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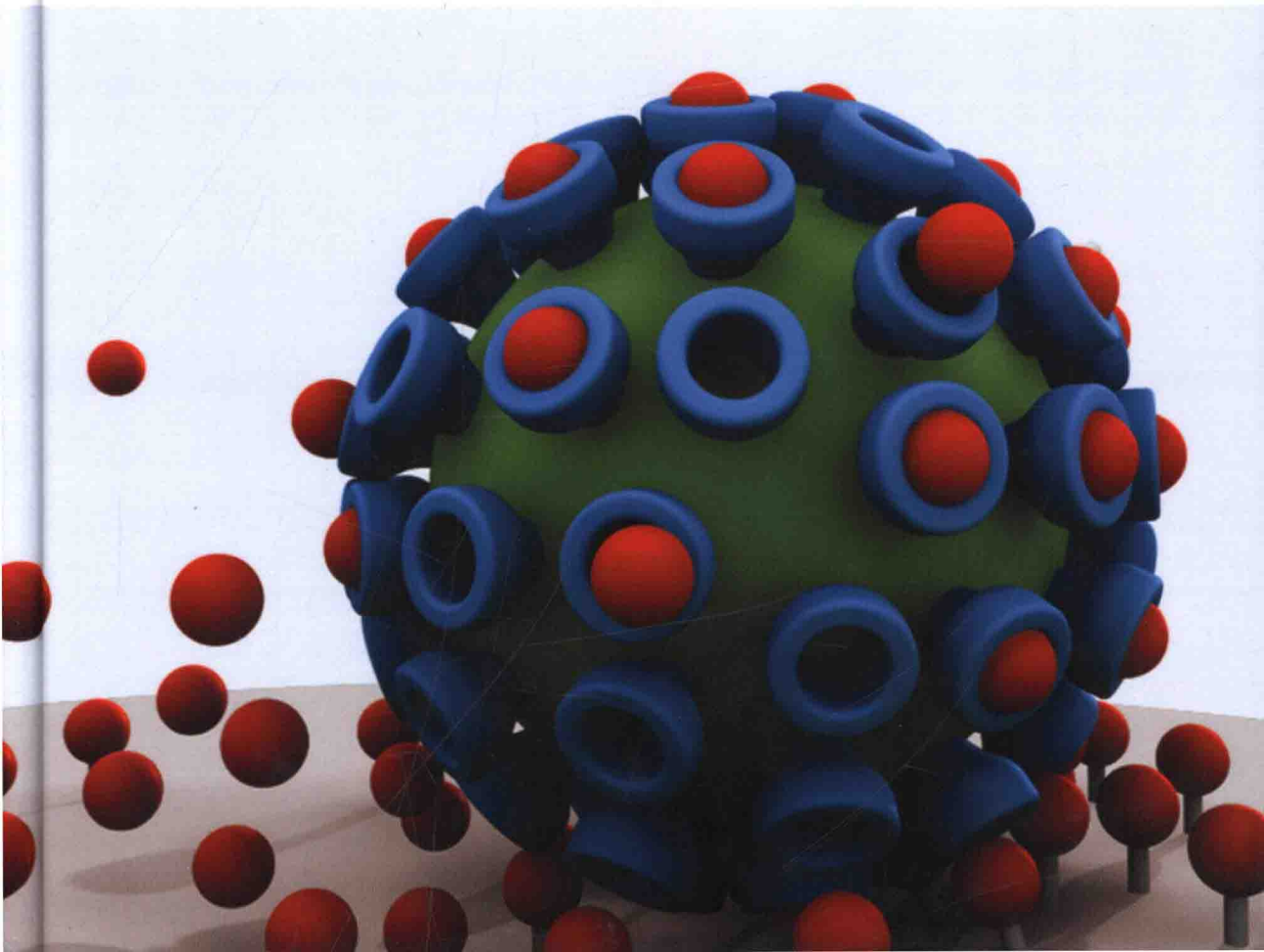
Edited by
Jurriaan Huskens, Leonard J. Prins,
Rainer Haag, Bart Jan Ravoo

Multivalency

Concepts, Research & Applications

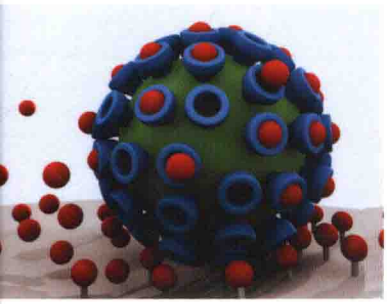


Connects fundamental knowledge of multivalent interactions with current practice and state-of-the-art applications

Multivalency: Concepts, Research & Applications is divided into three parts. Part one provides background knowledge on various aspects of multivalency and co-operativity and presents practical methods for their study. Fundamental aspects such as thermodynamics, kinetics and the principle of effective molarity are described, and characterisation methods, experimental methodologies and data treatment methods are also discussed. Parts two and three provide an overview of current systems in which multivalency plays an important role in chemistry and biology, with a focus on the design rules, underlying chemistry and the fundamental principles of multivalency. The systems covered range from chemical/materials-based ones such as dendrimers and sensors, to biological systems including cell recognition and protein binding. Examples and case studies from biochemistry/bioorganic chemistry as well as synthetic systems feature throughout the book.

- Introduces students and young scientists to the field of multivalent interactions and assists experienced researchers utilising the methodologies in their work
- Features examples and case studies from biochemistry/bioorganic chemistry, as well as synthetic systems throughout the book
- Edited by leading experts in the field with contributions from established scientists

Multivalency: Concepts, Research & Applications is recommended for graduate students and junior scientists in supramolecular chemistry and related fields. It is also highly useful to those working on research relating to multivalent and cooperative systems in supramolecular chemistry, organic chemistry, pharmaceutical chemistry, chemical biology, biochemistry, materials science and nanotechnology.



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Cover Design: Wiley
Cover Image: Image provided by Rainer Haag

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Also available as an e-book

ISBN 978-1-119-14346-8

9 781119 143468

Edited by
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This edition first published 2018

Registered Office(s)
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

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Library of Congress Cataloging-in-Publication Data

Names: Huskens, Jurriaan, 1968– editor.
Title: Multivalency : concepts, research & applications / edited by Professor Jurriaan Huskens, University of Twente, Enschede, NL [and three others].
Description: First edition. | Hoboken, NJ : Wiley, 2018. | Includes bibliographical references and index. |
Identifiers: LCCN 2017029790 (print) | LCCN 2017039365 (ebook) | ISBN 9781119143475 (pdf) | ISBN 9781119143499 (epub) | ISBN 9781119143468 (cloth)
Subjects: LCSH: Valence (Theoretical chemistry) | Multivalent molecules.
Classification: LCC QD469 (ebook) | LCC QD469 .M75 2018 (print) | DDC 541/.224–dc23
LC record available at https://lccn.loc.gov/2017029790

Cover design by Wiley
Cover image: Image provided by Rainer Haag

Set in 10/12pt Warnock by SPi Global, Pondicherry, India
Printed and bound in Malaysia by Vivar Printing Sdn Bhd

10 9 8 7 6 5 4 3 2 1

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Foreword

Scientific challenges come and go; only a few of them remain for a long time. Multivalency is one of those research topics that has been prominent for many years, as this intriguing phenomenon is of profound importance in many biological processes as well as very difficult to understand and mimic. Personally, I became intrigued by the challenge of multivalency when our group entered the field of dendrimers in 1990. The controlled number of end groups – 4, 8, 16, 32, and 64 amines of the polypropylene imines – opened many opportunities for us to explore the controlled use of multiple interactions. However, our ideas were more simple than our experiments in making full use of the potential of multivalency; many of them remained in the realm of dreaming. The broad potential of multivalency as well as its complex mode of action was beautifully illustrated by George Whitesides and coworkers [1] in the seminal *Angewandte Chemie* review paper in 1998. Their review initiated a world-wide search for synthetic mimics of these highly effective natural systems, a search that turned out to be long lasting.

Nature uses both similar interactions (homovalency) and different interactions (heterovalency) to control selectivity and specificity, even leading to ultra-sensitivity. Beautiful examples are found in substrate–cell interactions and immunology. Ever since this elegant mechanism and its importance in biological systems has been recognized, chemists have been intrigued to fully understand the enhancement factors obtained in binding multiple weak interactions through multivalency. Artificial systems are designed, synthesized, and studied, while a number of applications are proposed. Multivalent medication can have lower toxicity while simultaneously having higher medical efficacy.

Although the knowledge on the modus operandi of these systems has increased significantly in time and the systems synthesized have become more active, the full potential of the proposed applications remains. Hence, a number of challenging questions need to be answered before the potential of this intriguing concept can be explored. How to design the ideal structure to arrive at the theoretical maximum avidity and how to obtain scaling with valency are just a few of these intriguing questions. Theoretical and experimental studies of multivalent systems have revealed several design parameters that are critical in obtaining effective multivalent constructs. Next to the binding affinity, linker flexibility plays an important role, as rigid linkers require extremely precise ligand positioning to obtain high binding affinities and selectivity, while flexible linkers offer more freedom in molecular design at the cost of lower affinity and selectivity. Furthermore, additional competing equilibria can be used to enhance binding

selectivity or to steer an assembly towards a preferred state. However, the complexity of all these effects and their interference makes the field one of the most challenging areas in the molecular sciences.

Therefore, it is great to see that four outstanding scientists have edited a book on the intriguing topic of multivalent interactions. It is a book full of excellent chapters written by the most active experts in the field, covering all aspects of multivalent interactions with special emphasis on theory, synthesis, surfaces, chemical biology, and supramolecular chemistry. I am convinced that this book will be a great asset for all active in this intriguing field of science.

Eindhoven, May 2017 *E.W. Meijer*

Reference

1 Mammen, M., Choi, S.-K., Whitesides, G. M. Polyvalent interactions in biological systems: Implications for design and use of multivalent ligands and inhibitors. *Angew. Chem. Int. Ed.* **1998**, *37*, 2754–2794.

Preface

Multivalent interactions play a role in molecular and biomolecular systems in which molecules interact by multiple noncovalent bonds. Studying and describing these interactions in a quantitative manner constitute therefore an important way to obtain insight into the functional behavior of the biological and chemical systems in which they are involved. Over the past decades, the research of multivalent interactions has greatly expanded. This growth fits in the overall trends observed in the natural sciences which encompass the merging and overlapping of disciplines, like the biology and chemistry involved here. It also aligns with the emphasis on the study of complex systems, and the development of systems biology and systems chemistry, for example. Therefore, we have observed the need for a book that brings together fundamental aspects of multivalent interactions and relevant current examples of biological as well as chemical multivalent systems.

The disciplines of chemistry and biology are strongly represented in this area of science because they exert a mutual influence on both the understanding of fundamental aspects of multivalency as well as the development of practical research tools and applications. In biology, multivalent interactions play an eminent role in the immune system, but at the same time also describe the interactions between a virus and the host cell which the virus tries to infect. Tools from chemistry and nanotechnology are being developed that assist in studying such complex biological systems, for example, by synthesizing model cell membranes in which the interactions can be studied in a more controllable fashion. Likewise, probe techniques allow quantification of interactions at the single molecule level in individual cells. Conversely, the increase in understanding of the biomolecular interactions in living systems sparks the generation of new types of drugs and inhibitors that can make smart use of the multivalent character to improve both selectivity and activity.

A quantitative understanding of multivalent interactions is essential to promote progress in the field that deals with multivalent systems. Both experimental techniques as well as modeling can be used to stimulate this depth of understanding. Therefore, we decided that chapters with a strong educational character should be an essential part of this book. We present a section (Part I) of four chapters that serve to guide new researchers as well as more experienced researchers in their efforts to contribute to this lively area. These chapters provide a background in thermodynamics, data modeling and the description of multivalent equilibrium systems, numerical modeling of multivalent systems and superselectivity, and an introduction to multivalent biological systems. These chapters build on, and for some aspects briefly review, knowledge that most readers

with a background in chemistry or biology will have encountered in their regular academic education, but from there quickly integrate this knowledge into the description of multivalent systems.

Another explicit aim of the book is to expose the active nature of the research on multivalent systems. This is achieved in the two other sections of the book (Parts II and III), dealing with chemical and biological examples of multivalency, respectively. In the chemistry oriented chapters, timely topics such as the host–guest interactions of cyclodextrins and cucurbiturils are covered, as well as soft matter systems, such as vesicles, polymers, and nanoparticles. Not only equilibrium thermodynamics is shown, but also systems in which multivalent interactions control catalysis. In the more biological section, several biological interactions are put forward, such as protein–protein and lectin–glycan interactions. The strong connection between chemistry and biology in this area is emphasized by the examples that describe cell targeting by molecules and nanoparticles, as well as receptor inhibition by multivalent inhibitors.

We hope that this book will serve a need, for new and experienced researchers alike, both for those requiring a deeper understanding as well as those that try to get an overview of existing activities in the field. We thank all contributing authors for their efforts in summarizing and describing their research and that of others, as their joint work makes this book so much more than the individual chapters alone. We also express our gratitude to the Wiley staff for smoothing the pathway for the book that lies before you.

September 2017

Jurriaan Huskens, Leonard J. Prins, Rainer Haag, and Bart Jan Ravoo

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