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Book Review

Design and Optimization in Organic Synthesis.
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I once was at a lecture, given by a top organic synthetic chemist from a country known for its work ethic and obedience of students. At the end of the lecture, I asked the question whether the professor had ever considered using experimental design when optimizing his syntheses. The answer came, "I have many students, they work very hard." There goes one sale, perhaps, but this is a book for those other synthetic chemists not blessed with an inexhaustible supply of compliant students and who want to perform a minimum set of experiments to obtain the best optimum and in doing so learn a lot about their systems. The first edition was published in 1992, and as Trevor Laird writes in his foreword about the time since then, "... there have probably been more publications on statistical methods of optimization applied to organic chemistry than all the previous decades put together." To what extent organic chemists are reading these papers I do not know, but where it matters, in industry, there is a good realization that the methods described in this book do lead to demonstrable bottom-line savings.

The second edition is updated and revised. The authors are pleased to write that the new edition is no longer than the first, in part, by adoption of a smaller font, which for the older reader is not an entirely welcome change. There is a general rigorous approach that makes this a comprehensive textbook, although those who want a recipe book with the how rather than the why might be daunted by the maths. Chapter 14, which is a summary of strategies for exploring the experimental space, will be a welcome relief for these readers.

The first two chapters are a good introduction to the subject, with explanations of the nature of a desirable synthesis and how the system might be modelled and experimented with. The reader is led quite gently into the concepts of designing experiments. In one of the introductory chapters, it is shown how the basic quadratic model arises from a second-order Taylor expansion of the response as a function of the experimental variables, something that is not always found in other textbooks, but which is a fundamental rationale of the approach. The organization of the following chapters goes through screening designs followed by optimizations. Factorial designs are described in detail with due attention to fractionation as befits problems with many factors. Plackett–Burman and D-optimal designs are also introduced in Chapter 7. Optimization by steepest ascent leads the methods, but it and the simplex method that follows seem to be warm-up acts for a continuation of response surface methodology. Usefully covered is what to do with more than one response, for example, yield and selectivity. Chapter 13 demonstrates the utility of simple kinetic modelling.

In the next part of the book, after the summary mentioned above, the concept of reaction space is introduced and then principal components analysis in a chapter entitled "Principal properties." Calling scores and loadings of a principal component 'principal properties' follows a referenced 1996 paper, although I am not entirely happy with this nomenclature. Chapters follow on the selection of solvents (or other system parameters), multivariate regression methods for quantitative studies, discrete valued variables, and once again optimization of many response variables. The final didactic chapter considers

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the problem of order of introducing reagents into one-pot syntheses. Read Section 21.4, which is a note on ad hoc explanations based on limited data. The example of the self-condensation of a butanone using titanium tetrachloride and a tertiary amine is excellent, with yields from 1.5% to 66.4% depending on the order of introduction of the three reagents. Plausible explanations for any of the cyclic permutations of orders of addition being optimum are given. Without all the data, a completely false explanation could be given. The results of a given experiment might be consistent with a particular mechanism, but the extent to which the observations support the mechanism depends on all the other mechanisms that might operate, and to what degree the observations also support them. This brings me to one of the great strengths of the book, the examples are of real syntheses with real data and should resonate with organic chemists who are having a hard time with the matrices and vectors. Also read the concluding remarks in the final chapter—there are sensible words for any reader.

Apart from the small type, the production of the text is of quality, with a couple of exceptions. The Preface assures the reader that some of the errors in the first edition have been corrected and that the figures and other drawings have been re-drawn. Unfortunately, there is a rather glaring misspelling of temperature in the figure in the middle of page 1, and a grammatical error in the title of Chapter 20 (responses variables).

In conclusion, this is a unique book and should be mandatory reading for all PhD synthetic chemists.

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