Book Reviews *

Advances in Medicinal Chemistry. Volume 5. Edited by Allen B. Reitz and Scott L. Dax (The R.W. Johnson Pharmaceutical Research Institute). JAI Press: Stamford, CT. 2000. x + 201 pp. $115.00. ISBN 0-7623-0593-2.

This volume is the fifth in a series designed to provide first-hand accounts of industrial and academic research projects in medicinal chemistry. In this volume, four contemporary industrial projects are presented. Chapter 1, by G. S. Hamilton and C. Thomas, reviews the fascinating history of the immunophilins and the current state of knowledge about this field, while Chapter 2, by M. W. Holladay and M. W. Decker, describes the serendipitous twists and turns that led to the development and characterization of ABT-594, the first potent analgesic to act at nicotinic acetylcholine receptors. In Chapter 3, D. J. Wustrow discusses the numerous structure−activity relationships of dopamine agonists and partial agonists resulting from efforts to identify a useful drug for the treatment of schizophrenia. In the last chapter, S. Hagen, J. V. N. Vara Prasad, and B. D. Tait focus on their successful program to design non-peptide inhibitors of the human immunodeficiency virus (HIV) protease.

Immunophilins, the authors of Chapter 1 tell us, is the name given to a group of peptidyl prolyl isomerases (PPIases) that serve as targets for the immunosuppressant drugs cyclosporin A, FK506, and rapamycin. The term was coined by Stuart Schreiber, who directed many of the key experiments in this field, including one showing that the PPIase activity and immunosuppression were not linked. This result set off an intensive search for the cellular targets of the drug−immunophilin complexes and, as the authors note, led to the field of chemical biology, "in which fundamental research in cell biology occurs at the interface of the disciplines of chemistry and biology". Subsequently, the chapter covers the many experiments that elucidated the roles played by immunophilins in cellular processes, such as protein trafficking and modulation of signal transduction pathways. The authors also detail the insights gleaned from crystal and NMR structures of immunophilins and their ligands, and how these observations provide a structural framework for understanding the roles of immunophilins in cellular processes. The chapter concludes with a discussion of the neuroimmunophilins, which are immunophilins found in the central nervous system, and the exciting discovery that some small-molecule ligands of this group of immunophilins promote the regrowth of damaged nerves. The immunophilin story is a fascinating one, and the authors have done an outstanding job of recounting it.

The development and characterization of ABT-594 is also an intriguing story and the subject of the next chapter. The story begins when a group at Abbott Laboratories decided to focus on agonists of nicotinic acetylcholine receptors (nAChR) as potential drugs for the treatment of Alzheimer's disease. The group pursued a classic medicinal chemistry approach in which a number of analogues are synthesized and their structure−activity relationships established. In the course of these studies, it was reported that the potent analgesic properties of epibatidine, a substance from the skin of an Ecuadoran frog which shares structural similarities with nicotine, involved the activation of the neuronal nAChRs. The remainder of the chapter then discusses the efforts at Abbott to identify and develop a compound from their existing pool of nAChR ligands that retained the potent analgesic properties of epibatidine, but not its toxicity. The result was ABT-594, which is now on the verge of being tested in human clinical trials as an analgesic agent.

In Chapter 3, the author describes a program to identify dopamine agonists and partial agonists of the so-called dopamine D2 autoreceptors, which control the synthesis and release of dopamine from the neurons. This approach is a novel one in the search for more effective antipsychotic agents. The drugs currently in use are antagonists and block the dopamine D2 receptors. While these drugs can be effective, they cause debilitating side effects. Much of the chapter reviews the structure−activity relationships of several dopamine agonists and partial agonists. The author concludes by indicating that this program has not yet led to a successful drug candidate and the underlying premise remains to be proven.

The last chapter continues along the same lines as the previous two and discusses the program at Parke-Davis to identify and develop non-peptide inhibitors of HIV protease. Two initial lead compounds were discovered by high-throughput screening of approximately 150 000 compounds. One of the lead compounds, a pyrone derivative, was optimized into a preclinical candidate, using a combination of molecular modeling and X-ray crystal analysis. The chapter also discusses the structure−activity relationships that led to the final compound.

Prior to my review of this volume, I was unaware of this series. However, I enjoyed reading the four accounts presented in this volume, and found each one to be comprehensive and very informative. This volume would be especially useful to graduate students, faculty, and research scientists in chemistry as well as medicinal chemistry with an interest in one of these areas. In addition, it might be of interest to a broader audience, as each chapter gives a realistic portrayal of the various approaches that can be used to develop a drug. If the previous four volumes are comparable to this one, then the entire series would be a valuable addition to a chemistry library.

Christian P. Whitman, *The University of Texas at Austin*

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Automated Synthetic Methods for Speciality Chemicals. Edited by W. Hoyle (Consultant). Royal Society of Chemistry: Cambridge. 2000. viii + 114 pp. £49.50. ISBN 0-85404-825-1.

The eight chapters in this book evolved from the papers presented at a symposium organized by the Royal Society of Chemistry in September 1999. The contributions include overviews of and current practices in the application of automated techniques, including microreactors and robots, to the synthesis of specialty chemicals.

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Progress in the Chemistry of Organic Natural Products. Edited by W. Herz (Florida State University), H. Falk (Johannes-Kepler-University), G. W. Kirby (University of Glasgow), and R. E. Moore (University of Hawaii at Manoa). Springer-Verlag: New York. 2000. viii + 256 pp. $169.00. ISBN 3-211-83361-7.

This book contains two review articles: "Synthetic Aspects of Iridoid Chemistry", by H. Franzyk, and "The Defensive Chemistry of Ants", by S. Leclercq, J. C. Braekman, D. Daloze, and J. M. Pasteels. Both articles cover developments in the field over the decade ending in 1998. The chapter on the defensive chemicals produced by ants focuses on non-proteinous poisons delivered in venom or through the Dufour glands and covers both their chemical synthesis and biosynthesis. Author and subject indices complete the book.

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Catalysis by Metal Complexes. Vol. 21. Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes. By Alexander E. Shilov and Georgiy B. Shul'pin (Semenov Institute, Russia). Kluwer: Dordrecht, Boston, and London. 2000. xiv + 534 pp. $228.00. ISBN 0-7923-6101-6.

Alkane functionalization with homogeneous catalysts dates back to Fenton's reagent ($Fe(III)/H_2O_2$) of 1898. From the 1930s, metal-mediated radical autoxidation and, later, superacid catalysis via carbonium ion intermediates both led to important commercial processes. The discovery of the oxidative addition reaction in the late 1960s made this new pathway available for alkane conversion by low-valent transition metal complexes. Alex Shilov has the distinction of having reported the first example of the latter type as early as 1969.

Despite this long history, selective, general alkane functionalization by chemical means with adequate control of selectivity is still an unsolved problem. The "Barton challenge", the conversion of *n*-hexane to 1,6-hexanediol, is still unmet, for example. The area of alkane functionalization therefore remains one of the most significant contemporary challenges in organometallic chemistry.

This new book on the problem by Shilov and Shul'pin builds on

*Unsigned book reviews are by the Book Review Editor.

Shilov's 1984 related book, *Activation of Saturated Hydrocarbons by Transition Metal Complexes*. Not only is the earlier work completely reworked and brought up-to-date, but the scope is extended to include a number of new aspects, most notably bioinorganic applications and reaction pathways not involving metals. Oxidation processes are also given greater attention. The present book is nearly three times the size of the earlier one.

One strong point of this work is the broad coverage and very extensive and up-to-date bibliography. The majority of the references date from the 1990s and coverage goes right up to early 1999. The extensive Russian work is unfortunately still less well known in the West than it deserves, and the authors give this material appropriate emphasis. The discussions have a strong mechanistic flavor and draw on a very broad body of literature.

Apart from rare omissions, such as the Catalytica catalysts for methane conversion to methanol esters, the book gives a very valuable picture of the current state of the field and will be an essential item for academic and industrial libraries.

Robert H. Crabtree, *Yale University*

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Concerted Organic and Bio-organic Mechanisms. By Andrew Williams (University Chemical Laboratory, Canterbury, UK). CRC Press LLC: Boca Raton, FL. 2000. x + 286 pp. $79.95. ISBN 0-8493-9143-1.

This is an excellent and authoritative book that covers not only concerted reactions but also stepwise reactions originally proposed to be concerted. The book is very densely written, with much information, and with a careful reasoning style that demands concentration from the reader.

The classes of reactions considered are proton transfers, nucleophilic displacements at unsaturated carbon, nucleophilic displacements at saturated carbon, displacements at heteroatoms, cyclic reactions, and enzyme reactions. Addition reactions are omitted, and eliminations and electrophilic substitutions are discussed very briefly. Many readers may be interested in only one class of reaction, and it is possible to ascertain what Williams concludes about their mechanisms. In my view, the triumph of this book is the presentation of the epistemological principles. Following a brief introductory chapter of definitions, there is a very instructive chapter presenting the techniques used to draw inferences about the concertedness of reactions.

How is it ever possible to obtain evidence for a concerted reaction? How can the presence of an intermediate be rigorously excluded? Even if experimental results fail to support an intermediate, it might be too unstable to detect or trap. Yet there are convincing observations to exclude intermediates and support concertedness. Three of the most powerful are (1) a strictly linear free-energy correlation without the deviation associated with a change of rate-limiting step, (2) an estimated or extrapolated lifetime that is too short for a putative intermediate's existence, and (3) the absence of double isotope fractionation (isotope effect on an isotope effect) that arises from a change of the partitioning ratio in a stepwise reaction.

Williams's own major research contribution is the observation that many acyl transfers, such as the reaction of substituted pyridines with *N*-methoxycarbonyl isoquinolinium ions, are concerted. This is an example of a type of reaction that might automatically be assumed to proceed via a tetrahedral intermediate, like so many other carbonyl reactions (according to classic studies of ^{18}O incorporation into esters). Indeed, throughout the book there are frequent surprises for those who have not kept current with the vast range of mechanistic results. Unfortunately, there are no general principles to permit a priori judgment of whether a reaction is concerted or stepwise.

The book maintains a good balance between detailed reasoning and a summary of conclusions. The key logic behind the free-energy nonlinearity arising from a change of rate-limiting step is repeated several times, but the experimental results expected from such proposed mechanisms are sketched only briefly. There are many clarifying schemes and chemical structures that are essential for understanding; mechanisms are designated according to the IUPAC-recommended nomenclature of Guthrie and Jencks, rather than the older Ingold system ($D_N + A_N$ and A_ND_N, rather than S_N1 and S_N2).

There are few misprints or misstatements, but some criticisms should be noted. These include the failure to provide an explicit definition of β_{nuc} and β_{lg}, and the discrepancy between Scheme 6.26, which claims to illustrate intermediates in a $D_N + A_N$ mechanism, and Scheme 6.24, where it is indicated that these arise via $A_{xh}D_H + A_N$. Moreover, skepticism over the role of lone pairs antiperiplanar to a leaving group would have been appropriate, in view of results from amidine hydrolyses, which unfortunately were ignored. On another matter, it makes no sense to claim that front-side nucleophilic displacement at a saturated carbon would lead to racemization if the Nu−C−Lg angle were tetrahedral, and it is unclear why cyclization of squalene epoxide is considered to be a cyclic reaction, since it is not pericyclic like the other reactions in Scheme 7.1. Finally, a neglected clarification is that the femtosecond kinetics of the reverse Diels−Alder reaction of norbornene are of an electronically excited state. These deficiencies detract only modestly from the overall value of the book.

Each study that is discussed includes citations to the original literature, so that the reader can readily obtain additional details. There is a valuable list of general references for each topic and a useful subject index, including symbols, but no author index. References are included up to 1998.

In summary, this book offers a concise guide to a wide range of mechanistic studies. It will reward the careful student or researcher.

Charles L. Perrin, *University of California, San Diego*

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Inorganic Electronic Structure and Spectroscopy. Volume I. Methodology. Edited by Edward I. Solomon (Stanford University) and A. B. P. (Barry) Lever (York University). Wiley-Interscience: New York. 1999. xiv + 732 pp. $150.00. ISBN 0-471-15406-7. Set (with Volume II): $260.00. ISBN 0-471-32683-6.

This two-volume set (a separate review of Volume II follows) is an excellent compilation of very readable and up-to-date chapters by experts on a wide variety of spectroscopic and computational techniques of importance to a detailed understanding of transition metal species. The title, however, is misleading because, with only a few exceptions, the main-group, lanthanide, and actinide elements are virtually ignored. Thus, the volumes would be better entitled "Transition Metal Electronic Structure and Spectroscopy".

There are many excellent chapters in both volumes, most of which stand on their own. This reviewer found the first chapter of the second volume, "Bioinorganic Spectroscopy", by E. Solomon and M. Hanson, to be the most interesting and recommends it as a good place to start reading. Confining their discussion to bioinorganic iron and copper, they provide a vast array of methodology that has been used in bioinorganic chemistry. The chapter even brings in missing elements from the methodology chapters of Volume I. For example, the Q, S, L, and C bands of EPR spectroscopy and the methodology of magnetic circular dichroism are first discussed in this chapter.

Volume I, Methodology, begins with a chapter by the editors on ligand field theory and properties of transition metal complexes. This chapter provides the expected background on crystal field, ligand field, angular overlap, and molecular orbital descriptions as well as multielectron complications to spectroscopy and relations of ligand field theory to physical properties. Overall, the chapter is very well done. Chapter 2 (A. Bencini and D. Gatteschi) on electron paramagnetic resonance spectroscopy has very readable theoretical discussions and a valuable table of g values for d^n ions in pseudo-octahedral coordination. The following chapter, by P. Gütlich and J. Ensling, provides a very well written and well illustrated introduction to Mössbauer spectroscopy. Its weakest points are a lack of references beyond 1985 other than three from the authors' laboratory and only one non-iron example. Chapter 4 (M. A. Hitchman and M. J. Riley) is a welcome description of the polarized absorption spectroscopy of oriented single crystals. Where else would you learn that tetracyanoplatinate(II) salts, although colorless in solution, absorb visible light in the solid state with a strong counterion color dependence?

T. C. Brunold and H. U. Güdel provide a good discussion of theory and instrumentation for luminescence spectroscopy in Chapter 5, and in addition to the standard continuous wave method, they present four other experimental techniques in the field. Examples of determining geometry from emission spectra, d−d and charge-transfer luminescence spectra, and the problems of nonradiation competition, multiphoton