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Book Reviews *

Green Engineering: Environmentally Conscious Design of Chemical Processes. By David T. Allen and David R. Shonnard. Prentice Hall PTR: New Jersey. 2002. 552 pp. £51.99. ISBN 0-13-061908-6.

Lacking the word "chemistry" in its title, this excellent book may well have evaded online searches by chemists wishing to read about green chemistry. I am pleased to report that this is a very welcome addition to the green chemistry literature. Chemists should certainly not be put off by the word "engineering"!

Originating from the United States, the original goal of the book was to become a standard textbook to describe "green" design methods suitable for inclusion in the U.S. Chemical Engineering Curriculum. The result is a monograph with much wider potential appeal.

The book is well structured, being divided into three main parts. Part I (Chapters 1−4), "A Chemical Engineers Guide to Environmental Issues and Regulations", provides a basic introduction to the issues (local and global), risk concepts and environmental laws and regulations (U.S.) in terms of energy and materials use, and the types of wastes and emissions. Part II (Chapters 5−12), "Evaluating and Improving Environmental Performance of Chemical Processes", is structured around a hierarchy of design, beginning with tools for evaluating environmental hazards based on chemical structure and measurable or estimable physicochemical properties, continuing through unit operation and process flowsheet analysis, and concluding with a chapter on environmental cost accounting. Included in this section are methods for evaluating exposure, and a chapter on green chemistry. The final part, Part III (Chapters 13−14), "Moving Beyond the Plant Boundary", describes lifecycle concepts and industrial ecology, outlining tools for improving product stewardship and improving the level of integration between chemical processes and other material-processing operations. At the end of the book is a series of appendices including listings of U.S. federal environmental statutes, tables of environmental impact potentials, procedures for estimating hidden environmental costs, and a list of relevant web resources, databases, and software.

The writing style throughout is clear and readable, each chapter benefiting from introductory and summary sections, together with references. The concepts and tools are brought to life by worked examples, which clearly demonstrate their application. Every chapter concludes with some interesting and challenging problems, which test and stretch the understanding gleaned in the preceding pages. There are many useful data in the book, too. While the book is (perhaps understandably) U.S.-centric, that should in no way deter the non-U.S. reader, since the general concepts are of value to all, and anyway, an analogous non-U.S. text simply does not exist.

This is the complete professional's guide to cost-effective design, commercialisation, and use of chemical processes that minimise pollution at source, thus reducing the impact on health and the environment. It is one of the very best books available to those interested in designing chemical processes in an environmentally conscious way, and it beautifully complements existing publications in the area of green chemistry. It is strongly recommended for chemists *and* chemical engineers, whether students or practitioners.

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Biotransformations in Organic Chemistry: A Textbook, 5th Edition. by Kurt Faber. Springer-Verlag: Heidelberg. 2004. 454 + XI pp. £27 (paperback). ISBN 3-540-20092-5.

It is easy to see why Kurt Faber's textbook has remained popular since the first edition in 1992. Now in its 5th edition, it provides the organic chemist with a comprehensive picture of biotransformations, written from an organic chemist's viewpoint. For those chemists in process R&D, this is the book to read before carrying out a biotransformation. Not because it is the most up-to-date book (there are in fact few references beyond 2000) but because it gives the best practical advice and, with its emphasis on kinetics and mechanisms, helps the chemist to understand the reactions and potential scale-up issues (e.g., mass transfer). The practical aspects are best illustrated by reference to the chapter on special techniques which covers enzymes in organic synthesis, immobilisation, and modified and artificial enzymes. In the section on use of organic solvents the advantages and disadvantages of the three alternatives, namely (1) using water-miscible solvents, (2) using two-phase mixtures with a water-immiscible solvent, and (3) suspending the enzyme in the solvent are clearly delineated. But Faber discusses how much water to have present and why and then explains why this amount might vary for each enzyme. Exactly what a development chemist needs!

The book opens with an excellent introduction and is followed by a mammoth chapter on biocatalytic applications (304 pages), split into hydrolysis, reduction, oxidation, C−C bond formation, addition and elimination reactions, glycosyl transfer, and halogenation and dehalogenation. This is

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followed by the special techniques chapter mentioned earlier and a state of the art/outlook discussion. In the latter chapter, he perhaps does not give enough emphasis to the great strides that have occurred in directed evolution, particularly in the work of Arnold on oxidation of simple alkenes and cycloalkenes, and in the use of directed evolution for optimising the performance of an organism or enzyme for industrial use (e.g., Degussa).

There is an appendix, which not only emphasises safety aspects of working with enzymes and cells but also lists suppliers of enzymes—with the changing names of companies and mergers and acquisitions this list is a little out of date. Commonly used enzyme preparations, major culture collections, and pathogenic bacteria and fungi are all listed in the appendix. A comprehensive 17-page index is included.

I have not compared this edition with the 4th edition (2000), but the publisher claims that the new edition has an improved style and greater emphasis on dynamic resolution, stereoinversion and enantioconvergent processes. These sections are very readable—Faber's style is easy to assimilate and makes for an enjoyable experience—I read the book cover-to-cover and learned a lot. For example, the separation of E/Z isomers of trisubstituted allylic alcohols can be achieved by selective acylation using a lipase catalyst, and an acylating agent other than Ac_2O. "Not a lot of people know that." The textbook will be a good source of reference, although the small number of recent references is a potential drawback.

In conclusion, this is an outstanding textbook, which should be on every organic chemist's bookshelf. Excellent value for the money, too.

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Pharmaceutical Substances. By Axel Kleeman, Juergen Engel, Bernhard Kutscher, and Dietmar Reichert. Thieme (Online Version). Price on Application.

Pharmaceutical Substances is a compendium of more than 2300 of the most significant pharmaceutical compounds of industrial interest. It has been available in hard copy printed form for a number of years. The latest edition (4th) was published in 2001.

Pharmaceutical Substances is now available online at http://www.thieme-chemistry.com.

All of the information in the hard copy is, of course, provided in the online version. Thus, for each drug the following information can be accessed: chemical structure, synthetic route, intermediates, nomenclature (INN standard, trivial names, synonyms), CAS registry number, ATC codes, medical applications/therapeutic category, toxicological data, patent information (number, origin, holder, and application date), commercial information, bibliographic information (including CASSI codes). Furthermore, newly approved substances are added biannually. The bibliographic information provided is good, but the references would be much more useful if the titles of the papers and patents were also included. It should be noted that this compendium does not claim to be comprehensive.

The key advance provided by the online version is searchability. Particularly powerful is the structure and substructure searching (including reaction searching), which will be of particular use to those designing synthetic routes to active pharmaceutical ingredients, intermediates, and related compounds. The online version supports ChemDraw and ISISDraw and has a built-in JAVA applet so that researchers can use whichever is their preferred structure drawing tool. A slight irritation is the need to constantly scroll left and right and/or to resize windows to fully view the content and navigate the search system.

In stark contrast to the structure searching, text searching is very weak as the following examples show.

(i) A search for "polymorph" yielded only two hits, while "polymorphic" yielded three (different) hits and "polymorphism" two (different again!) hits. A search for "crystal form" gave two hits and "crystal modifications" three (different) hits.

(ii) Searches for "pde5" and "PDE5" gave no hits, but "PDE 5" gave two hits (sildenafil and vardenafil, but not tadalafil, although the latter is present in the database). A complementary search for "phosphodiesterase" gave five hits (tadalafil plus four others—but neither sildenafil nor vardenafil!).

(iii) Amazingly, a search for "statin" gave no hits at all (although the statins are of course present in the database!)

(iv) Text inconsistencies meant that to find all mesylate salts one would have to search for "mesilate" and as well as "mesylate". (A substructure search using the mesylate counterion did not yield all mesylate salts in the database.)

Overall then, this is a valuable compendium for those working in the pharmaceutical and allied industries. Some may find the online version particularly useful, owing to its excellent structure searching capability, but a strong recommendation is withheld until the text searching and indexing function has been improved. Only then will the full potential of this work have been realised.

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Directory of World Chemical Producers. Chemical Information Services: Dallas, Texas. 2004. 2200 pp. £615. ISSN 1093-2933.

The latest edition of DWCP contains almost 157,000 products from over 18,000 manufacturers in 99 countries. It is an ideal source to locate raw materials, reagent intermediates, and final product chemicals and is much more comprehensive than most other databases. It includes all sectors of the chemical industry including bulk pharmaceuticals, fine

and speciality chemicals, agrochemicals, flavours and fragrances, colour chemicals, and radiochemicals.

The compendium is in three sections, bound in one mammoth volume. The main section (1156 pages) lists chemicals in alphabetical order by chemical name and gives the CAS registry number where known. Each entry is followed by a code for suppliers such as 35-EJT or 44-CKD. The first number is a code for the country (e.g. 35 is China), and the second series of letters pinpoints the manufacturer in that country—these are listed in section 3 (768 pages). For each supplier, the company name, address, phone, fax, website, and sometimes a contact number is given. Section 2 is a cross-reference of CAS number against chemical name. Section 1 also cross-references alternative names for chemicals and points the reader to the listed name.

The list of suppliers is comprehensive. In the UK section, the list ranges from laboratory catalogue suppliers such as Avocado through agrochemical companies (Bayer Cropscience), pharmaceuticals (Abbott), oil companies (Exxon Mobil), as well as the expected intermediates and fine chemical companies. I checked the contact names on some UK companies, and these were all accurate.

Recent company name changes have been incorporated. In fact, the directory lists in a four-page appendix all the mergers and acquisitions that took place in 2003 and the resultant name changes.

As expected these days, the listings for India and China are vast—over 5000 Chinese companies are listed. In contrast to a competitive directory, one cannot see the list of products for each company, but it is an easy job to go to the corresponding website for this.

In conclusion, this is an excellent directory which allows the quick location of commercial sources of chemicals on a worldwide basis. The disadvantage for those needing bulk (i.e., kilogram) amounts is that catalogue companies and agents (i.e., not primary manufacturers) are listed so that even if the chemical is only made by one company, it may appear as several suppliers. This is a minor inconvenience. This directory should be on the bookshelf of all chemical development departments and purchasing managers. It is not cheap, but is excellent and the information is as accurate as can be expected. It compares favourably with other directories, and its comprehensive nature means that this will be the first port of call for chemists designing synthetic routes and wishing to know the availability of raw materials.

Highly recommended!

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Phosgenations - A Handbook. By Livius Cotarca and Heiner Eckert. Wiley-VCH: Weinheim. 2004. 656 pp. £217.50. ISBN 3-527-29823-1.

To many chemists, "phosgene" and "phosgenation" are things they feel they would prefer to avoid. This book, written by two genuine experts in the field, challenges that somewhat emotional perspective by providing a balanced and comprehensive view of the state of the art in phosgenation chemistry up to mid-2003.

A brief introductory chapter intriguingly entitled "Contradictions" puts the perceived toxicity of phosgene and phosgene chemistry into context, and sets out the aims of the book. The next two chapters (Chapters 2 and 3) describe the key phosgenation reagents and evaluate them in terms of reactivity (including mechanistic considerations), physical properties, and physiological data. This encompasses phosgene, diphosgene and triphosgene, oxalyl chloride, 1,1-carbonyldiimadazole, dimethyl carbonate, and (more briefly) numerous other (>70) phosgene equivalents and substitutes. Of particular note are the descriptions of phosgene manufacturing processes, especially the "on demand" approach, in which phosgene is generated only when needed, so that inventories can be minimised. The main body of the book (Chapters 4 and 5) takes the form of a systematic and comprehensive review of phosgenation reactions, grouped into predominantly four major areas: chloroformylation (making chloroformates and carbamoyl chlorides), carbonylation (making isocyanates, carbamates, carbonates and ureas, as well as more complex heterocycles and, indeed, ketones), chlorination (making alkyl chlorides, acid chlorides, anhydrides, and esters), and dehydration (making cyanides, isocyanides, and carbodiimides). These chapters are packed with examples (there are more than 1700 references to the primary literature in these two chapters alone), each of which includes a reaction scheme and experimental details—something which seems to be increasingly rare in monographs. Chapter 5 is devoted to specific synthetic applications in active pharmaceutical ingredient and agrochemical manufacture, with a focus on taxol chemistry, as well as some examples from the polymer industry. Chapter 6 is an evaluation of phosgenation reactions (as opposed to reagents covered in Chapter 3) and makes some interesting direct comparisons of different chemistries. There then follows a short chapter on "Materials and Resources for Phosgenation Reagents" (Chapter 7), including a description of the "safety phosgenation" approach using commercially available cartridges prepacked with a defined amount of triphosgene to generate phosgene gas on demand. The book concludes with a chapter entitled "Monitoring Phosgene and Phosgene Substitutes: Analytical Methods" (Chapter 8), which considers both plant and lab analytical issues, and finally a very brief "Outlook" (Chapter 9), in which it is suggested that, in the drive for greener chemistry, phosgene itself might ultimately become redundant but that the term "phosgenation" may live on.

The organisation and ordering of the shorter chapters could be reconsidered in future editions of the book (for example, the contents of Chapters 7 and 8 might perhaps have been better placed within a larger, more holistic Chapter 2), and there are a number of minor typographical errors, but these criticisms are small and should not deter the reader. The encyclopaedic nature of this book, combined with its critical,

informed, and comprehensive approach, makes it a very valuable source for synthetic chemists in academia and in industry.

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Chemical Process Research: The Art of Practical Synthesis. Edited by Ahmed F. Abdel-Magid and John A. Ragan. ACS Symposium Series 870. American Chemical Society: Washington, DC. 2004. 211 pp. Price $125. ISBN 0-8412-3824-3.

This book is based on a symposium held at the 222nd National Meeting of the American Chemical Society: *The Role of Organic Synthesis in Early Clinical Drug Development*. It contains 11 chapters, which mainly consist of case studies in process research and development. The exceptions are an introductory chapter in which Ed Grabowski reflects on his 38 years in Process R&D with Merck, a review of synthetic approaches to retinoids, and an overview of the use of Design of Experiments (DoE) in Pharmaceutical Process R&D.

In many ways, this is just another book of process R&D case studies, and there are already quite a few similar books available, including book number 817 in the Symposium Series, *From Bench To Pilot Plant*. However, the examples presented are of a uniformly high standard and present a good cross-section of the sorts of problems and challenges faced when trying to develop safe, scaleable, cost-effective syntheses of pharmaceuticals. None of the material presented has been published before in full, although aspects of some of the syntheses have been published. Indeed it is interesting to note that six of the nine examples used to exemplify the use of DoE in process development were published in this journal, and one is previously unpublished.

Some of the projects described were carried out on 1−20 kilogram scale, whilst others were scaled up to several hundred kilograms; whilst there were often problems encountered on scale-up, these are described very much from a chemist's viewpoint as one would expect from the book's title. A wide variety of chemistry is covered including chiral alkylation, alicyclic chemistry, heterocyclic chemistry, Friedel−Crafts reactions, Suzuki couplings, photochemistry, Wittig−Wadsworth−Horner−Emmons reactions and protein synthesis to name but a few. Much of the chemistry involves adaptations, modifications, and new examples of reactions already in the literature, but there are also examples where completely new reactions have been developed to solve a particular problem. In addition there is some discussion of the use of reaction calorimetry and assessment of thermal hazards, but perhaps surprisingly, there is little or no mention of polymorphism. I felt that the overview of DoE could perhaps have been a little clearer, but the main points are covered and one or two that are often not covered. The examples used to exemplify the use of DoE, on the other hand, are well described and illustrate the benefits of using the DoE approach.

At $125 the overall price of the book is not prohibitive, but for 211 pages, it is on the high side. Overall, the book provides a useful addition to the growing library of process R&D case studies, and the editors are to be congratulated on the variety of chemistry covered. Recommended, with a slight reservation on the price.

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Riegel's Handbook of Industrial Chemistry, 10th Edition. Edited by James A. Kent. Kluwer Academic Publishers. Dordrecht, The Netherlands. 2003. IX + 1373 pp. $595 (607 Euro). ISBN 0-306-47411-5.

Riegel's Handbook, now in its 10th edition, has always focused on bulk and speciality chemicals and appeals to industrial chemists and chemical engineers. The authors of the 31 chapters are predominantly from the United States, with many industrial representatives from Dow. Thus, the "industry" in the title means U.S. industry, and despite comments by the editor in the preface, a global approach is lacking. Also the units used in several chapters are imperial rather than metric.

The coverage is of such diverse areas as Animal and Vegetable Fats, Oils and Waxes, and Industrial Cell Culture, a very wide scope indeed. Chapters of most interest to *Organic Process Research & Development* (OPRD) readers include the following:

• *Applied Statistical Methods and the Chemical Industry*. This new chapter provides an overview of the key aspects including simplex and factorial designs but does not cover principle component analysis.

• *Synthetic Organic Chemicals*. The 58 pages allocated to this vast subject are too few, and the authors have focused only on the basic industrial chemicals—the fine chemicals industry is not really covered. With only four main references, this chapter does not assist the reader in finding out more details of the chapter contents.

• *Dye Application, Manufacture of Dye Intermediates and Dyes*. This chapter is one of the best in the book and, at 81 pages, can do the subject justice; it is, however, weak on photographic chemicals.

• *Industrial Fermentation*. The 83 pages allotted allow a full discussion of this important topic.

• *Chemistry in the Pharmaceutical Industry*. Only 24 pages and nine references are in this short but interesting chapter. Future editions should expand this, possibly segregating medicinal chemistry from process R&D in separate chapters.

• *The Agrochemical Industry*. The 82 pages in this chapter are mostly tables, giving chemical structures and a small amount of information but only eight references overall.

Overall, the approach seems rather dated, with the emphasis on the heavy chemicals and large tonnage products, rather than the low volume, higher added value chemicals. There are surprising omissions (e.g., flavours and fragrances), and some chapters are too narrow (e.g., sugars and other sweeteners only covers carbohydrates, not artificial sweeteners). There is a tremendous variation in the style of the individual chapters; for example, some chapters have less than 10 references, others have over 200.

In conclusion, this comprehensive one-volume work is more appropriate for those working in the bulk and specialty chemicals industries and has little of interest for those in fine chemicals and pharmaceuticals.

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Analytical Method Validation and Instrument Performance Verification. Edited by Chung Chow Chan, Herman Lam, Y. C. Lee, and Xue-Ming Zhang. Wiley-Interscience: New York. 2004. 303 pp. £52.95/82.90 Euro/122 SFR. ISBN 0-471-25953-5.

Excellence in process chemistry would be impossible without good analytical methods to support it. The requirement to track and quantify impurities and degradants at ever more demanding threshold levels provides the analytical chemist with significant challenges. In the pharmaceutical and related industries, there are regulatory requirements for compliance with good analytical practices (GAPs) to support good manufacturing practices (GMPs) enabling development and product release. This book provides practical guidance and procedures for using tools and analytical methods in such a regulated laboratory setting.

As the title demonstrates, it focuses on validation and instrumentation verification. (The training aspect, which is essential for the provision of reliable analytical data, has been consciously omitted by the editors, since they believe that this will vary with organisational culture and strategy and is therefore best left to individual organisations.)

The editors are all based in Canada, but the author base is international, encompassing pharmaceutical companies, vendors, and contract manufacturers. The contributing companies are Eli Lilly (Canada, Germany, Japan, United States of America), Vicuron Pharmaceuticals (Italy), Agilent Technologies (Germany), GlaxoSmithKline (Canada), Patheon (Canada), and Novex Pharma (Canada).

The introductory chapter provides an overview of pharmaceutical development from discovery to market, and where and how the CMC analytical activities fit into this context. Chapters 2−5 discuss the validation of common analytical methods (potency, related substances, dissolution, and automated methods), dealing concisely and clearly with the concepts of accuracy, precision, specificity, linearity, and range. Chapters 6 and 7 describe validation practices for pharmaceutical excipients and heavy metals, while Chapter 8 is devoted to bioanalytical method validation.

The ensuing chapters (9−16) provide detailed guidance on instrument performance verification, covering UV−vis spectrophotometry, high-performance liquid chromatography (HPLC), capillary electrophoresis, LC−MS, Karl Fisher, pH meters, and environmental chambers. An overview of procurement, qualification, and calibration principles is also included (Chapter 10).

The book closes with chapters covering computer systems validation (with associated equipment qualification) and Excel spreadsheet validation, in recognition of the central role of computers in the modern analytical laboratory, and of course the associated regulations such as the FDA's 21CFR Part 11.

As would be expected, an ICH perspective is taken throughout the book. Differences in regulatory perspective from the three main regions (U.S.A., Europe, Japan) are highlighted where appropriate (particularly heavy metals and dissolution). There is a slight emphasis on the analysis of formulated drug product (not least because the analytical challenges are greatest there), but there is naturally much commonality with API analysis. Those chapters dealing with chromatographic methods focus on HPLC, but of course the same principles apply to thin-layer chromatography, which hopefully is not a forgotten quantitative technique in the pharmaceutical analytical laboratory.

The layout and style of the book make for a pleasurable read, being concise and pragmatic. Each chapter contains general requirements, the strategies and steps taken to perform these activities, and a section highlighting common practical problems and their solutions.

In conclusion, this is a very useful reference text for research and development scientists, quality assurance professionals, analytical laboratory managers, equipment users, and IT personnel working in the pharmaceutical and allied industries. It will increase the process chemist's awareness of what his or her analytical colleagues are grappling with daily (and perhaps might explain why it sometimes takes so long to get those results!). It is warmly recommended.

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