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BOOK REVIEWS

The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging. Edited by André E. Merbach and Éva Tóth (University of Lausanne). J. Wiley & Sons: Chichester, New York, Weinheim, Brisbane, Singapore, Toronto. 2001. xii + 472 pp. $160.00. ISBN: 0-471-60778-9

MRI has become synonymous with technologic sophistication and power in medical diagnosis and biomedical research. Twenty million MRI examinations are conducted each year in the U.S. to determine anatomic as well as physiologic characteristics of abnormal tissues. Amazing new uses, such as MRI visualization of coronary arteries and faster scanning techniques to allow inexpensive whole body screening, are hotly researched. Five million of these examinations will use intravenously administered pharmaceuticals. These contrast agents generate extreme signals in MRI images, which are used to indicate the presence, absence, or character of abnormalities, blood flow, water diffusion in and blood perfusion of tissues, or organ function through metabolism of the agents.

This book attempts, for the first time, to review the whole spectrum of involved chemical disciplines in this technique. It is a collection of chapters, each by different authors, that grew out of an annual conference supported in part by the European Union. The authorship is somewhat biased toward Europeans, which generates occasional grammatical hiccups, but this is not a significant limitation. Each of the authors' chapters is within the scope of their published fields, and industrial authors are represented to some extent. The breadth of coverage is wide, with only a few shortcomings addressed below. Illustrations are of good quality, but biological data are sparse. This may limit some potential uses, but it does not detract from the book's purpose. There is little cross-referencing among chapters, although this is mitigated by a useful index. Inorganic nomenclature is inconsistent from chapter to chapter and is generally not standard after Chapter 2. Certain chapters have exceptional competition in the form of a previously published, comprehensive review of structure and dynamics of Gd(III) MRI agents by Caravan, Ellison, McMurry, and Lauffer (*Chemical Reviews*, **1999**, 2293−2352). This book, with the addition of the Caravan review, a medically oriented review, and a few recent references, would make an interesting special topics course at the graduate level.

The signal intensity in MR images depends in large part on the relaxation times of the water protons in the tissue. MR agents are unique among pharmaceuticals in that they are catalysts for water proton relaxation. Most of the agents studied are, therefore, paramagnetic metal systems: soluble strong chelates of Gd(III), Fe(III), Mn(II), and insoluble iron oxides. Chemists who wish to do research on these entities should acquire at least familiarity with the wide range of involved fields: organic, inorganic, analytical, physical, and biochemistry, MR physics, and basic physiology. Certain specialties also involve polymer and computational chemistry. The book covers the basic chemistries, MR physics, and the most important techniques used by chemists in the characterization of MR agents.

In Chapter 1, the physics of MRI is introduced, starting with the definition of the magnitude of nuclear spin and NMR basics through relaxation processes, imaging hardware, and the most important categories of pulse sequences. The transition to MR images could have used an explanation for chemists who do not know brain imaging presentations and anatomy, but the other images are anatomically self-evident. The sections attempting to classify contrast agents are too brief to be very useful except to inform a novice of what is to come in future chapters.

Chapter 2 begins a review of the most charming aspect of MRI contrast agents, relaxivity. This parameter is a second-order rate constant describing the catalytic effectiveness of any agent. I am not aware of any other drug type that is a catalyst. Chemical modification of ligands to improve the effectiveness of a pharmaceutical attracts inorganic and physical chemists with the lure of creating new generations of chelates with many times the relaxivity of existing agents. The chapter's aims are achieved, focusing a little more on teaching at the expense of comprehensiveness in data presentation, as compared to the Caravan opus.

The following two chapters are unique and practical contributions dealing with an often-ignored but crucial subject: the synthesis of the multidentate ligands most frequently used in the generation of new contrast agents. Both chapters are clearly written reviews packed with information. There are over 250 references and 200 numbered structures discussed and highlighted in the figures and text.

The next generation of clinically useful contrast agents will be noncovalently bound to human serum albumin, and the following generation, if there is one, will likely be bound to proteins expressed on cell surfaces, with the aim of biochemically characterizing the cells. Important principles governing the relaxivity of bound metal chelates are discussed in Chapter 5, which adequately covers the groundwork required for research in the area. The chapter pays particular attention to the effect of protein binding and chelate structure on the correlation times governing relaxivity. The chapter is more didactic than the previous two. It is sometimes difficult to differentiate facts from hypotheses, and it is not polished, leaving some typographical and grammatical errors.

In the chemistry of MRI agents, tolerance is partly related to stability and lability of the metal ions; hence, the continued interest in the mechanisms of formation and dissociation of highly stable multidentate chelate systems, which is the subject of the competently executed Chapter 6. Correlations among toxicity of Gd(III) chelates, thermodynamics, and dissociation kinetics are actually rare, and the limits are generally well-understood and -met by existing structures; however, the reemerging field of targeted radiotherapy for cancer uses radioactive lanthanides such as ^{90}Y and ^{177}Lu attached to targeting entities (e.g., antibodies) with the metals bound by

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the same chelates as those used in Gd(III) MRI agents. In this application, there are most stringent requirements on the chelates because of the propensity of free Ln to target bone marrow, the most radiosensitive organ. Chapter 6 is, therefore, surprisingly important and timely.

The important subject of particulate contrast agents is covered in Chapter 10. It is strong in theory, but only briefly mentions the syntheses, structure, and characterization of the iron oxide superparamagnetic particles. The superparamagnetic particles probably deserve more space, because they are currently the only agents available with sufficient relaxivity to become biochemically targeted agents.

The remaining chapters are devoted mainly to methods of investigation. Computational studies, the subject of Chapter 7, are interesting, but not apparently ready yet to predict properties a priori. In Chapter 8, the author does a creditable job of reviewing solution structures determined mostly by NMR methods. Solid state structures are little covered in the book (they are extensively covered in Caravan, however). EPR methods and photophysical methods are reviewed in Chapters 9 and 10, respectively. Additional chapters for a possible next edition could profitably include solid state structures, hyperpolarized gases, and metabolically active contrast agents.

The future of MRI contrast agents is uncertain. Tolerance of the current agents is so high and the chemistry is so relatively inexpensive compared to the regulatory hurdles in the way of drug creation that there is only one obvious direction for MRI contrast agents to go—more signal to allow them to be targeted to receptors. Molecular medicine is arriving as a blizzard of new genes and their proteins. The sheer number of these new biological entities will almost guarantee an ever more mechanistic understanding of human biology and disease and the many new drug molecules that interact with the new entities. Wherever regionally defined biological information is useful, there will lie fertile ground for new imaging contrast agents, for it is the regionally sorted information, obtained noninvasively, that is the strength of in vivo medical imaging. Contrast agents of the future will yield *regional protein expression*. MRI, the preferred imaging modality, uses contrast agents that are currently detected only at greater than 10 micromolar levels, but biochemistry is primarily occurring at nanomolar levels. A very bright future for MRI contrast agents will require that the relaxivity be increased by at least ten-fold, and therein lies the challenge to chemists and the value of this first monograph on the chemistry of MRI contrast agents.

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Valid Analytical Methods and Procedures. By Christopher Burgess (Burgess Consultancy, County Durham, U.K.). Royal Society of Chemistry: Cambridge. 2000. viii + 88 pp. £29.50. ISBN: 0-85404-482-5.

The aim of this book is "to provide a best practice approach which will meet the basic needs of the bench practitioner and at the same time provide links to more exacting and specialist publications". To achieve this goal, the author provides a framework for the development and validation of "best practice" analytical methods; guides the reader to more detailed works by including a select bibliography of publications by the Analytical Methods Committee as well as a comprehensive list of references; shows the reader how to use certain statistical procedures for comparison of methods; and illustrates, through examples, "main statistical procedures for the calculation, display and reporting of the results". The book contains 10 chapters, entitled as follows: Introduction; Nomenclature: Terms and Parameters; Samples and Sampling; Method Selection; Equipment Calibration and Qualification; The Method Development Process; Method Validation; Data Evaluation, Transformation and Reporting; Technology Transfer; and Selected Publications of the AMC.

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Medicinal Chemistry: Into the Millennium. Edited by Malcolm M. Campbell and Ian S. Blagbrough (University of Bath, U.K.). Royal Society of Chemistry: Cambridge. 2001. x + 398 pp. £69.50. ISBN: 0-85404-769-7.

This book was derived from the Proceedings of the European Federation of Medicinal Chemistry Symposium held in Edinburgh in September 1998. The 30 chapters are organized under the following subject headings: New Technologies for Drug Discovery; Ion Channels; Glycine Antagonists; 7TM Receptors; Growth Factors; Intracellular Signalling; Protease Inhibition; Glycochemistry and Clycobiology; Nitric Oxide Synthase Inhibition; and Predicting DMPK. References are current to 1998.

JA0153316

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Supported Catalysts and Their Applications. Edited by D. C. Sherrington (University of Strathclyde, Glasgow, U.K.) and A. P. Kybett (Royal Society of Chemistry, Cambridge, U.K.). Royal Society of Chemistry: Cambridge. 2001. x + 270 pp. £69.70. ISBN: 0-85404-880-4

In this book, which was derived from the proceedings of the July 2000 4th International Symposium on Supported Reagents and Catalysts in Chemistry at the University of St. Andrews, U.K., is presented the state-of-the-art in the design, synthesis, and application of solid-supported reagents and catalysts. Some of the topics covered include supported reagents for multistep organic synthesis, the use of Zeolite Beta in organic reactions,

and polymer-bound organometallic complexes as catalysts for use in organic synthesis. The convergence of traditional heterogeneous catalysts based on inorganic oxide materials and polymer-based heterogeneous catalysts can also be seen in this book as an emerging theme in solid-supported catalyst research. References are current up to 2000.

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Emerging Themes in Polymer Science. ETiPS. Edited by A. J. Ryan (University of Sheffield). Royal Society of Chemistry: Cambridge. 2001. x + 324 pp. £59.50. ISBN: 0-85404-890-1.

This book presents the proceedings of the Macro Group U.K. meeting of the same title held at The University of Sheffield in April 2000. Its 23 chapters cover not only the latest developments in polymer synthesis, characterization, processing, properties, and applications but also the likely future of polymer research, such as its interactions with biological research and the use of polymers in electronics and nanotechnology. The chapters are organized under the following subtopics: The Future of Industry, Polymer Characterization and Colloids, Biomaterials and Tissue Engineering, Surfaces and Their Modification; Biopolymers, Rheology and Processing, Theory Modelling, Measuring Structure and Dynamics, and Molecular Machines. References are current through the 1990s.

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Annual Review of Physical Chemistry. Volume 52, 2001. Edited by Stephen R. Leone (University of Colorado at Boulder), Paul Alivisators (University of California, Berkeley), and Ann E. McDermott (Columbia University). Annual Reviews: Palo Alto, CA. 2001. xvi + 942 pp. ISBN: 0-8243-1052-7

Like the other volumes in this series, Volume 52 covers a wide range of topics in physical chemistry, from crossed-beam neutral-reaction studies to light-emitting electrochemical processes to RNA folding research, by leading experts in the field. References are current through the late 1990s.

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Plasma Source Mass Spectrometry: The New Millennium. Edited by Grenville Holland (University of Durham, UK) and Scott D. Tanner (PE-Sciex, Concord, Ontario, Canada). Royal Society of Chemistry: Cambridge. 2001. x + 428 pp. £69.50. ISBN: 0-85404-895-2.

This book is composed of the proceedings of the 7th International Conference on Plasma Source Mass Spectrometry: The Millennium Conference held at the University of Durham in September 2000, which was organized to provide an open forum for the discussion of both the state-of-the-art of this analytical technique and its future prospects. The wide variety of ICPMS topics covered is organized under the following headings: Sample Preparation and Introduction, Mass Analyser Instrumentation, Reaction Cells for ICPMS, Applications, Isotope Ratio Measurement, and Speciation. References through the 1990s are provided.

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