Desktop or Laptop	14
2.3.1	Choices for a Laptop Machine	14
2.3.2	Choices for a Desktop Machine	15
2.3.3	The Other Alternatives	18
2.3.4	The choice of a display	18
2.3.5	The use of a projector for display	20
2.4	RAID Computer Systems	20
2.5	The Linux Operating Systems	20
2.6	Having the Best of Both Worlds - Windows and Linux	20
2.6.1	Two or More Machines	20
2.6.2	Dual Boot Machines	21
2.6.3	The Windows Subsystem for UNIX-based-Applications	21
2.6.4	Using Cygwin	21
2.6.5	Virtual Machines	23
2.6.6	Clusters of Computers	24
2.7	Networking	24
2.8	Security	24
2.9	Compatibility of 32-Bit and 64-Bit operating systems	24
2.10	Further Reading	25
	References and Endnotes: Chapter 2	26
Chapter 3	Software for Molecular Modelling and Computational Chemistry	31
3.1	Chemical Structure and Molecular Modelling	31
3.1.1	Structures obtained from experimental methods	31
3.1.2	The Born-Oppenheimer principle	31
3.2	Molecular Mechanics	32
3.2.1	Molecular mechanics - the basics	32

3.2.2	Force field parameters	33
3.2.3	Molecular mechanics - how it works	34
3.2.4	Molecular mechanics - limitations	34
3.2.5	The choice of force fields	35
3.2.6	The extended use of molecular mechanics	36
3.3	Method based on quantum mechanics	36
3.3.1	Semi-empirical molecular orbital programs	37
3.3.2	<i>Ab initio</i> molecular orbital methods	38
3.3.3	Methods based on density functional theory	38
3.3.4	Basis sets	39
3.3.5	Internal coordinates and Z matrices	39
3.3.6	Atomic units	42
3.3.7	Scaling in computational programs	42
3.4	Graphical display software	42
3.4.1	The requirements of molecular modelling	43
3.4.2	How OpenGL satisfies these requirements	43
3.7	Molecular modelling software suppliers	45
	References and Endnotes: Chapter 3	46
Chapter 4	Using INTERCHEM for Molecular Modelling	51
4.1	Some words of advice	51
4.2	Building structures	51
4.2.1	Using INTERCHEM Sketch - basics	53
4.2.2	INTERCHEM Sketch Modifying your drawing	55
4.2.3	Using INTERCHEM Sketch - aliphatic structures	55
4.2.4	Generating structures using SMILES strings	57
4.2.5	Accessing the SMILES facility	57
4.2.6	Building structures from fragments	62
4.2.7	Using the INTERCHEM merge tool for building	65
4.3	The reliability of structures obtained by building	68
4.3.1	Refining a structure using quantum mechanics (quinine)	70
4.3.2	Getting the energies of structures using quantum mechanics	72
4.4	Getting structures from the published literature	73
4.4.1	Getting structures from X-ray crystallographic data	74
4.4.2	Information from X-ray crystallographic data files	74
4.5	Analyzing Structures	79
4.5.1	Bond lengths	79
4.5.2	Inter atomic distances	79
4.5.3	Bond angles	79
4.5.4	Torsion angles	80
4.5.5	Pseudo torsion angles	80
4.5.6	Inter planar angles	80
4.5.7	Molecular mechanic calculations - geometric measurement	81
4.5.8	Molecular volume	81
4.5.9	Molecular formula and molecular weight	81
4.5.10	Hydrophobicity	83

4.6	Stereochemistry	83
4.7	Geometric isomerism (cis/trans or E/Z isomerism)	84
4.8	The use of random numbers in INTERCHEM	84
4.9	Problems for you to solve, and questions for you to answer	84
	References and Endnotes: Chapter 4	86
Chapter 5	Molecular Modelling of Proteins and Nucleic acids	89
5.1	Introduction	89
5.2	The nature of proteins	89
5.2.1	The structure of proteins	89
5.2.2	The structures of nucleic acids	100
5.2.3	Further reading	100
5.3	Obtaining Structures for Proteins and Nucleic Acids	104
5.3.1	Accessing the Protein Data Bank	104
5.3.2	The options provided by the program PROTEINS	106
5.3.3	How the extra data is stored in INTERCHEM 'D' Files	106
5.3.4	Displaying proteins and nucleic acids structures	107
5.3.5	Editing Protein and Nucleic Acid Structures	108
5.3.6	Analyzing Protein Structures	109
5.4	Protein Sequences	116
5.4.1	Some Definitions	117
5.4.2	Sequence Matching	117
5.4.3	Background of Aligning Protein Sequences	118
5.5	The program PRESTO	118
5.5.1	Introductory exercise	118
5.5.2	Aligning sequence Sets Globally and Locally	122
5.5.3	Questions arising from the alignment experiments	123
5.5.4	Making inferences from alignments	123
5.5.5	Storing images from the screen in PRESTO	124
5.6	Racemic protein crystals as sources of protein structures	124
5.7	Problems for you to solve and questions for you to answer	125
5.7.1	General instructions applicable to most of these problems	125
	References and Endnotes: Chapter 5	128
Chapter 6	Essentials of Stereochemistry and Conformational Analysis	131
6.1	Chirality	131
6.2	Conformation and conformational analysis	135
6.3	Isomerism involving double bonds and rings	138
6.3.1	Chirality in biphenyl derivatives and allenes	139
	References and Endnotes: Chapter 6	140
Chapter 7	Molecular Modelling and the Solid State of Materials	141
7.1	Introduction	141
7.2	Classification of solids	142
7.3	Crystallography and the specification of crystalline structures	143
7.3.1	The lattice concept	143
7.3.2	The crystal lattice in two dimensions	144
7.3.3	The crystal lattice in three dimensions	151
7.3.4	Examining crystal structures with INTERCHEM	156

7.3.5	Chirality and crystallography	162
7.4	Origin of cohesive forces in solids	164
7.5	Thermodynamics of crystalline solids and molecular modelling	168
7.6	Lattice energy calculations	169
7.6.1	Worked example---calculation for sodium sulfate	170
7.6.2	Lattice energy calculations for organic molecular materials	175
7.7	The shape of crystals	177
7.7.1	BFDH approach for crystal habit prediction	178
7.7.2	Potential deficiencies in the BFDH approach	180
7.7.3	Attachment energy approach for habit prediction	181
7.8	Envoi	182
References and Endnotes: Chapter 7		184
Chapter 8	The Source of Archived 3D Chemical Structure Information	189
8.1	Introduction	189
8.2	Structures of small organic molecules from X-ray crystallography	189
8.3	Structures of inorganic compounds and metals	190
8.4	The Protein Databank	190
8.5	ZINC	190
8.6	Interprobe Chemical Services 3D Database	191
8.7	File formats	191
8.7.1	XR Format	192
8.7.2	TRIPOS MOL2 Format	192
8.7.3	PDB format	195
8.7.4	MDL format	198
8.7.5	Crystallographic Information Files (CIF format)	202
8.7.6	INTERCHEM D format	202
8.7.7	Multi-structure files	204
8.8	General comments about files of 3D coordinates	204
8.8.1	Right handed coordinate systems	204
8.8.2	The rules of engagement	205
References and Endnotes: Chapter 8		206
Chapter 9	Molecular Modelling and Medicinal Chemistry	209
9.1	The need for new (legal) drugs	209
9.1.1	Recent history	209
9.1.2	The economics of drug development	210
9.1.3	The plight of pharma	210
9.2	What makes a compound a drug	210
9.2.1	The way drugs work - a basic classification	211
9.2.2	How modern drugs are designed	211
9.2.3	Some definitions	211
9.2.4	Natural products as leads	213
9.2.5	How molecular modelling helps drug design	213
9.2.6	The drug design pathway	213
9.2.7	High throughput screening	213
9.3	Molecular modelling in drug design	214
9.3.1	Virtual high throughput screening	214
9.3.2	Docking	215

9.3.3	Additional filtering processes	218
9.3.4	Isosteres - Variations on a theme	219
	References and Endnotes: Chapter 9	222
Chapter 10	Using Interprobe Software for Drug Discovery	227
10.1	Overview	227
10.2	Setting up the database using Cygwin	227
10.2.1	The importance of the full stop (and some other hints)	228
10.2.2	How the databases are organised	229
10.2.3	Setting up the databases for use by QUICKSCAN	231
10.2.4	Using QUICKSCAN	232
10.2.5	Viewing the structures extracted using INTERCHEM	236
10.3	Docking experiments using INTERCHEM	236
10.3.1	Getting the necessary files	236
10.3.2	Docking of the ligand into the protein	240
10.3.3	Docking of analogues of tamoxifen	242
10.3.4	Generating series of ligands for docking experiments	242
10.3.5	Other targets for tackling malaria	245
10.4	Drugs from natural products	248
10.5	Problems for you to solve	251
10.6	Envoi	251
	References and Endnotes: Chapter 10	252
Appendices		253
Appendix A1	Mathematical Background	254
Appendix A2	Data Tables	261
A2.1	Table of Standard Bond lengths	261
A2.2	Crystallographic Space Groups	262
Appendix A3	Numbering of Steroid Structures	265
Appendix A4	Essential Information for mounting Interprobe software	267
A4.1	Software that is included on the compact disc	267
A4.2	Copying the contents of the CD onto your computer	267
A4.3	Setting up the program INTERCHEM	267
A4.3.1	Testing the program INTERCHEM	267
A4.3.2	Problems due to mismatched dynamic linked libraries	268
A4.3.3	Problems due to the file STEER.DAT	269
A4.3.4	Errors due to the settings on your display screen	270
A4.3.5	Errors in other display parameters	270
A4.4	Setting up the program PRESTO	271
A4.4.1	Testing the program PRESTO	271
A4.4.2	Problems in running PRESTO	271
A4.4.3	Effects of screen resolution on PRESTO	271
A4.4.4	Effects of other screen settings when using PRESTO	271
A4.5	Setting up the other Interprobe programs	273
A4.6	Setting up other programs	274
A4.6.1	Setting up MOPAC	274

A4.6.2 Miscellaneous programs and scripts	275
A4.7 Other problems - errors in the programs	275
A4.8 Removing and updating Interprobe software on your computer	276
References and Endnotes: Appendix A4	276
Appendix A5 File Compression and Transfer of Files between Computers	277
A5.1 File compression	277
A5.2 Transfer of files between computers and operating systems	278
Answers to 'Problems for you to solve and questions for you to answer'	279
Chapter 4	279
Chapter 5	280
Chapter 10	280
Subject Index	287

Chapter 1

Introduction

1.1 The beginnings – Some history

In 1929, in a paper entitled “Quantum Mechanics of Many-Electron Systems”, the physicist P. A. M. Dirac made the following provocative statement:¹

“The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too difficult to be soluble. It therefore becomes desirable that approximate practical methods of applying quantum mechanics should be developed, which can lead to an explanation of the main features of complex atomic systems without too much computation.”

Presumably, the physicists who read this paper were mollified to some extent because some of their number would still be employed, but it seems that the paper was (fortunately) ignored by chemists, who carried on as usual. Indeed, in the eighty two years that have followed the appearance of Dirac’s paper, it is likely that more new chemical compounds have been recorded than in all the previous years. What also happened was the “approximate practical methods”, envisaged by Dirac, appeared, because of something that he only hinted at: “computation”. Dirac shared the Nobel Prize for Physics in 1933 with Erwin Schrödinger.

While the majority of chemists were doing their own things (“Stamp Collecting” according to Ernest Rutherford – another physicist, who ironically got a Nobel Prize for Chemistry!) some physical chemists and chemical physicists did take Dirac’s words to heart, and so ‘Theoretical Chemistry’ and then (when computers were invented) ‘Computational Chemistry’ came about.

1.2 About the book

This book is about “Molecular Modelling”. We have given it a subtitle “Computational Chemistry Demystified” because we believe that *modelling* provides an easy entry point into computational chemistry, a branch of chemistry that has hitherto been misunderstood and undervalued, and thence into the rest of chemistry. While chemists have used many sorts of models for a long time, we concentrate our attention on *computer based modelling* because now this is the method of choice, and the necessary equipment is, if not already available, easily affordable.

We follow the present introductory chapter with one that deals with the choice of computer equipment. We do this because we believe that success in modelling and computation can be critically dependent on making the right choice. However, if you have already purchased your computer for other purposes, do not despair, what we have written may still help you in improving its performance, and to adapt it for molecular modelling.