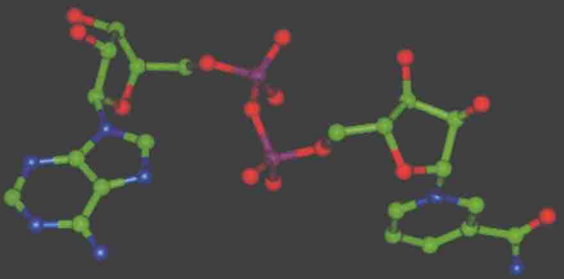

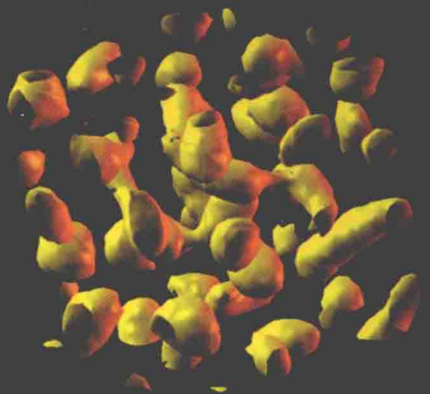

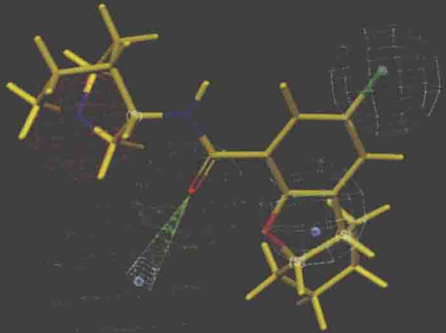

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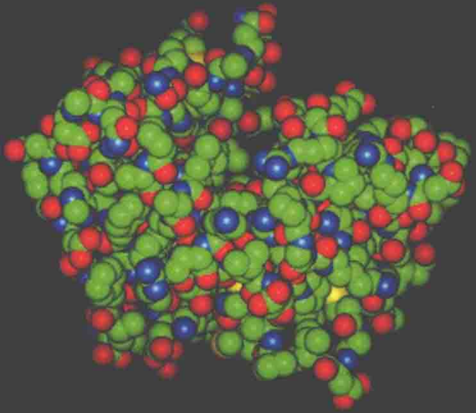

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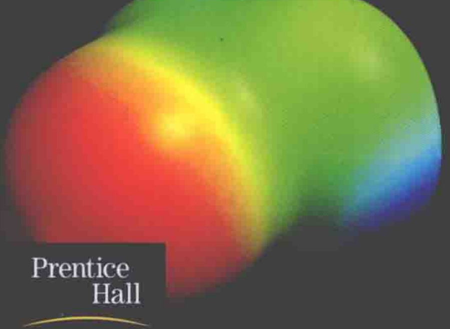

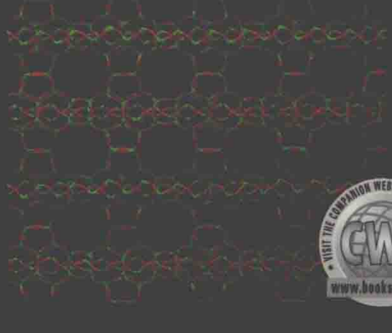

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PRINCIPLES AND APPLICATIONS

Second edition

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Preface to the Second Edition

The impetus for this second edition is a desire to include some of the new techniques that have emerged in recent years and also extend the scope of the book to cover certain areas that were under-represented (even neglected) in the first edition. In this second volume there are three topics that fall into the first category (density functional theory, bioinformatics/protein structure analysis and chemoinformatics) and one main area in the second category (modelling of the solid state). In addition, of course, a new edition provides an opportunity to take a critical view of the text and to re-organise and update the material. Thus whilst much remains from the first edition, and this second book follows much the same path through the subject, readers familiar with the first edition will find some changes which I hope they will agree are for the better.

As with the first edition we initially consider quantum mechanics, but this is now split into two chapters. Thus Chapter 2 provides an introduction to the *ab initio* and semi-empirical approaches together with some examples of the uses of quantum mechanics. Chapter 3 covers more advanced aspects of the *ab initio* approach, density functional theory and the particular problems of the solid state. Molecular mechanics is the subject of Chapter 4 and then in Chapter 5 we consider energy minimisation and other 'static' techniques. Chapters 6, 7 and 8 deal with the two main simulation methods (molecular dynamics and Monte Carlo). Chapter 9 is devoted to the conformational analysis of 'small' molecules but also includes some topics (e.g. cluster analysis, principal components analysis) that are widely used in informatics. In Chapter 10 the problems of protein structure prediction and protein folding are considered; this chapter also contains an introduction to some of the more widely used methods in bioinformatics. In Chapter 11 we draw upon material from the previous chapters in a discussion of free energy calculations, continuum solvent models, and methods for simulating chemical reactions and defects in solids. Finally, Chapter 12 is concerned with modelling and chemoinformatics techniques for discovering and designing new molecules, including database searching, docking, *de novo* design, quantitative structure–activity relationships and combinatorial library design.

As in the first edition, the inexorable pace of change means that what is currently considered 'cutting edge' will soon become routine. The examples are thus chosen primarily because they illuminate the underlying theory rather than because they are the first application of a particular technique or are the most recent available. In a similar vein, it is impossible in a volume such as this to even attempt to cover everything and so there are undoubtedly areas which are under-represented. This is not intended to be a definitive historical account or a review of the current state-of-the-art. Thus, whilst I have tried to include many literature references it is possible that the invention of some technique may appear to be incorrectly attributed or a 'classic' application may be missing. A general guiding principle has been to focus on those techniques that are in widespread use rather than those which are the province of one particular research group. Despite these caveats I hope that the coverage is sufficient to provide a solid introduction to the main areas and also that those readers who are 'experts' will find something new to interest them.

A Companion Web Site accompanies *Molecular Modelling: Principles and Applications, Second Edition* by Andrew Leach

Visit the ***Molecular Modelling*** Companion Web Site at *www.booksites.net/leach*
The website contains general information about the book, up-to-date hyperlinks to related chemistry sources on the web, reference copies of appendices of relevant acronyms, and twenty-six full screen, full-colour graphical representations of molecular structures.

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Preface to the First Edition

Molecular modelling used to be restricted to a small number of scientists who had access to the necessary computer hardware and software. Its practitioners wrote their own programs, managed their own computer systems and mended them when they broke down. Today's computer workstations are much more powerful than the mainframe computers of even a few years ago and can be purchased relatively cheaply. It is no longer necessary for the modeller to write computer programs as software can be obtained from commercial software companies and academic laboratories. Molecular modelling can now be performed in any laboratory or classroom.

This book is intended to provide an introduction to some of the techniques used in molecular modelling and computational chemistry, and to illustrate how these techniques can be used to study physical, chemical and biological phenomena. A major objective is to provide, in one volume, some of the theoretical background to the vast array of methods available to the molecular modeller. I also hope that the book will help the reader to select the most appropriate method for a problem and so make the most of his or her modelling hardware and software. Many modelling programs are extremely simple to use and are often supplied with seductive graphical interfaces, which obviously helps to make modelling techniques more accessible, but it can also be very easy to select a wholly inappropriate technique or method.

Most molecular modelling studies involve three stages. In the first stage a model is selected to describe the intra- and inter-molecular interactions in the system. The two most common models that are used in molecular modelling are quantum mechanics and molecular mechanics. These models enable the energy of any arrangement of the atoms and molecules in the system to be calculated, and allow the modeller to determine how the energy of the system varies as the positions of the atoms and molecules change. The second stage of a molecular modelling study is the calculation itself, such as an energy minimisation, a molecular dynamics or Monte Carlo simulation, or a conformational search. Finally, the calculation must be analysed, not only to calculate properties but also to check that it has been performed properly.

The book is organised so that some of the techniques discussed in later chapters refer to material discussed earlier, though I have tried to make each chapter as independent of the others as possible. Some readers may therefore be pleased to know that it is not essential to completely digest the chapters on quantum mechanics and molecular mechanics in order to read about methods for searching conformational space! Readers with experience in one or more areas may, of course, wish to be more selective.

I have tried to provide as much of the underlying theory as seems appropriate to enable the reader to understand the fundamentals of each method. In doing so I have assumed some background knowledge of quantum mechanics, statistical mechanics, conformational analysis and mathematics. A reader with an undergraduate degree in chemistry should have covered this material, which should also be familiar to many undergraduates in the final year of their degree course. Full discussion can be found in the suggestions for further reading at the end of each chapter. I have also attempted to provide a reasonable selection of original references, though in a book of this scope it is obviously impossible to provide a comprehensive coverage of the literature. In this context, I apologise in advance if any technique is inappropriately attributed.

The range of systems that can be considered in molecular modelling is extremely broad, from isolated molecules through simple atomic and molecular liquids to polymers, biological macromolecules such as proteins and DNA and solids. Many of the techniques are illustrated with examples chosen to reflect the breadth of applications. It is inevitable that, for reasons of space, some techniques must be dealt with in a rudimentary fashion (or not at all), and that many interesting and important applications cannot be described. Molecular modelling is a rapidly developing discipline and has benefited from the dramatic improvements in computer hardware and software of recent years. Calculations that were major undertakings only a few years ago can now be performed using personal computing facilities. Thus, examples used to indicate the 'state of the art' at the time of writing will invariably be routine within a short time.

Symbols and Physical Constants

This list contains the most frequently used symbols and physical constants ordered according to approximate appearance in the text.

λ	Lagrange multiplier
r, θ, ϕ	spherical polar coordinates
$\mathbf{i}, \mathbf{j}, \mathbf{k}$	orthogonal unit vectors along x, y, z axes
ϕ, θ, ψ	Euler angles
$\langle x \rangle$ or $\bar{x}$	arithmetic mean value of x
$\mathbf{I}$	unit matrix
i	square root of -1
$\hat{\mathbf{r}}$	unit vector
α	exponent in Gaussian function (normal distribution)
σ	standard deviation
σ^2	variance
h	Planck's constant ($6.626\,18 \times 10^{-34}$ J s)
$\hbar$	$h/2\pi$ ($1.054\,59 \times 10^{-34}$ J s)
m	particle mass
Ψ	molecular wavefunction
∇^2	$\partial^2/\partial x^2 + \partial^2/\partial y^2 + \partial^2/\partial z^2$ ('del-squared')
$\mathscr{H}$	Hamiltonian
ψ	spatial orbital
α, β	spin functions ('spin up' and 'spin down')
χ	spin orbital (product of spatial orbital and a spin function)
ϕ	basis function/atomic orbital (usually labelled $\phi_\mu, \phi_\nu, \phi_\lambda, \phi_\sigma$)
$d\nu$ or $d\mathbf{r}$	indicates an integral over all spatial coordinates
$d\sigma$	indicates an integral over all spin coordinates
$d\tau$	indicates an integral over all spatial and spin coordinates
r_{ij}	distances between two particles i and j (usually electrons in quantum mechanics)
R_{AB}	distance between two nuclei A and B
δ_{ij}	Kronecker delta ($\delta_{ij} = 1$ if $i = j$; $\delta_{ij} = 0$ if $i \neq j$)
$\mathscr{K}$	exchange operator
$\mathscr{J}$	Coulomb operator
$\mathscr{H}^{\mathrm{core}}$	core Hamiltonian operator
$\mathbf{F}$	Fock matrix
$\mathbf{S}$	overlap matrix
S_{ij}	overlap integral between orbitals i and j
$\mathscr{f}$	Fock operator
$\mathbf{C}$	matrix of basis function coefficients

$\mathbf{E}$	matrix of orbital energies
$\mathbf{P}$	density matrix
ζ	Slater exponent
K	number of basis functions
N	number of electrons
M	number of nuclei
α	Coulomb integral in Hückel theory
β	resonance integral in Hückel theory
α	atomic or molecular polarisability
$\rho(\mathbf{r})$	electron density at $\mathbf{r}$
$\phi(\mathbf{r})$	electrostatic potential at $\mathbf{r}$
a, b, c	lengths used to describe unit cell
α, β, γ	angles used to describe unit cell
$\mathbf{G}$	reciprocal lattice vector
$\mathbf{T}$	translation within real-space lattice
$\mathbf{k}$	wavevector used in solid-state quantum mechanics
q_i	partial charge on atom i
Z_A	nuclear charge on atom A
μ	dipole moment
Θ	quadruple moment
l	bond length
k	force constant
θ	bond angle
τ, ω	torsion angle
$\mathbf{E}$	electric field
χ	electronegativity
ε	well depth parameter in Lennard-Jones pairwise potential function
σ	collision diameter used in Lennard-Jones function
r^*, r_m	separation corresponding to minimum in Lennard-Jones function
A	coefficient of r^{-12} in Lennard-Jones function
C	coefficient of r^{-6} in Lennard-Jones function
ε_o	dielectric constant *in vacuo*
ε_r	relative permittivity
ε	dielectric constant ($\varepsilon = \varepsilon_\mathrm{o}\varepsilon_r$)
k_B	Boltzmann's constant ($1.380\,66 \times 10^{-23}\,\mathrm{J\,K^{-1}}$)
N_A	Avogadro's number ($6.022\,05 \times 10^{23}\,\mathrm{mol^{-1}}$)
N	number of particles in system
$\mathbf{r}$	atomic or molecular position
$\mathbf{r}^N$	denotes positions of the N particles in the system
$\mathbf{p}$	linear momentum
$\mathbf{p}^N$	denotes momenta of the N particles in the system
$\mathbf{p}$	total linear momentum of system
$\mathscr{V}$	total potential energy of system (often written as a function of $\mathbf{r}^N$)
v	pairwise potential energy
$\mathbf{x}_k$	$3N$ Cartesian vector at point k

$\mathbf{g}_k$	gradient at point k (first derivative of $\mathscr{V}$ with respect to the coordinates)
$\mathscr{V}''$	Hessian matrix of second derivatives of $\mathscr{V}$ with respect to the coordinates
ν	normal mode vibrational frequency
$\mathbf{H}$	inverse Hessian matrix
Q	canonical ensemble partition function
Z	configurational integral
$\mathscr{K}$	kinetic energy
ρ	density
T	temperature
Λ	de Broglie wavelength ($= \sqrt{h^2/2\pi m k_B T}$)
t	time
P	pressure
V	volume
E	instantaneous energy
U	internal energy
A	Helmholtz free energy
G	Gibbs free energy
C_v	heat capacity at constant volume
$g(r)$	pair radial distribution function
S	switching function
L	length of box in periodic simulations
s	statistical inefficiency
ω	angular velocity
μ	reduced mass
W	virial
$\mathbf{v}$	velocity
$\mathbf{a}$	acceleration
$\mathbf{b}$	third derivative of position with respect to time ($d^3\mathbf{r}/dt^3$)
δt	time step in molecular dynamics simulations
$\mathbf{f}_{ij}$	force between particles i and j
$\langle A \rangle$	Ensemble average value of property A
q	generalised coordinate
C_{xy}	un-normalised correlation function
c_{xy}	normalised correlation function
τ	coupling parameter
κ	isothermal compressibility
γ	collision frequency/friction coefficient (in stochastic dynamics)
S	order parameter
ρ	probability density function
$\boldsymbol{\pi}$	transition matrix
$\boldsymbol{\alpha}$	stochastic matrix
ξ	random number (usually in range 0 to 1)
z	activity
μ	chemical potential
W	Rosenbluth weight

$\mathbf{G}$	metric matrix (in distance geometry)
p_i	ith principal component
$\mathbf{Z}$	variance–covariance matrix
λ	coupling parameter (used in free energy calculations)
$\mathcal{W}(\mathbf{r}^N)$	weighting function used in umbrella sampling
$\mathcal{N}$	number density ($= N/V$)
S_{AB}	similarity coefficient between two molecules A and B
D_{AB}	'distance' between two molecules A and B
σ	Hammett substitution constant
P	partition coefficient of solute between two solvents
π	$\log(P_x/P_{\mathrm{H}})$ for a substituent X relative to a hydrogen substituent
r^2	squared correlation coefficient
R^2	squared correlation coefficient in multiple linear regression
Q^2	cross-validated R^2

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Any errors that remain are of course my own responsibility. If you do find any, I would like to know! I will also be pleased to receive any constructive suggestions, comments or criticisms. We plan to set up a web site that will provide access to various material from the book (such as electronic versions of the colour images) together with email contacts. This can be accessed via www.booksites.net.

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