Molecular Modeling

Basic Principles and Applications

by Hans-Dieter Höltje and Gerd Folkers

in collaboration with Thomas Beier,
Wolfgang Sippl and Didier Rognan

Weinheim · New York · Basel · Cambridge · Tokyo

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Methods and Principles in Medicinal Chemistry

Edited by
R. Mannhold
H. Kubinyi
H. Timmerman

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This publication has been generously supported by Tripos GmbH, Munich.

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The financial support of Tripos GmbH, Munich, is gratefully acknowledged.

Published jointly by
VCH Verlagsgesellschaft mbH, Weinheim (Federal Republic of Germany)
VCH Publishers, Inc., New York NY (USA)
Editorial Director: Dr. Michael Bär

Library of Congress Card No. applied for.
British Library Cataloguing-in-Publication Data: A catalogue record for this book is available from the British Library.
Deutsche Bibliothek Cataloguing-in-Publication Data:
Höltje, Hans-Dieter:
Molecular modeling : basic principles and applications / by Hans-Dieter Höltje and Gerd Folkerts. In collab. with Thomas Beier ... – Weinheim ; New York ; Basel ; Cambridge ; Tokyo : VCH, 1996
(Methods and principles in medicinal chemistry ; Bd. 5)
ISBN 3-527-29384-1
NE: Folkerts, Gerd:; GT

Composition: Kühn & Weyh, D-79111 Freiburg
Printing: Betz Druck GmbH, D-64291 Darmstadt
Bookbinding: Großbuchbinderei J. Schäffer GmbH & Co KG, D-67269 Grünstadt
Printed in the Federal Republic of Germany.

Distribution:
VCH, P.O. Box 10 11 61, D-69451 Weinheim (Federal Republic of Germany)
Switzerland: VCH, P.O. Box, Ch-4020 Basel (Switzerland)
United Kingdom und Irland: VCH (UK) Ltd., 8 Wellington Court, Cambridge CB1 1HZ (England)
USA and Canada: VCH, 220 East 23rd Street, New York, NY 10010–4606 (USA)
Japan: VCH, Eikow Building, 10-9 Hongo 1-chome, Bunkyo-ku, Tokyo 113 (Japan)

Preface

The fifth volume of the series "Methods and Principles in Medicinal Chemistry" focuses on molecular modeling. Progress in modern ligand design is intimately coupled with the access to and the continuous refinement of molecular modeling techniques. They allow the computer-aided generation of molecular structures as well as the computation of molecular properties. Predictions of the three-dimensional structures of drug and receptor molecules, visualizations of their molecular surface properties and optimizations of drug–receptor interactions by visual inspection can be realized today.

The present volume offers an introduction to the field of molecular modeling. The book is organized in two parts: the first deals with the modeling of small molecules whereas the second examines biological macromolecules, in particular proteins.

The first part describes in detail the basic know-how necessary for generating 3D coordinates of small molecules, the computational tools for geometry optimization and conformational analysis, the determination of molecular interaction potentials, approaches for the identification of pharmacophores and last but not least the use of databases. The application of this spectrum of methodical approaches is exemplified by a case study dealing with pharmacophore definition in the field of serotonin receptor ($5\ HT_{2A}$) ligands.

The second part gives an introduction to protein modeling. After a description of terminology and the principles governing protein structures, approaches for knowledge-based protein modeling are summarized, followed by chapters on refinement and validation of protein models and on methods for the description of structural properties of proteins. The case study in the second part illustrates the application of experimental procedures to the modeling of protein–ligand complexes (design of non-natural peptides as high-affinity ligands for a MCH I protein).

The editors would like to thank the contributors for their encouragement in compiling this volume. We are sure that scientists entering the fascinating field of computer-aided ligand design will find in this volume the adequate support they need to apply molecular modeling techniques successfully.

April 1996

Düsseldorf — Raimund Mannhold
Ludwigshafen — Hugo Kubinyi
Amsterdam — Hendrik Timmerman

Methods and Principles in Medicinal Chemistry

Edited by
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H. Kubinyi
H. Timmerman

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Hugo Kubinyi
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Han van de Waterbeemd (ed.)
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Lipophilicity in Drug Action and Toxicology

Volume 5
Hans-Dieter Höltje, Gerd Folkers
Molecular Modeling

A Personal Foreword

> "A Model must be wrong, in some respects, else it would be the thing itself. The trick is to see where it is right."
>
> *Henry A. Bent*

We humans receive our data through the senses of vision, touch, smell, hearing and taste. Therefore, when we have to understand things that happen on the submicrosopic scale, we have to devise a way of simulating this activity. The most immediate and accessible way to represent the world that is unobservable is to make a model that is on our scale and that uses familiar forms.

Many physical and chemical properties and behaviors of molecules can be predicted and understood only if the molecular and electronic structures of these species are conceived and manipulated in three-dimensional (3D) models. As a natural follow up nowadays the computer is used as a standard tool for generating molecular models in many research areas.

The historical process of developing concepts leading to molecular modeling started with the quantum chemical description of molecules. This approach yields excellent results on the ab initio level. But the size of the molecular systems which can be handled is still rather limited. It is therefore that the introduction of molecular modeling as a routine tool owes its beginning to the development of molecular mechanics some 25 years ago together with the appearance of new technologies in computer graphics.

The goal of this book is to show how theoretical calculations and 3D visualization and manipulation can be used not simply to look at molecules and take pretty pictures of them, but actually to be able to gain new ideas and reliable working hypotheses for molecular interactions such as drug action.

It is our intention to reach this goal by giving examples from our own research fields more than reporting literature's success stories. This is because stepwise procedures avoiding pitfalls and overinterpretation can at best be demonstrated by data from our own laboratory notebooks.

Most of the contents will therefore reflect our own ideas and personal experiences, but nevertheless represent, what we believe to be an independent view of molecular modeling.

We gratefully acknowledge the technical assistance of Matthias Worch, Frank Alber and Oliver Kuonen. Finally we wish to express our sincere gratitude to Heide Westhusen for her excellent secretarial and organizational help.

Spring 1996

Berlin — Hans-Dieter Höltje
Zürich — Gerd Folkers

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1 Introduction

"Dear Venus that beneath the gliding stars ..." Lukrez (Titus Lucretius Carus, 55 B.C.) starts his most famous poem *De Rerum Natura* with the wish to the Goddess of love to reconcile the wargod Mars, which in this time when the Roman Empire starts to pass over its zenith, ruled the world.

Explanation is the vision of Lukrez. His aim is in odd opposition to his introductory wish to the goddess of love: the liberation of people from his fear of God, from the dark power of unbelievable nature.

The explanation of mechanism from the common is the measure with which Lukrez will take away the fear from the ancient people, the fear of the gods and their priests, the fear of the want of nature and the power of the stars.

Lightning, fire and light, wine and olive oil have been perhaps the simple things of daily experience, which people needed, which people was afraid of, whom has been dear to him:

> "... again, light passes through the horn
> of the lantern's side, while rain is dashed away.
> And why? – unless those bodies of light should be
> finer than those of water's genial showers.
> We see how quickly through a colander
> the wines will flow; how, on the other hand
> the sluggish olive oil delays: no doubt
> because 'tis wrought of elements more large,
> or else more crook'd and intertangled ..."

The atom theory of Demokrit leads Lukrez to the description of the quality of light, water and wine. For this derivation of structure–quality relationships he uses models. The fundamental building stones of Lukretian models look a little like our atoms, called *primodials* by Lukrez, elementary individuals, which were not cleavable anymore. Those elementary building stones could associate. Lukrez even presupposes recognition and interaction. He provides his building stones with mechanic tools that guarantee recognition and interaction. The most important of these conceptual tools are the complementary structure (sic!) and the barked hook. With these primordials Lukrez built his world.

How well the modeling fits is shown in his explanation of the fluidity of wine and oil. A comparison of the space-filling models of the fatty acid and water molecules amazes, because of its similarity with the 2000-years old image of Lukrez.