imately 50% for all runs to give an overall yield of 24%. TLC: R_f I, 0.15; II, 0.24.

Prothrombin Precursor 13–29 Cyclic Disulfide. A 13.1-mg (5.96 μmol) sample of the *S,S'*-bis-Acm fragment 13–29 was dissolved in 3 mL of 50% aqueous acetic acid. A 48-mg (150 μmol) sample of $Hg(OAc)_2$ was added to this solution and stirred for 4 h. The reaction mixture was then placed under an atmosphere of N_2, and 2 mL of mercaptoethanol was added to the reaction via syringe. After the mixture was stirred for 20 h, the mercuriomercaptide and excess mercaptoethanol were removed by gel filtration on a 1.7 × 30 cm Sephadex G-15 column equilibrated with 0.1 N acetic acid.[11] Fractions containing the peptide were lyophilized to give 7.1 mg (58%) of the deprotected peptide, which was immediately suspended in 160 mL of 0.1 N HOAc. The peptide completedly dissolved when the pH was adjusted to pH 8.5 with 3 N NH_4OH to give a peptide concentration of 0.02 mM. The solution was titrated with 3 mL of 0.010 N $K_3Fe(CN)_6$[12] and stirred for 1 h at room temperature. To remove the ferrocyanide, the pH was adjusted to 5.0 with 50% aqueous acetic acid and the solution stirred with 2 g of Amberlite IR-45 (Cl^- form) for 20 min. After filtration of the resin, the peptide was isolated by lyophilization. The peptide was desalted by gel filtration over a 2.6 × 65 cm Sephadex G-15 column equilibratated with 20% aqueous acetic acid. A 3.4-mg sample of product was obtained for an overall yield of 7%. TLC: R_f II, 0.31.

Molecular Weight Determination. The apparent molecular weight was estimated by gel permeation chromatography in 1.0 N acetic acid with a Sephadex G-25 column (1.1 × 45 cm). Molecular weight standards were ribonuclease A (13 700), insulin (5500), oxidized insulin B chain (3496), bovine prothrombin precursor fragment -9–9[19] (2074), encephalomyocarditis virus protein fragment 1501–1515[20] (1765), and bovine prothrombin precursor fragment 1–9[18] (1006). All eluants were monitored at 254 nm. The molecular weight determination was carried out as described by Andrews.[21]

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(19) Pottorf, R. S., unpublished results.
(20) Parks, G., unpublished results.
(21) Andrews, P. *Biochem. J.* **1965**, *96*, 595–606.

Book Reviews

Molecular Connectivity in Structure–Activity Studies. By Lemont B. Kier and Lowell H. Hall. Research Studies Press, Lechtworth, Hertfordshire, England. 1986. xvii + 262 pp. 15 × 24 cm. ISBN 0471 909831. $59.95.

One of the most abstract aspects of chemistry, especially organic chemistry as it relates to the design and study of biologically significant molecules, is the representation of structures in a manner relevant to the problem of biological activity. The objective of structure–activity studies in the general sense, and quantitative structure–activity relationships (QSAR) specifically, is to develop predictive constructs that can be used to design more effective compounds. This requires that structures of interest be reduced in some way to a numerical scale. The extension and use of graph theory and connectivity by Kier and Hall is a contemporary attempt at this very significant problem. These workers have published a number of papers and a book on this topic over the past decade and their work has been accepted by some and criticized by others. This book contains a review of the more significant papers, mostly by the authors, which have been published on the topic along with extensions of the use of connectivity in the expression of chemical bonding and structure.

The book begins with a preface by Professor Kier and a forward by Michael Tute of Pfizer Central Research. This is followed by nine chapters and appropriate indexes. Chapter 1 contains, to this reviewers knowledge, the most extensive discussion and development of the connectivity concept as proposed by Professors Kier and Hall. It begins with the idea of connection tables and is developed through Randic's use of connectivity as an index of branching in hydrocarbons. The idea of valence connectivity is then developed and this leads to the discussion in Chapter 2 of the correlation of the indexes with various physicochemical properties. Chapter 3 deals with topological information in the connectivity indexes and the use of specific connectivity indexes to rank compounds in terms of conformation, density, and flexibility is developed. Chapter 4 contains a discussion of electronic properties and connectivity. Here the Kier/Hall electronegativity scale is developed. The remainder of the book deals with connectivity and drug design. Chapter 5 is a very readable chapter dealing with statistical considerations. This is followed by strategies for the use of connectivity (Chapter 6), applications (Chapter 7), published studies (Chapter 8), and future directions (Chapter 9). This book represents considerable work on the part of the authors.

Since the book was written mainly for those involved in QSAR, comments based on more detailed considerations of the work are now presented. There is a phenomenological basis for QSAR studies and this is true of connectivity as developed by Professors Kier and Hall. There is certainly no theoretical basis for any of the material presented in this work. Most of the arguments presented for its validity are intuitive and in some cases border on conjecture and are rather shallow. For example, a flexibility index for alkanes is developed on pages 58 and 59 and then it is stated as not being useful for butane, 2-methylbutane, and pentane since the algorithm used to calculate the index has a minimum. On page 60 a table of values of the flexibility indexes is given for several alkanes. This table is footnoted with emperical rules for treating the index for several compounds to which the algorithm for various reasons cannot be applied in a straightforward manner.

Another difficult to understand discussion appears on pages 79–84. This deals with the use of connectivity to develop the Kier/Hall electronegativity scale. On page 82 a term E_{XY} is introduced, but not defined, as eq 10.

$$E^{\pi}_{xy} = .6\,E^{\sigma}_{x} + .6\,(E^{\sigma}_{y} - E^{\sigma}_{x}) \qquad (10)$$

This, of course, reduces to

$$E^{\pi}_{xy} = .6\,E^{\sigma}_{y}$$

which has not been defined. The identity in eq 10 is then substituted into a function that is used to interpret substituent effects in terms of connectivity. To this reviewers knowledge none of this material has been published and there are no journal references to work by Kier and Hall in the discussion that appears in the above referenced section.

It is accepted by everyone doing research in QSAR that this is a multivariable problem. So why do a large number of workers, including the authors of this book, still rely almost entirely on linear regression methods as the technique for model development? There are very appropriate uses of this technique in QSAR work but Chapter 5, "Statistical Considerations", while rather readable, has some very significant shortcomings and contains some very poor advice about the utility of multiple regression. There is a general rule of thumb that for such studies the ratio of independent variables to cases (compounds), *initially*, should be in the range of 1/5 or 1/4. This minimizes the possibility of

obtaining spurious models due to chance correlations, always a possibility with multiple regression. This advice is ignored by the authors. Then on page 131, it is stated "When the stepwise procedure seems inappropriate, then calculation of all possible regressions is the method of (sic) choice". Multiple regression should not be used at all in cases when the number of independent variables approaches the number of compounds.

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Cell Surface Receptors: A Short Course On Theory And Methods. By Lee E. Limbird. Martinus Nijhoff, Boston. 1986. xiii + 196 pp. 16 × 24 cm. ISBN 0-89838-740-X. $39.95.

There often exists a major gap between what is theoretically possible in a given area of technology and what is feasible from a practical standpoint. For instance, the limitations of the use of analogue recording techniques (sound compression, deterioration of storage format) as compared with laser digital methodology (the compact disc) have not precluded the preservation of many important events in musical history.

In pharmacology, the characterization of receptors and their interactions with various types of potential therapeutic agents are described in terms such as K_d and K_i, working designations that adequately and appropriately allow the process of drug design to successfully proceed. Beneath such innocuous and generally well understood terms lies a wealth of theory, much of which has changed very little since the beginning of the century, that is very controversial. In the present volume, Lee Limbird a former associate of Robert Lefkowitz, undertakes an explanation and elaboration of this theory and the methods used to delineate and identify receptors. Since many books of a similar ilk are far from being bedtime reading material, Dr. Limbird must be complimented on what has been achieved in the present volume for, overall, it is very good.

After discussing the various receptor theories and the all important (but still poorly understood) concept of efficacy, the author describes the various classical techniques used for determining such parameters as K_{d_a}, K_{d_b}, and K_{d_p} (dissociation constants for agonist, antagonist, and partial agonist, respectively), providing unusually clear examples from the classical work of Furchgott, Kenakin, and others. The remainder of the book (four chapters) is devoted to more molecular aspects of receptor function including radioligand binding techniques and receptor isolation and turnover.

The mathematical sections are easy to follow and the discussions attendant on the various types of data analysis very logical. In dealing with the more controversial areas, especially that related to the identification of receptor subtypes, there is, however, a tendency to be somewhat dogmatic and to oversimplify what still remains a very complex area, one in which much of the theory is not readily testable by the techniques currently available and where mathematical precepts are applied to an area where the vagaries of Nature still have significant impact. In the last decade, experimentation in the area of binding and receptor subtypes has moved from pencil and paper, through linear regression to relatively sophisticated (LIGAND, SCAFIT, EBDA, LUNDON) computerized curve fitting programs that are still unable to adequately address the very likely probability of receptor–receptor interactions and ternary complex kinetics. Statements such as "usually only two receptor subtypes have been demonstrated per ... category" (p 111—what about the $5HT_{1c}$ receptor?) and (p 133) that "rigorous proof for the existence of receptor subtypes requires ... a purified preparation" tend to illustrate these aspects of the volume. For instance, the latter statement has yet to be validated even for the well-characterized *Torpedo* nicotinic receptor, and the possibility that the contribution of associated membrane elements and coupling systems to the tertiary structure of the receptor is as important as the nature of the receptor protein per se cannot easily be dismissed. For instance does receptor subtype Y become type X when it is removed from its membrane microenvironment? In addition, while the tremendous usefulness of the technique cannot be discounted, radioligand binding, the methodology nearest to the primary receptor–ligand interaction is unable to address several physiological aspects of receptor function, notably efficacy and, in many instances, the ability to distinguish between agonists and antagonists. In the past, the overenthusiastic interpretation of binding data in a vacuum that precluded other, more physiologically relevant data has led the experimenter rather than the experiment to delineate receptor subtypes, an existentialist approach somewhat reminscent of that proposed by the controversial psychiatrist R. D. Laing, in relation to the origins of schizophrenia. The lack of the irrefutable, unambiguous identification of receptor subtypes as finite entities has not significantly hindered the drug discovery process. Knowledge of the primary structure of the *Torpedo* receptor while an outstanding feat of modern research has had little, if any, impact on compound design in this area.

Such iconoclastic considerations apart, Dr. Limbird has suceeded in writing a excellent overview of this complex area with its good points well balancing its weaker ones. From a practical viewpoint, the author's use of EC_{50} (p 82) instead of the more commonly used IC_{50} is unfortunate as is the failure to emphasize, irrespective of the origin of the mathematical aspects of the theory (p 69), that because the Scatchard and Rosenthal plots of saturation isotherms contain the term "bound" on both the ordinate and abcissa, linear regression analysis of such data is inappropriate, if not wrong. The new concept of inverse agonists (antagonists with negative efficacy) is also overlooked. Another minor point that has caused major problems in validating receptor binding assays and which the author cites as necessary without any accompanying caveats, is to demonstrate similar time courses for the elicitation of a physiological response by a given compound and the time required for binding of its radioactive counterpart (p 88). In the majority of instances, this relationship cannot be proven, and it is an anomaly of the binding methodology that in some instances hours are required for binding while the related physiological response occurs in seconds. The reader should bear in mind that facts do not always follow theory and to the open minded the theory, rather than the experiment, requires reappraisal. The computer is no substitute for biological objectivity and rigorousness.

While the index for the book is sporadic and verges on useless, the volume is generally well-produced (only three typos noted) in addition to those mentioned in an insert on typographics. This volume, together with a copy of *Neurotransmitter Receptor Binding* (Yamamura et al., 2nd ed., Raven, New York, 1985) will ensure that the reader is well equipped to follow current trends in receptor research.

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Neuromethods. Series 1: Neurochemistry. Volume 4: Receptor Binding. Edited by A. A. Boulton, G. B. Baker, and P. D. Hrdina. Humana Press, Clifton, New Jersey. 1986. xix + 584 pp. 15.5 × 23.5 cm. ISBN 0-89603-078-4. $64.50.

Receptors are today where enzymes were 25 years ago. Although this book helps close the gap, the dramatic advances being made in receptor purification and genetic sequencing are omitted. The 15 chapters cover the ligand-binding properties of receptors for catecholamines, serotonin, tryptamine, acetylcholine (muscarinic), amino acids, GABA (γ-aminobutyric acid), peptides, opiates, purines, benzodiazepines, antidepressants, phencyclidine, and amphetamine. The introductory chapter by P. D. Hrdina has elementary appeal, but might have more indelibly stressed the principle that it is *not the ^{3}H-ligand which defines the receptor but rather the rank order of drugs which inhibit that binding which defines the receptor.* This principle could prevent many an innocent medicinal chemist from falling into the same trap that many of we biologists have encountered. For example, [^{3}H]spiperone binding is most effectively inhibited in striatal tissue by dopamine, indicating that [^{3}H]spiperone binds to dopamine receptors; in the frontal cortex, however, [^{3}H]spiperone is most effectively inhibited by serotonin, indicating that in this tissue [^{3}H]spiperone binds to serotonin receptors. Although β-adre-

noceptors and acetylcholine receptors are in the most advanced stages of all the neurotransmitter receptors, the two chapters on these topics tend to be more introductory and historical rather than tabulatory, analytic, or selective. Such selection is essential for anybody to survive the avalanche of papers on receptors. S. J. Peroutka's chapter on serotonin receptors attempts to do this with an appropriate selection of data. The tryptamine chapter by K. J. Kellar and C. S. Cascio also does this, but biological correlations would have assisted. The amino acids chapter by J. W. Ferkany and J. T. Coyle is thorough, as is that by K. G. Lloyd on GABA receptors. The chapters on opiate sites (P. L. Wood), purine sites (M. Williams), benzodiazepine receptors (I. L. Martin), antidepressant sites (P. D. Hrdina), phencyclidine and amphetamine receptor sites are all very well done. Since all the different receptors are in radically different stages of being identified, characterized, purified, etc., it is not surprising that the general plan of each chapter tends to be very different. Some chapters stress methods, others stress computer-assisted analysis, others survey the large literature, while an occasional chapter merely mentions the author's current research as of 1983 when presumably this book was assembled. Editors A. A. Boulton, G. B. Baker, and P. D. Hrdina have done a commendable task in preparing this book. In some cases, such as the chapter on benzodiazepines, the information is "all you need to know", but in other cases the reader is left with an appetite whetting for an encore by these editors.

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