Strategies and Tactics in Organic Synthesis

Edited by

THOMAS LINDBERG

STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS

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Thomas Lindberg
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PREFACE

The inspiration for this book came from an article by I. Ernest on R. B. Woodward's prostaglandin synthesis.[1] In his paper Ernest describes the trials and tribulations that had to be endured before success was finally attained. As Ernest states in his introduction ". . . the sober and dispassionate form of today's scientific publications does not leave much room to express or even suggest the creative motivation and atmosphere in which ideas originate and are further developed." At that time there were no books in which chemists described their syntheses in the way that Ernest did in his paper. I felt that such a book would be especially valuable to students learning organic synthesis. To try and remedy this situation I asked a group of outstanding chemists to give a ". . . sincere and more or less complete account of the chronological development of ideas and experimentation which finally led to the solution of the problem."

Many syntheses only appear as terse communications in journals. Very rarely do chemists discuss the blind alleys and dead ends that were encountered in a synthesis. This is unfortunate for the student who wants to learn about synthesis. I think many students have the mistaken impression that organic chemists conceive a brilliant "paper" synthesis in 1 hour and hand it over to their graduate students who see it through to completion without any problems or difficulties. However, in almost every synthesis there are problems to be overcome and obstacles to be surmounted. The outstanding chemists in this book have done an excellent job in describing the strategies and tactics that they have used in synthesis. One can easily see that the road from a "paper" synthesis to the final product is a long and difficult one. I believe that students and

[1]Ernest, I. (1976). *Agnew. Chem. Int. Ed. Engl.* **15**, No.4, 207.

chemists will find these accounts of synthesis to be interesting and informative.

Finally, I would like to express my sincere appreciation to the contributors, for without their efforts there would be no book.

Thomas Lindberg

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Amos B. Smith III

Chapter 1

THEME AND VARIATIONS: A SYNTHESIS OF SUPERPHANE*,†

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I. Introduction, Goals, and Synthetic Philosophy

The word cyclophane designates the general class of bridged aromatic compounds. The field was pioneered by Cram and Steinberg,[1] who first synthesized [2.2]paracyclophane (**1**) and who invented the nomenclature used for these compounds. The numbers in the brackets indicate how many

* I have long felt that painting and the composition of music, more than most other academic disciplines, have much in common with the conceptional aspects of scientific research. The intellectual ferment leading to the creation of a painting or a musical composition seems quite akin to the intellectual ferment leading to the creation of a new idea, a new concept, or a new principle in science. Just as the style of eighteenth century music is replete with compositions that are a theme with variations, so also are scientific ideas often exploited by variations to discover the limits and generality of the idea. This aside is offered in explanation of the title.

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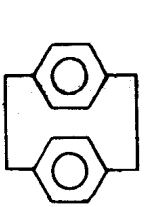
bridges there are and how many bridging atoms in each bridge. Although the prefixes ortho-, meta-, and para- continue to be used, the positions of bridging are more commonly indicated by numbers in parentheses following the brackets. Thus, [2.2]paracyclophane can equally as well be designated as [2.2](1,4)cyclophane. Where all of the bridges have the same number of bridging atoms, the number of bridges may be indicated by a subscript number. For example, structure **5** is $[2_3](1,3,5)$cyclophane.



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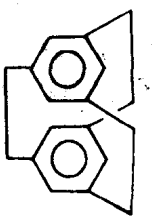

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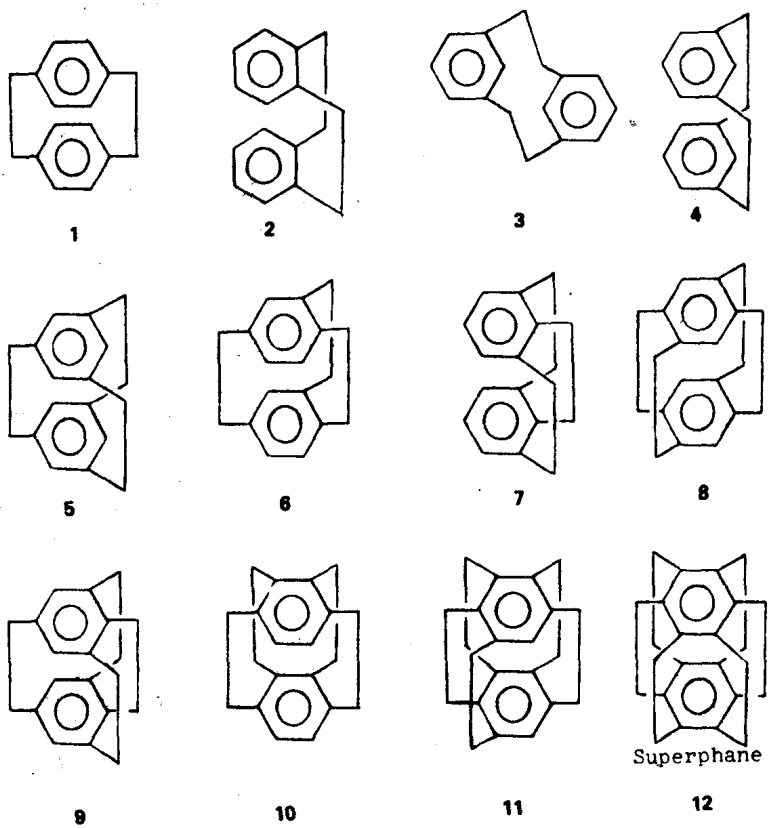
From the very beginning of his work, Cram appreciated the great value such rigid, caged structures would have in providing insight into questions of ring strain, bond stretching, bond angle distortion, aromatic ring deformation, and π–π orbital interactions. The extremes for such behavior are to be found in examples where the aromatic rings are forced together face-to-face in the closest proximity possible. Thus the multibridged cyclophanes having two bridging atoms in each bridge are of special interest. There are only 12 such possible $[2_n]$cyclophanes with the same substitution pattern in each deck. These are shown in Scheme 1.

At the time we began the work under discussion only compounds **1**, **2**, **3**, **5** and **6** shown in Scheme 1 were known. It was important to devise syntheses for the remaining members of the series so that a complete correlation could be made of the variations in physical properties with variations in geometry, particularly in the distance between aromatic decks. It was already well appreciated that molecules such as [2.2]paracyclophane exhibit a strong, between decks, π–π orbital interaction, and how much this interaction would be intensified as the distance between decks was shortened was of prime interest. For this purpose the molecule most desired was $[2_6]$-(1,2,3,4,5,6)-cyclophane (**12**), bearing the trivial name superphane.[2] Superphane is the ultimate in bridging in the series, is the most symmetrical, and should have the aromatic rings forced in closer proximity than for any other member.

Before discussing possible synthetic routes to the multibridged $[2_n]$cyclophanes and superphane, some basic points in the philosophy of designing any synthesis need to be restated. A synthesis should be designed to be efficient, short, and, if possible, display either novel chemistry or new applications of known chemistry. Because our purpose in making these molecules was to

examine their physical and chemical properties, we had an additional requirement: the synthesis must be convenient and practical enough to provide sufficient quantities for studying these properties. Specifically, we felt that a good synthesis should be capable of providing at least 1 g of the final product.

This latter requirement of designing a synthesis to provide the final product in adequate quantities, whether it be for biological testing, studying its chemical and physical properties, or preparing analogs, is frequently neglected in the design of syntheses and deserves greater emphasis. All too often in the competition for syntheses of natural products or novel structures, success is judged by who is the first to accomplish the goal rather than whether a useful synthesis has been developed. Developing new syntheses that fail to provide the target molecule in useful quantity may have heuristic value, but modern



SCHEME 1. Possible symmetrical [2$_n$]cyclophanes. (Although **3** and **4** appear to be conformational isomers, the energy barrier for interconversion is sufficiently high that the separate structures can be isolated.)

synthetic chemistry should now have the ability to advance beyond that point. One of the requirements for any significant new synthesis should be that it provide the desired product in adequate quantity to satisfy the avowed purposes for which the synthesis was undertaken.

Also, before designing the synthesis of a particular molecule, the status of the field needs to be examined to ascertain whether the goal can be reached efficiently by simple extension of known methods or whether a completely new approach is needed. The first two decades of cyclophane syntheses were dominated by two methods: (1) the Wurtz coupling reaction [3] and (2) the 1,6-elimination of *p*-methylbenzylammonium hydroxides.[4] Around 1970 the dithiacyclophane route to cyclophanes was introduced and quickly became an important general method for making all types of cyclophanes.[5–7] Then, in 1972, Hopf introduced a Diels–Alder method for making polysubstituted [2.2]paracyclophanes, which had important advantages of convenience and adaptability for preparing large quantities.[8]

Thus valuable methods for synthesizing cyclophanes were already at hand. However, to apply these to the synthesis of the highly bridged cyclophanes looked to be a cumbersome and tedious task, involving many steps for the introduction of each bridge beyond those of [2.2]paracyclophane itself.

II. Theme

The present account, describing a trail of research leading to the synthesis of superphane, begins in the fall of 1974 with a remarkable graduate student, Richard T. Gray. At the time, our interest in a synthesis of superphane was somewhat remote.

Gray had begun his doctoral research on a project directed toward a synthesis of cyclophanes having cyclooctatetraene units as decks, a project not yet accomplished but still of much interest. My suggestion to Gray regarding a possible route to the desired cyclooctatetraene cyclophane involved first synthesizing $[2_4](1,2,4,5)$cyclophane (**8**) as a precursor. Based on our experience in developing the dithiacyclophane route to cyclophanes, it seemed that this synthetic method would be appropriate for a synthesis of $[2_4](1,2,4,5)$-cyclophane. In fact, as shown in Scheme 2, Gray's first successful synthesis of $[2_4](1,2,4,5)$cyclophane (**8**) followed this approach.[9]

While pursuing experimentally the synthetic route shown in Scheme 2, Gray, as is typical for a good graduate student, gave serious thought to how to improve on his mentor's proposal. As a result he conceived the idea of a one-step synthesis of $[2_4](1,2,4,5)$cyclophane (**8**), as outlined in Scheme 3. The exploitation of Gray's idea led to some false starts and some disappointments, as will be pointed out, but eventually to a new, general method for preparing