Organic Chemistry Masterclasses

By S. Ranganathan
Foreword

The Masterclass series of eBooks published by the Indian Academy of Sciences, Bengaluru brings together pedagogical articles on single broad topics reproduced from Resonance, Journal of Science Education that is published monthly by the Academy since January 1996. Primarily directed at students and teachers at the undergraduate level, the journal has brought out a wide spectrum of articles in a range of scientific disciplines. Articles in the journal are written in a style that makes them appealing to readers from diverse backgrounds, and in addition, they provide a useful source of instruction that is not always available in textbooks.

It is fitting that the first book in this series, Organic Chemistry Masterclasses, is by a legendary teacher, Professor Subramania Ranganathan, highly acclaimed and distinguished Organic Chemist. Ranga, as he is fondly known to generations of students at the IIT Kanpur where he taught for over three decades, has been a regular contributor to Resonance and his articles enjoy wide popularity among the journal’s readership. Indeed his first contribution to Resonance was in the very first issue of the journal.

We are also delighted that this collection of over fifteen articles, reformatted as an eBook will mark his 80th birthday. Those of us who were fortunate to have learned some of these topics as he was devising ways of teaching them will be very pleased that some of Ranga’s masterly instructions can reach a much wider audience through this means. While the book will primarily be available in a digital format, like the earlier series Echoes from Resonance, there will also be a limited print run to augment visibility.

Ram Ramaswamy
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About the Author

Prof. Subramania Ranganathan is *Distinguished Scientist* at the Organic Chemistry Division of the Indian Institute of Chemical Technology, Hyderabad.

Ranga, as he is fondly called by his several generations of students, received his B.Sc and M.Sc (1957), both from Madras University. After a brief stint in the Biochemistry Department at Central Leather Research Institute (CLRI), Chennai, he pursued his studies at the Ohio State University where he held the Sloan Kettering Foundation Fellowship for three years. He was elected to the *Phi Beta Kappa* Society and received his PhD there in 1962, under the guidance of Harold Shechter. He then worked with R B Woodward at Harvard University (1962–1964). From 1964–1966 he was a member of the Woodward Research Institute at Basel, Switzerland and worked on the total synthesis of Cephalosporin C, which constituted Prof. Woodward’s Nobel Lecture. While working with Woodward, Ranga played a key experimental role in the development of the Woodward–Hoffmann Rules in the course of Vitamin B₁₂ synthesis.

Prof. Ranganathan joined the Chemistry Department, IIT Kanpur in 1966 and held various positions including Professor, Head of the Department, and Dean (Professor-in-Charge) before retiring in 1994. He was INSA Senior Scientist (1994–1999), first at RRL Trivandrum and then at Indian Institute of Chemical Technology (IITC), Hyderabad where he has been Honorary Scientist since. His major research contributions involve organic synthesis, reaction mechanisms, protein engineering, crafting of new reagents and designing of new reactions, non-covalent self-assembly, protein evolution, role of zinc in molecular biology, and biosilicification. During his long research career, he has authored/co-authored over 200 peer reviewed papers and a dozen books, including the very popular (among students, for sure) *Current Organic Chemistry Highlights* that provided a critical analysis of the literature every month.

Prof. Ranganathan has been conferred many prestigious awards that include the Basudev Banerjee Medal and Prize (1975), S S Bhatnagar Award (1977), Silver Medal by the Chemical Research Society of India (2000), R C Mehrotra Endowment Gold Medal (2000), and Lifetime Achievement Award by the Chemical Research Society of India (2006). He also received lectureship awards such as the Prof. K Venkataraman Lecturer (1979), UGC National Lecturer (1979–1980), Prof. A B Kulkarni Lecturer (1982); Prof. N V Subba Rao Memorial Lecturer (1985); SERC National Lecturer (1991); Prof. T R Seshadri Memorial Lecturer (1993); Maitreyi Memorial Lecturer (1994); and DAE-Raman Lecturer (2001). He is an elected Fellow
of the Indian Academy of Sciences, Bangalore (1975), Indian National Science Academy, New Delhi (1981) and the National Academy of Sciences (India), Allahabad (1991). He has been Honorary Professor at the Jawaharlal Nehru Centre for Advanced Scientific Research (1999) and was President of the Indian Society of Bio-organic Chemists (1994–2001).
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Fascinating Organic Transformations:
Rational Mechanistic Analysis*

The Wagner Meerwein Rearrangement and the Wandering Bonds

A carbocation can stabilize itself by a series of C-H and C-C shifts to reach the most stable form. Several examples are shown in which relatively strained systems upon such cationic rearrangements produce diamondoid systems.

The Ganges flows to neutralize the water potential, electricity flows to compensate an electron gradient. Naturally therefore, an electron deficiency in a carbon framework generates a “bond flow”. This phenomenon, in its most simple representation (Figure 1), is the Wagner Meerwein rearrangement.

Figure 1. The Wagner Meerwein rearrangement.

A natural property of an electron deficient centre is to make the system dynamic, thus opening the possibilities for charge dissipation. This can be illustrated with what is called the Grotus mechanism (Figure 2). One can see how effectively the proton excess on the left side is transmitted by the medium to the right. Similarly, charge deficiency created at a location can be evenly, and quite effectively, spread swiftly.

Figure 2. The Grotus mechanism.

The process that takes place in the norbornylcation system (1, Figure 3), leads to a total charge dissipation, as shown in Figure 4.

The Series on Fascinating Organic Transformations: Rational Mechanistic Analysis

Rational analysis of organic reaction mechanisms was initiated in the early decades of this century, when the now well-known ‘arrow pushing’* to describe the flow of an electron pair, gained popularity among chemists. Subsequently, in the 1930–1960 period, the combined efforts of several great organic chemists established mechanistic organic chemistry on a firm ground. Every organic transformation is, however, unique, in the sense that there is always some twist when you carry out a new reaction (or else many of us would have been out of business!). Thus, in order to understand new transformations, one must have a very good appreciation of the basic principles of mechanistic analysis.

Many of us feel that at the undergraduate level rational mechanistic analyses of exciting transformations are seldom taught. The examples available in many textbooks tend to be somewhat routine (and perhaps boring), and many good examples are left out. S Ranganathan, one of the most popular organic chemistry teachers at IIT, Kanpur for almost three decades, has put together for Resonance readers, six examples that demonstrate a step-by-step approach to rationalize fascinating organic transformations.

In this series of articles, he will cover Wagner Meerwein rearrangement, molecular self-assembly, Woodward–Hoffmann rules, ‘lone pairs’, von Richter reaction and synthesis vs. biosynthesis of indigo. We are certain that students and teachers alike will enjoy the simple and classroom-type discussions provided in each of these examples.

Uday Maitra

*When organic chemists started using curved arrows a well-known chemist reportedly remarked: “Curved arrows never hit the target”.

Figures 3 & 4 permit the definition of very basic aspects associated with this type of bond migrations. By definition, whenever a sigma bond (other than a C-H bond) shifts, it is called the Wagner Meerwein shift [WM]. The hydrogen sigma bond migrations are denoted as proximate [1,2] or through-bridge[1,3] shifts.

The WM shift in substituted derivatives of 1 [1, 2 ⇄ 2, 1] takes place with incredible speed*, of the order of ≈10^{12} \text{sec}^{-1} at room temperature [RT]. This is an estimate, since

* The structure of the unsubstituted 2-norbornyl cation is highly controversial. Do 1 and 2 rapidly interconvert or does the ion exist as an intermediate ‘non-classical’ form? Spectroscopic and theoretical studies are currently interpreted in favour of the latter proposal. However, tertiary derivatives have classical structures and undergo fast WM shifts.
no ‘eye’ can see this because of the swiftness of the operation. We enjoy the video because we cannot ‘see’ it! The frames move at a rate faster than the eye can discern \( \approx 16 \text{ frames sec}^{-1} \); thus one frame merges into another creating an illusion of continuity.

**Figures 3 & 4. Rearrangements in the norbornyl cation system.**

At one time the WM in 1 was called the windshield wiper [WW] effect. The WW of a car operates (if at all!) at the rate of one per second. So one can see how rapid the WM in 1 is. The [1,3] is slower \( \approx 10^8 \text{ sec}^{-1} \), and the [1,2] even more so \( \approx 10^6 \text{ sec}^{-1} \). The last two could be focused to the eye of the NMR which can distinguish events that take place at \( 10^4 \text{ sec}^{-1} \). So, cooling down the norbornyl cation 1 can bring down the rates to lie in the vision range of NMR and this has been done. Charge dissipation naturally opens avenues for equilibration leading to stable systems from not-so-stable precursor cations. This is well-documented in organic chemistry, and in this presentation is taken to esoteric heights leading to options for making diamond!
A profile of diamond structure is shown in Figure 5. Note how beautifully the chair cyclohexanes are stacked leading to a thermodynamically stable constellation. This would imply that such shuffling of bonds can lead to diamondoids from unrelated precursors having the same carbon framework. This was dramatically illustrated with the transformation of 2 - readily formed by hydrogenation of cyclopentadiene dimer – to adamantane (3) in excellent yields, thus making a rather expensive compound very commonplace! Like in a ‘random walk jogging’ we can start in several directions from 2 and reach 3. We have shown here one such pathway (Figure 6). One can trace other pathways and doing so can be fun! To reinforce the notion of equilibration leading to diamondoids, another example is given in Figure 7, wherein the aesthetically pleasing C-10 triquinane (4) possessing a three-fold axis of symmetry, is transformed to adamantane (3).
While adamantane (3) was known before the era of the understanding of carbocation rearrangements, its logical homolog 5, notionally formed by placement of additional chair cyclohexanes was unknown. The fascination for this molecule was such that it was the motif for an international congress (IUPAC Conference in 1963) and the compound itself was named, before birth, as Congressane; additionally, a reward was offered for anyone who could make it before the next congress, scheduled in two years.

But no one could claim this reward! The facile synthesis of adamantane (3) by wandering of sigma bonds opened up possibilities, not only for congressane, but also for higher members of the family. In the event, congressane, now formally called diamantane (5) was magically made, in excellent yields from 6 and 7 which are easily derived from the dimerization of the C-7 bicycloheptadiene. Indeed, dimer 6 gave a 90% yield of 5 under equilibrating conditions! The transformation of 6 and 7 to diamantane (5) has been rationalized in Figure 8 and Figure 9, respectively, by pathways precisely similar to those discussed earlier. A recent addition to this family is triamantane (8), which has a true tetrahedral carbon, attached to four other carbons as in diamond.
Based on the above principles and illustrations, one could develop a computer program to identify appropriate precursors for a specific diamondoid.

Even in the case of C-10 adamantane (3), the number of possible C-10 precursors would be huge. For higher members of the series the options could be astronomical. A reasonable guess is that it would take 500-1000 such rearrangements for substances that would have the properties of diamond. Thus it is obvious that if the carbocation strategy is to be adopted to make diamondoids, a listing of all possible precursors be secured using a computer and based on the three pathways involved.
The task could be simplified by incorporating restrictions in the program. Although using this strategy for diamond appears far fetched, it could lead to novel diamondoids and related precursors having desirable properties. The iterative pattern is simple, and each generation produces three possibilities, as shown in Figure 11 (the three arrows here represent, WM, [1,3] and [1,2]).

**Suggested Reading**


Fascinating Organic Transformations*

The Ubiquitous Hydrogen Bond

Hydrogen bonds can transform simple molecules into beautiful architectures. This is well-illustrated in this article.

Organic transformations are generally assumed to involve reactions in which covalent bonds are made, broken or rearranged. We can think of a wider connotation for the term ‘transformation’ if we include changes brought about by non-covalent forces. Although such interactions are weaker, the transformations can be quite dramatic, in terms of resulting structures and properties. In this article, let us consider the most important non-covalent interaction, viz., the hydrogen bond and the wide variety of ways in which this bond can lead to almost magical transformations of even simple organic molecules.

Definition of a Hydrogen Bond

A hydrogen atom bonded to an electronegative atom like oxygen or nitrogen has a small positive charge, due to bond polarization. It can therefore have an attractive interaction with any electron rich group in the vicinity. Usually, electronegative atoms have residual lone pairs available for such interaction. Hence, a fragment such as X-H . . .Y, in which both X and Y are electronegative atoms, has a stabilizing interaction. This weak force is called the hydrogen bond.

Electrostatic interactions are quite common in molecules with uneven charge distributions. The importance given to hydrogen bonds is due to several reasons. Hydrogen bonds are ubiquitous and easily recognisable. Importantly, the interaction has sufficient directional character for it to be classified as a ‘bond’. The X-H unit prefers to be collinear with the electron pair on Y.

But some flexibility is allowed, since the interaction is not quite strong (especially compared to covalent bonds). The directionality of hydrogen bonding is responsible for creating beautiful structural frameworks from simple building blocks. It is possible to create chains, sheets, helices, three-dimensional networks, etc., using hydrogen bonds as the principal glue. The resultant shapes are not merely aesthetically pleasing but the transformed molecules become endowed with remarkable properties as a result of hydrogen bonding.

The importance of the hydrogen bond was stated clearly and forcefully as early as in 1939 by Linus Pauling in the first edition of his celebrated book *The Nature of the Chemical Bond*:

“Although the hydrogen bond is not a strong bond (its bond energy, that is, being in most cases in the range 2 to 10 kcal/mol) the energy of the reaction X-H+Y → XH...Y, it has great significance in determining the properties of substances. Because of its small bond energy and the small activation energy involved in its transformation and rupture, the hydrogen bond is especially suited to play a part in reactions occurring at normal temperatures. It has been recognized that hydrogen bonds restrain protein molecules to their native configurations, and I believe that as the methods of structural chemistry are further applied to physiological problems, it will be found that the significance of the hydrogen bond for physiology is greater than that of any other single structural feature”.

Seldom in science has any statement been so prophetic. In the intervening five and a half decades, the mural that encompasses the domain of hydrogen bonds has covered a wide area. Even a reasonable coverage of the theme in these pages would be difficult. Faced with this predicament, only a few representative examples are provided to highlight the art and science in hydrogen bonding networks.

**Hydrogen Bonding in Water**

As the most abundant liquid on the earth’s surface, water is vital for the support of life. Even though the molecular formula of water is H\textsubscript{2}O, it does not exhibit properties which you would expect from comparison with H\textsubscript{2}S (or with NH\textsubscript{3})! Strong hydrogen bonding in water increases the density, the melting and boiling points, and lowers the acidity as proton transfer interferes with the hydrogen bonded network. Hydrogen bonding in water is also primarily responsible for the well-known fact that water and oil do not mix. The ‘oiling-out’ effect is schematically shown in *Figure 1*.

![Figure 1. A dispersion of oil in water quickly gets oiled out.](image-url)
We showed how diamondoids can be made using wandering sigma bonds in a previous article (Resonance, Vol. 1, No. 1, 1996). It may come as a surprise that water can form similar structures entirely through hydrogen bonds. The water molecule has two donor sites (the O-H bonds), and two acceptor sites (the lone pairs on the O atom). This creates a perfect setup for a self-assembly to diamondoid structures, which is conceptually presented in Figure 2. It can be estimated that the transformation of 18 g of H\textsubscript{2}O to 18 g of water can give rise to ca. 50 kJ stabilization. Such high stabilization to weight ratio cannot be matched through other non-covalent interactions.

![Figure 2. Assembly of water molecules in diamondoids.](image)

The existence of carboxylic acids as dimers, even in the gas phase, is also because of strong hydrogen bonding. Hydrogen bonding can also significantly affect chemical reactivities.

**Hydrogen Bonding in Biological Systems**

Life in simple terms represents a symbiosis of the functional systems (enzymes, proteins) and the information system (DNA, RNA) driven by regulated external energy inputs. It is interesting to see that one of the main structural motifs of proteins and enzymes, the $\alpha$-helix, is stabilized by intrachain hydrogen-bonds which are parallel to the helix axis (Figure 3), whereas, the double-helical structure of DNA has the base-pairing hydrogen bonds perpendicular to the helix axis (Figure 4). It is pertinent to mention here that in proteins there is another distinct sheet like structural element (a $\beta$-sheet) which is also produced by hydrogen-bonding between extended chains of polypeptides.
Hydrogen Bonding in Biomimetic* Systems

The Watson-Crick DNA duplex highlighted the importance of the specificity of hydrogen bonding between the base pairs Adenine (A) and Thymine (T), and Guanine (G) and Cytosine (C), (shown in Figure 5) in determining the properties of DNA. The proposal stimulated interest in creating other sets of molecules which bind specifically to each other, leading to the birth of a new discipline called ‘Molecular Recognition’.

Of the thousands of examples available in this area, the most imaginative perhaps is the molecular replication model invented by Rebek. Avoiding the molecular complexity involved, the principle can be best understood by a model for replication shown in Figure 6. A template, drawn as a hacksaw, is shown on the left of this figure. It carries complementary hydrogen bonding sites for two molecular pieces. As a result of hydrogen bonding, the two partners are ideally aligned so that they can react to form a covalent bond. Breaking of the hydrogen bonds with the template would release the daughter molecule and let the template carry on the

* ' The word ‘biomimetic’, coined by Ronald Breslow, essentially means imitating (or mimicking) a biological process (or a key part of it) using simple organic and/or inorganic molecules and complexes.
Organic Chemistry Masterclasses

catalysis. In the extreme example in which the template and the daughter are the same, the molecules effectively self-replicate.

Figure 5. Hydrogen-bond directed mutual recognition of Adenine-Thymine (left) and Guanine-Cytosine (right).

Figure 6. Model showing catalysis of a reaction by a template which holds reacting partners through H-bonds.

Hydrogen Bonding and New Materials

The planned growth of hydrogen bonds in two dimensions can lead to materials with interesting shapes. The first example shown in Figure 7 corresponds to a collection of identical molecules held together by hydrogen bonds. The strategic location of the interaction sites allows the formation of a two-dimensional sheet. Additional interactions between the benzene rings on adjacent sheets (through a different type of non-covalent interaction) result in a stack. Overall, a porous structure with interlocking columns is obtained.
Another example of a sheet-like structure resulting from hydrogen bonds is given in Figure 8. Here two different molecules, cyanuric acid and melamine, with complementary hydrogen bonding sites arrange themselves in a beautiful architecture.

In Figure 3, the α-helix is characterised by a sequence of parallel hydrogen bonds within the molecule along the helix axis. Other variations are possible, e.g., by mixing parallel and antiparallel arrangements of hydrogen bonds. A lovely example of a structure resulting from intermolecular hydrogen bonding with this type of directional character is shown in Figure 9. The tubular assembly has been demonstrated by X-ray crystallography. Such peptide-based nanotubes can transport small molecular or ionic fragments, such as water, ammonia and proton. Hydrogen-bonding directed recognition has also been utilized to design new types of liquid crystalline materials by Lehn.
Hydrogen Bonding, the Magical Glue

Hydrogen bonds in the hands of a practical dreamer can open up infinite possibilities. During the past few decades chemists have concentrated on the art of making and breaking very high energy (200–400 kJ/mol) covalent bonds. The edifices built and broken here are as made from concrete! In the present decade, chemists increasingly prefer to have more flexibility. Hydrogen bonding has proved to be very useful in this approach. The ubiquitous glue has transformed mundane molecules to potential information storage systems, molecular switches of all kinds, materials, surfaces, cavities, sieves, catalysts and on and on.
In the fourth part of the series article (pages 31-40) we have discussed an alternative way of looking at pericyclic reactions. Even though several textbook examples have been provided, it is always best for a beginner to try to understand a new reaction mechanistically. For this purpose, two multi-step reaction sequences are shown in (Schemes 1 and 2). The steps marked A-I should be understood in terms of mechanistic principles. Note however, that not all these steps involve pericyclic reactions! Some of them are interesting (and important) for other reasons.

Scheme 1 and 2.
Can you answer the following questions?

[1] Which steps (A-I) involve apericyclic reaction mechanism?

[2] Which of these are thermal reactions and which are photochemical?

[3] One of the (non-pericyclic) steps shown in Scheme 1 is a well-known name reaction. Can you identify it? What is the name reaction?

[4] What is compound X?

[5] What is the stereochemistry of compound Y? Why is it formed exclusively?

[6] Do you know the mechanism of the non-pericyclic steps in Schemes 1 and 2?

Suggested Reading

The mechanism of formation of indigo from 2-nitrobenzaldehyde and acetone is discussed in this article. Some new methods of making indigo are also described.

The organic chemist is a creator. It is this fact that contributed a great deal to the early development of organic chemistry. The early realisation that many useful compounds could be made more economically in the laboratory than from natural sources and the pursuit of such prospects in the dye industry were responsible for the development of organic chemical industries. Discoveries became the logical outcome of prolific and intuitive experimentation as exemplified by Perkin’s synthesis of mauve in 1856 and Baeyer’s synthesis of indigo in 1878. The remarkably simple synthesis of indigo (1) from 2-nitrobenzaldehyde and acetone in the presence of aqueous alkali (eq. 1) must have come as a most pleasant surprise.

Today we can explain the reaction; yet, by any standards it is still fascinating. In this article, we will try to analyse the steps involved in the synthesis of indigo. The mechanistic approach will be further simplified through a short discussion on oxidation numbers of organic compounds.

Even to this day, the mechanism of the alkali-mediated chemical transformation shown in equation 1 is some food for thought! We will try to understand the details of this transformation in two stages, through the analysis of the changes in oxidation numbers.

The concept of oxidation numbers has greatly simplified the analysis of transformations in the inorganic area, such as balancing equations. A similar concept, although too simplistic, is equally useful in organic chemistry. The rules for determining the oxidation numbers of atoms in organic molecules are summarised in the box on Page 27.

Indigo [from Greek *indicon*, Indian substance] is perhaps the oldest dye known and has a history dating back to 5000 years. Indigo has attracted merchant ships to India since ancient times. No other naturally occurring material could give cotton the kind of lovely blue as indigo could. The trade suffered badly towards the later part of the last century, since the industrial preparation of indigo virtually wiped out indigo cultivation. Interestingly, we may end up going back to the natural sources for getting indigo, albeit in a different way, through genetically engineered organisms.

The increase in the demand for indigo is a direct result of the fascination for blue jeans, that has neither gender nor age bias. The origin of jeans as an apparel makes an interesting story. The city of Genoa in Italy specialized in making sail ships. The sails were, naturally, made of rough and tough cotton. An entrepreneur found that old, dirty, torn sails could be dyed with indigo and sold as dress material. Thus jeans were born. People liked jeans, for they were comfortable. Nowadays jeans come in different hues, like stone washed, bleached and machine gunned! It seems that jeans are here to stay. With increasing demand the price of jeans is going up and along with it the price of indigo. This and environmental factors will in the very near future make the preparation of indigo by natural means a preferred option.

Johann Friedrich Adolf von Baeyer (1835-1917) was awarded the chemistry Nobel prize in 1905 in recognition of his services to the development of organic chemistry and chemical industry through his work on organic dyes and hydroaromatic combinations. Baeyer’s name is synonymous with indigo and his impact on science was profound. His life is an inspiration to scientists. His first achievement was the preparation of barbituric acid, commonly known as sleeping pills. By 1880 he became well known for his work on indigo and other synthetic organic compounds, which were patented and marketed successfully. With his student, William Perkin, he formulated the Baeyer strain theory which indicated why rings of five and six carbon atoms are most common. Among the other notable students were Thiele, Schlenk, Wieland, Meyer, Emil Fischer and Otto Fischer.

Baeyer studied chemistry at Heidelberg University with Bunsen, whose emphasis on the importance of physics in chemical training and research is well known. Additionally, he had the good fortune of having Kekule as his teacher. One of the greatest characteristics of Baeyer’s research was his ability to use simple equipment. His dictum was that good research can be done in simple, home-made fashion (an aspect our chemists could take note of!). One day a student brought a mechanical stirrer to the laboratory. Baeyer spotted the gadget and was immediately apprehensive and suspicious of its merits. He sought the opinion of Mrs Baeyer and her first remark on seeing it was, “what a lovely way of making mayonnaise!” [whipped egg and olive oil, essentially]. Baeyer, it appeared, was speechless; the stirrer stayed and proliferated!
Analysis of the Oxidation Number of Organic Compounds

1. For a bond that connects the same atoms [regardless of the nature of ligands attached to it] the oxidation number count is zero. For example, the contribution from each carbon below is '0':

Examples:
\[ \text{H}_2\text{C}-\text{CH}_3, \text{H}_2\text{C} = \text{CH}_2, \text{H}_3\text{C}-\text{CH}_2\text{OH}, \text{H}_5\text{C}-\text{CH}_2-\text{CH}_3 \]

2. The oxidation number contribution of bond A-B will be related to the electronegativities or dipole moments. That is, the positive end contributes +1 and the negative end -1.

Examples:

\[ \text{H}_2\text{C}-\text{CH}_3, \text{H}_3\text{C}-\text{CH}_2\text{OH}, \text{H}_3\text{C}-\text{CH}=\text{O}, \text{H}_3\text{C}-\text{COOH} \]

\[ -3 -3 -3 -1 -3 +1 -3 +3 \]

This example shows how the progressive two-electron-oxidation of ethane to acetic acid, changes the oxidation number of the oxidised carbon by two units at a time.

3. Over and above the computed number, for every positive charge +1 should be added and for every negative charge -1 should be added.

Examples:

\[ \text{H}_4\text{C}^-, \text{H}_3\text{C}, \text{H}_3\text{C}^+, \text{H}_4\text{N}, \text{H}_4\text{N}^+ \]

\[ -4 -3 -2 -3 -3 \]

An analysis similar to the one above would show that for the progressive two electron reduction of a nitro compound to an amine, the oxidation number of the nitrogen atom decreases by two units at a time.

From this perspective, eq. 1 can be rewritten with the oxidation numbers of the important atoms as follows:

\[
\begin{align*}
\text{amine} + \text{aldehyde} &\rightarrow \text{product} \\
\text{NO}_2 \rightarrow \text{NHR} &\text{ change} \\
\end{align*}
\]

There is a remarkable change in the oxidation number of the nitrogen atom during the reaction. Of the six electrons needed for the \( \text{NO}_2 \rightarrow \text{NHR} \) change, five have come from acetone and one from the aldehyde group. Here the transfer of electrons has been ‘done’ in a clever manner through a series of transformations shown in Schemes 1 and 2.

The presence of alkali is important in deprotonating acidic hydrogens to produce nucleophilic species, which undergo reactions characteristic of them. The acid-base equilibria also promote hydrogen transfers. With these general ideas in mind, we can divide the overall transformation...
of 2 to 1 into two segments. The first cascade of reactions is triggered by the addition of CH$_3$COCH$_2^-$ (formed by an acid-base reaction of acetone with OH$^-$) to the aldehyde group of 2. This ultimately leads to the formation of compound 3 via nucleophilic addition, hydrogen transfer and dehydration steps. The sequence is shown in Scheme 1. The changes in the oxidation number of nitrogen at crucial stages are also indicated.

Scheme 1. A: nucleophilic addition; B: hydrogen shift; C: aromatization and protonation; D: dehydration; E: deprotonation and F: intramolecular nucleophilic addition.

The second sequence of reactions begins with the coupling of two species, both generated from 3. Through a series of nucleophilic addition, fragmentation and tautomerisation steps (Scheme 2) indigo is ‘magically’ formed!
The structure of indigo as 1 was established only in 1883, five years after Baeyer’s synthesis. Later, routes to indigo were discovered rapidly and many of these were commercially exploited. These endeavours were facilitated by the understanding of the formation of indigo in nature. Indigo does not occur in the free form. In plants it is present as indican (4), which can readily be hydrolysed to indoxyl (5) and which can be oxidised to indigo.

\[ \text{(3)} \]

Indoxyl has been reached by many commercially viable routes, two of which are given below:

\[ \text{(4)} \]

The quantitative transformation of 4-hydroxycarbostyril (6) to indigo (eq. 5) is a process of recent origin. It demonstrates that the quest for indigo by exotic pathways is by no means over.

\[ \text{(5)} \]

It would be challenging to work out how the 6 $\rightarrow$ 1 change takes place.

Although it may not strike us as elegant, many compounds currently prepared by organic synthesis can be made by genetically manipulated organisms. This trend will not only cut down costs but would also obviate environmental hazards, invariably associated with synthetic procedures. The case of indigo provides an excellent example. This route may prove to be the preferred procedure for large scale preparation of indigo.
Modern chemistry is also emerging from molecules derived from the modification of 1. In 1995 indigo was converted into sheet materials by thermolysis. The thioindigo [NH=S] skeleton has been used as a photochemical switch.

A problem, once solved, usually loses its charm. Occasionally, the same problem resurfaces in a different context and generates renewed interest. The story of indigo belongs to this category. The need for making indigo has changed. So have the parameters that have to be taken into account during the synthesis. But, the challenge to one’s creative ability remains the primary motivation for the organic chemist.

**Suggested Reading**


A Tale of Two Topologies: Woodward–Hoffmann Rules At Your Fingertips!*

A simple procedure for determining whether a pericyclic reaction is thermally allowed is described. The focus is on the potential aromaticity of the transition state of the process, which is inferred from the topological features of the interacting orbitals and the number of electrons involved.

Introduction

A major breakthrough in our understanding of an important class of chemical transformations known as pericyclic reactions was achieved in the mid-sixties. The mysterious manner in which some thermal processes occur readily, while apparently related ones do not, the way the preferences are reversed when the reactions are tried under photochemical conditions, and most importantly, how some stereochemical features are faithfully followed were all sorted out by Robert Woodward and Roald Hoffmann. The validity and predictive power of Woodward–Hoffmann (W–H) rules were repeatedly demonstrated by subsequent work. Not surprisingly, the understanding and application of W–H rules now forms a core component in the organic chemistry curriculum.

Usually, W–H rules are taught following the original derivations, which emphasise the role of symmetry in orbital correlation diagrams. The procedure is quite involved and often appears nebulous for teachers and students alike. It is also not obvious why the symmetry rules are so rigidly obeyed in reactions of unsymmetrical derivatives used as illustrations.

Several alternative descriptions have been proposed over the years. While the original W–H approach is quite comprehensive and also aesthetically attractive, simpler strategies may be more appropriate for undergraduates. I have found over the years that a programme for the understanding and application of W–H rules, based on the approach of Dewar and Zimmerman, is the easiest.

W–H Rules in a Nutshell

We define W–H rules simply as, reactions wherever possible proceed through aromatic transition states.

Aromaticity in the ground state of cyclic systems is a familiar concept. But how does one infer the aromatic nature of transition states of pericyclic reactions? One can do so by identifying the geometric relationship of the interacting orbitals and the number of electrons involved.

The orbital topology in cyclic systems can be classified as two categories, viz., Hückel and Möbius. Hückel systems are aromatic with $4n + 2$ electrons, while Möbius aromaticity requires $4n$ electrons ($n$ is an integer). Let us see how the classification is done and also examine the basis of the simple electron counting principle.

**Orbital Topologies**

Consider a cyclic array of $s$ orbitals. It is obvious that each orbital can have an energetically favourable in-phase overlap with its immediate neighbours. This is also true if the interacting orbitals are $p(\pi)$ orbitals. Side-on overlap is possible in this case. This type of orbital topology which resembles a smooth ribbon is termed a Hückel system (*Figure 1a*).

*Figure 1. Cycle of orbitals with (a) Hückel and (b) Möbius topologies.*

If a $p$ orbital is introduced in the cycle of $s$ orbitals, in-phase interaction throughout the ring is no longer possible. A $d(\pi)$ orbital in a cyclic array of $p(\pi)$ orbitals also has the same disruptive effect (*Figure 1b*). The node (change of orbital phase) within the additional orbital necessarily makes a pair of adjacent orbitals somewhere in the cycle have out-of-phase overlap. It is no longer possible for every orbital to have favourable overlap with each of its neighbours. A twist has been introduced in the ribbon of orbitals. This topology is classified as a Möbius system (see *Box 1* for procedures to make models of twisted ribbon topologies).
Box 1. How to make Hückel and Möbius strips, catenanes and knots.

**Hückel pericycle:** Bring the ends of a 1” × 12” paper strip together and glue the ends. The pericycle will have two surfaces (inner and outer) and no nodes (dislocations). Cut the ring around the middle to get two identical pericycles with no nodes.

**Möbius pericycle:** Bring the ends of a 1” × 12” paper strip together. Hold firmly one end by the left hand and the other by the right. Give the right hand end a 180° twist and glue the ends. We now have a Möbius pericycle with 1 node. Möbius pericycle has only one surface. Check this by drawing a line around the middle of the strip. The line will cover the entire surface of the strip. Carefully cut the strip around the middle. A large pericycle with two nodes will result.

**Catenanes:** Bring the ends of a 1” × 18” paper strip together. Hold firmly one end by the left hand and the other by the right. Give the right end two successive 180° twists and glue the ends. The pericycle will have 2 nodes. Carefully cut around the middle. Two pericycles which are interlocked and have two nodes will result.

**Knots:** Bring the ends of a 1” × 18” paper strip together. Hold firmly one end of the strip by the left hand and the other by the right. Give the right end three successive 180° twists and glue the ends. The pericycle will have 3 nodes. Cut along the middle carefully. A single pericycle with a knot (6 nodes!) will result.

A more general definition can be proposed. Hückel systems correspond to a cyclic array of orbitals with zero or an even number of nodes along the ring. Möbius systems, on the other hand, are characterised by an odd number of nodes around the cycle.

The orbital topology determines the pattern of molecular orbital (MO) energies that result from mutual interaction. The MO energies in Hückel systems can be derived using simple calculations. The results can also be understood qualitatively since they follow a simple, regular pattern. For each ring of N orbitals, there is a highly stabilised MO, followed by pairs of higher energy orbitals, all adding up to N molecular orbitals (Figure 2). This is because it is possible to form a molecular orbital which has in-phase overlap around the circuit, i.e., with zero nodes along the interaction cycle. This unique combination is more stable than its counterpart in an acyclic arrangement. Increasingly higher energy combinations can be derived by introducing out-of-phase combinations or nodes. These orbitals with non-zero nodes come in pairs, with equal energy.
Figure 2. MO energy patterns for Hückel and Möbius ring systems. The energy of an MO can be derived from the points at which the polygons touch the enclosing circles. Points below the centre are bonding, those above are antibonding and those along the centre are nonbonding. For example, the $\pi$ orbitals of square cyclobutadiene (a Hückel system) form a highly stabilised bonding MO, two non-bonding MOs and a highly destabilized antibonding MO.

The MO energy pattern of a Möbius system is quite different. Due to the intrinsic nodal pattern, it is not possible to construct a combination with zero nodes. The unique stabilised orbital found in Hückel systems is therefore not present in a Möbius ring. Instead one finds pairs of MOs with increasing energy (Figure 2).

In order to have maximum stability, the bonding orbitals should be filled and there should be a closed shell configuration. In a Hückel system, these conditions can be met only if there are 2, 6, 10, ... electrons. Hence, Hückel systems with $4n + 2$ electrons (where $n$ is an integer) are aromatic. In the case of Möbius systems, with doubly degenerate bonding orbitals, closed shell configurations are possible only with $4n$ electrons. As an interesting corollary, Hückel systems with $4n$ electrons and Möbius systems with $4n + 2$ electrons would have open shells. These are not aromatic. They are quite destabilised and hence termed antiaromatic.

There are numerous examples of molecules and ions which are Hückel aromatic systems. Benzene, cyclopropenium cation, and cyclopentadienyl anion are some of the most famous
examples. But Möbius aromatic molecules are quite rare. Severe geometric constraints would be involved in the construction of twisted molecular rings.

Interestingly, both Hückel and Möbius topologies are repeatedly encountered in transition state structures of pericyclic reactions. Therefore, by determining the topology and the number of electrons involved, one can readily discern whether the system is aromatic or not. The reaction is allowed if the transition state is aromatic and forbidden otherwise. Let us consider a few specific cases.

**Applications**

For applying the topological approach, we have to consider the nature of the idealised transition state (TS) of the pericyclic process of interest. The orbitals associated with the bonds being formed, broken and rearranged are monitored. The number of nodes in the cycle of interacting orbitals at the TS geometry is determined. This immediately reveals whether the TS is a Hückel or a Möbius system. After taking into account the number of electrons involved in the process, the prediction of aromaticity (or the lack of it) is straightforward.

All reactions within the purview of W–H are reversible. The transition state analysed is common for both the forward and reverse reactions. The preferred direction of the reaction will be controlled by thermodynamic factors. It must also be borne in mind that the predictions refer to thermal reactions. There is a reversal on going to photochemical processes since MO occupancies are altered in the excited states. For detailed predictions of the feasibility of photochemical reactions, the traditional correlation diagram approach is more powerful.

The application of the above principles will now be illustrated with important areas where W–H is useful.

**Electrocyclic Reactions**

In an electrocyclic process, a chain of π orbitals is closed to form a ring by forming a new σ bond between the ends. Equivalently, one can visualise the reverse process of a σ bond connecting a π framework in a ring being opened up to form a chain of π orbitals. There are two ways the reaction can occur. In the disrotatory mode, the σ bond is broken by twisting the ends in opposite directions (*Figure 3*). Alternatively, the end groups can both be twisted in the same direction, leading to the conrotatory mode. The mode of the reaction determines the stereochemistry of the products.

The orbitals to be considered are the $p$ orbitals of the π unit and the hybrid orbitals of the σ bond being broken or formed. The latter are shown as pure $p$ orbitals for the sake of simplicity.
The orbital topology differs for the two modes of electrocyclic reactions. In the TS of the disrotatory path, it is possible to arrange all the interacting orbitals in a cycle without any nodes (Figure 3). So this process is governed by Hückel topology. In contrast, the idealised transition state for the conrotatory process involves a twist at the σ bond being broken. In the cycle of orbitals, the phase changes at this point leading to one node (Figure 3). Hence the TS corresponds to a Möbius system.

![Figure 3. Schematic representation of two modes of electrocyclic reactions. The orbital topology of the idealised transition state is shown above the arrow.](image)

A direct consequence of the above classification is that electrocyclic reactions involving 6 electrons would occur via the disrotatory path, while the conrotatory mode should be preferred in systems with 4 electrons. Ring opening of cyclobutenes involves reorganising 4 electrons. Hence, only the conrotatory path is thermally allowed. In the case of 1,3-cyclohexadiene, the disrotatory path is the allowed pathway. These results and the associated stereochemistry are shown in Figure 4.

![Figure 4. W–H predictions for typical electrocyclic reactions.](image)

**Cycloaddition Reactions**

Formation of cyclobutane from two ethylene molecules is a simple example of a cycloaddition reaction. Two π bonds are converted to two new σ bonds resulting in the
cyclic product. The well-known Diels–Alder reaction involves the addition of an olefin to a diene. In this process, three $\pi$ bonds are reconstructed to form two $\sigma$ bonds and a rearranged $\pi$ bond. More complex examples involving multiple components, combinations of $\sigma$ and $\pi$ bonds, heteroatoms, cyclic reactants, etc., are all known. Here we shall focus on cycloadditions between two simple conjugated systems.

The mechanism following the *concerted* pathway, i.e., with a transition state characterised by partial bond formation and breaking, is of interest since it leads to well-defined stereochemistry in the products. Hence, the idealised TS to be considered is a cyclic structure. The simplest of these is obtained by bringing the reactant $\pi$ orbitals face to face. This mode is known as the *suprafacial* approach with respect to each of the reactants. In this case, the interacting orbitals can all have favorable overlap with immediate neighbours (*Figure 5*). Hence the topology is obviously that of a Hückel system. An aromatic TS is obtained with 6 electrons, but not with 4. Hence, $\pi^2s + \pi^2s$ cycloaddition (indicating the type of bond, number of electrons and mode of approach for each component) is a thermally forbidden process. But Diels–Alder reaction ($\pi^4s + \pi^2s$) involving an aromatic TS is allowed. Möbius type transition states are encountered if one of the reactants is brought in an *antarafacial* manner.

*Figure 5. Schematic representation of two cycloaddition reactions. The topology of the interacting orbitals at the idealised transition state is shown in the middle.*

Hence, $\pi^2s + \pi^2a$ would be an allowed thermal reaction. However, this places severe geometric constraints on the TS structure. An antarafacial approach is more likely in systems containing large rings.
**Sigmatropic Reactions**

In several systems, it is possible to rearrange a $\sigma$ bond to a new location across a $\pi$ periphery. Such reactions are called sigmatropic shifts. For example, $[1,3]$- and $[1,5]$-shifts are shown in Figure 6. The migrating group can be hydrogen or a more complex unit. The well-known Cope and Claisen rearrangements correspond to $[3,3]$-shifts. A remarkable example of a molecule undergoing multiple $[3,3]$-shifts is discussed in Box 2 on Page 39.

In the simplest stereochemical possibility, the migrating group, say hydrogen, is smoothly transferred across the $\pi$ framework in a suprafacial manner. In the idealised transition state, the orbital on the migrating hydrogen and the $p$ orbitals of the $\pi$ unit form a Hückel framework (Figure 6). Counting the electrons in the migrating $\sigma$ bond and those in the $\pi$ part, it is clear that $[1,3]$-h kidnide shift is thermally forbidden while $[1,5]$-shift is allowed. Since 6 electrons are involved in the rearrangement, $[3,3]$-shifts are also allowed.

*Figure 6. Typical sigmatropic shifts are shown. The topology of the interacting orbitals at the transition state is shown in the middle.*
Box 2. Fluxional Molecules

The low activation energy associated with [3,3]-shifts has enabled the design of structures where, in the extreme case, bond reorganization can lead to any number of equivalent structures.

Bullvalene provides an ideal illustration. Bullvalene has a three-fold axis of symmetry. Each of the cyclopropane bonds is part of a 1,5-hexadiene unit capable of undergoing Cope rearrangement. With each [3,3]-shift, the atomic and bond positions change, but the structure is regenerated! In bullvalene the shifts take place rapidly even at moderate temperatures making all the 10 carbon atoms equivalent.

This can be readily shown by labeling the atoms. Note that there are four non-equivalent positions, a, b, c and d in a static structure of bullvalene. Choose four adjacent atoms 1, 2, 3 and 4 in each of the above positions. After one [3,3]-shift, atoms change types. By migrating bond I, atom 1 changes to a type ‘d’ position, 2 to ‘c’ and so on. A different scrambling occurs by moving bond II or III. It can be shown that each of the four positions could become any of the non-equal positions. Thus bullvalene around 100°C can be viewed as ten points in a three-dimensional surface! Bullvalene is a perfect example of a fluxional molecule, one capable of giving rise to any number of equivalent structures by bond reorganization. In the present case, the possibilities are 10!/3=1.2 million.
Sigmatropic reactions with Möbius transition states can be visualised in two cases. The migrating group which initially forms the $\sigma$ bond with one face of the $\pi$ unit ends up forming the bond at the opposite face. Alternatively, the migrating group undergoes an inversion during the rearrangement. In either case, a combination of antarafacial and suprafacial stereochemistry is involved. In the idealised TS, one node is present in the orbital cycle. With this stereochemistry, [1,3]-shifts are allowed, but not [1,5]-shifts.

**Conclusions**

A simple procedure was outlined for determining whether a pericyclic process is likely to be facile under thermal conditions. The analysis does not require detailed knowledge of MO theory and symmetry arguments. It can be applied even for complex substrates. The emphasis is on topology, rather than on symmetry. It enables one to appreciate why W–H rules hold good even in highly unsymmetrical systems.

**Suggested Reading**


The modes of action of two enzyme ensembles that perform critical life operations are described.

There is a perfection, not commonly seen, in the award of the Nobel Prize in Chemistry this year to P D Boyer, University of California, Los Angeles and J E Walker, Medical Research Council, Laboratory of Molecular Biology, Cambridge, for their elucidation of the mechanism of ATP formation in environments of a proton gradient and to J C Skou, Aarhus University, Denmark for the first discovery of an Na$^+/K^+$ ion transporting enzyme, now called ‘Na$^+$-K$^+$ ATPase’.

The trinity, information – function – energy, manifests in all forms of life. Sun is the primary energy source and plants directly use this in forming energy rich bonds like glucose, starch, cellulose, etc., by forcing a combination of carbon dioxide with water. In bacteria, plants and animals such energy rich compounds are ‘burned’ and the energy released by this combustion of such nutrients is captured universally in the form of ATP (adenosine triphosphate), a ‘broker–extraordinary’ in consummating union between reluctant partners, in the generation of nerve impulses, in swimming against osmotic pressure and several others. The transformation of nutrients to ATP occurs, in all life forms, largely by similar pathways and in ours by a subsystem called mitochondria (generally used as a plural, since this organ is present in numbers in all cells). Energy rich bonds are transformed to water and carbon dioxide, in mitochondria, generating almost all the ATP in our system. For example, glucose (C$_6$H$_{12}$O$_6$) when degraded to 6CO$_2$ + 6H$_2$O generates 38ATP of which 36 are synthesised in mitochondria. The shuffling of carbon bonds in mitochondria results in the formation of energy rich NADH (nicotinamide adenine dinucleotide phosphate) at the expense of energy poor CO$_2$. In the process called ‘respiration’ NADH is oxidized to NAD$^+$ in the cascade, resulting in the reduction of oxygen to water:

\[
\text{NADH} + \frac{1}{2} \text{O}_2 + \text{H}^+ \rightarrow \text{NAD}^+ + \text{H}_2\text{O} = -53 \text{ kcal/mole} \tag{1}
\]

The overall reaction here leads to the formation of 3ATP:

\[
\text{ADP} + \text{Pi} + \text{H}^+ \rightarrow \text{ATP} + \text{H}_2\text{O} = 7.3 \text{ kcal/mole} \tag{2}
\]
Thus part of the energy in NADH is captured in the formation of ATP from adenosine diphosphate (ADP) and inorganic phosphate (Pi).

The deciphering of pathways by which the combustion of NADH results in ATP formation was not easy. Eventually novel concepts linking the electron gradient in respiration with a proton gradient and the identification of the latter as responsible for ATP formation was established.

Such unusual phenomena are possible due to the extraordinary architecture of the mitochondria (Figure 1).

A general picture of the major events taking place in mitochondria is presented in Figure 2.
The generation of a proton gradient concomitant with respiration was demonstrated in the early sixties. Simultaneous endeavours with the enzyme ensemble ATP synthase led to the understanding of pathways by which the proton gradient can result in the generation of ATP. The bold prediction of Boyer based on enzymatic studies was subsequently verified by Walker on the basis of structural studies including X-ray crystallography.

The heart of ATP synthase lies largely in the heart itself, an organ which works every moment of our life using ATP. Thus when horse heart muscle yielded a homogeneous enzyme complex which promoted ATP generation in the presence of a proton gradient many surprises were in store!

ATP synthase (Figure 3) consists of two sub units $F_0$ and $F_1$. $F_0$ is hydrophobic and spans the mitochondrial inner membrane and is the proton channel for the synthase. It consists of 6 proteins of ~8 kD each. $F_1$ is the catalytic site. It is placed beyond the mitochondrial inner membrane facing the matrix (Figure 4). $F_1$ consists of 9 protein chains designated as $\alpha_3\beta_3\gamma\delta\varepsilon$, each ~30 kD in size.
ATP Synthase (Figure 4) in construction is a marvel. The alternating $\alpha$, $\beta$ proteins in a hexagonal arrangement generate a hollow channel into which the $\gamma$ unit fits snugly!

Sustained efforts by Boyer and his colleagues over decades have unravelled how ATP synthase generates ATP. Boyer showed that the role of the proton gradient was not to form ATP as originally thought but to release it from the enzyme. *Further ATP synthase harbours both ADP and ATP, but ATP does not leave the catalytic site unless protons flow!* So, when the protons flow ATP is continuously produced and released.

Boyer’s ‘binding change mechanism’ which was verified largely by Walker, provided science the details of the working of the ATP generating machine, ATP-synthase (Figure 3), the salient features of which are summarized below.

*Figure 3. A schematic view of the enzyme ATP synthase. (Courtesy: The Royal Swedish Academy of Sciences).*
The \( \alpha_3 \beta_3 \) cap of ATP synthase provides a channel into which the \( \gamma \) unit fits snugly, as noted above. At the other end \( \gamma \) is anchored to the subunits of \( F_0 \) (Figure 3). When \( H^+ \) flows through \( F_0 \) these subunits are twisted as in a water wheel. Since the \( \gamma \) unit of \( F_1 \) is attached to these, it also gets twisted. Two events of importance arise from twisting of the \( \gamma \) unit. The \( \alpha_3 \beta_3 \) cap is stationary and normally they have identical conformations. The catalytic site, harbouring substrate (ADP+Pi) and product (ATP), residing in the \( \beta \) unit, due to the twisting of the \( \gamma \) unit,
becomes asymmetric and unequal with respect to changing interactions with $\gamma$. This results in the 3 catalytic sites in the $\alpha_3\beta_3$ cap becoming non-equivalent. Second, a continuous proton push would rotate the $\gamma$ unit and this, as in the transmission system in a car, will lead to continuous ATP production.

Based on these clues, Boyer suggested that the ATP synthase operates similar to a water gradient operated minting press and that for every rotation of $\gamma$, three fresh and bright ATP will be released!

Basic to this is the assumption that the rotation of $\gamma$ produces catalytic sites having tight binding (T), loose binding (L) and open (O) profiles, which naturally interchange on rotation. A complete rotation involving these sites is presented in Figure 4. The generation of 3 ATP as a result can easily be seen.

Finally how does the proton gradient run the unfavourable ADP+Pi→ATP+H$_2$O reaction? It can be seen from Figure 4 that a proton gradient makes the $\beta$ unit bind tightly to ADP+Pi. This in presence of protons would make ejection of water quite advantageous.

The mitochondria and the subsystems therein reflect high science which nature adopts as a hallmark of evolution. Put in a nutshell, glucose when burned in a calorimeter yields 686 kcal/mole energy; the same process when put through the mitochondria yields 38ATP or 277 kcal equivalent with a remarkable 277/686 = 40% efficiency!

In the living cell, the sodium ion concentration (Na$^+$) is lower than that outside, whilst that of potassium ions is higher. The Na$^+$/K$^+$ gradient controls cell volume, nerve and muscle excitation, transportation of sugars and amino acids and several others. In cells, the so called Na$^+$/K$^+$ pump operates in the forward direction by pumping out Na$^+$ and pumping in K$^+$. Since both these events work against the concentration gradient, energy in the form of ATP has to be supplied. This activity, being basic for nerve function, is important. Indeed, more than a third of ATP consumed by a resting animal is involved in the pump. The reverse flow is passive.
Skou isolated from finely ground crab nerve membranes, a homogenous enzyme complex which promoted controlled transport of Na⁺/K⁺ across the membrane at the expense of ATP. The enzyme was inactive in the absence of any of the key players, namely ATP, Na⁺ and K⁺. This was the first enzyme complex that promoted the vectoral transport of substances across the cell membrane.

Several additional observations conclusively proved that the Na⁺-K⁺ ATPase is responsible for the operation of the pump. First, the maximum efficiency of the enzyme matched with that corresponding to the inflow/outflow of ions in the cell. Further, sodium and potassium ions bind to the enzyme with great affinity at different sites. Also, ATP phosphorylation of enzyme becomes viable only when complexed with Na⁺ ions. In sharp contrast, when complexed with K⁺ ions, dephosphorylation is promoted.

*Figure 5* shows how the Na⁺/K⁺ pump is associated with ATP activation.

The enzyme complex consists of four protein chains arranged as shown in *Figure 6*. The β chain is not essential for Na⁺/K⁺ transport, but plays a role in the stabilization of βααβ ensemble, which is largely buried in the membrane.
The Na\(^{+}\)-K\(^{+}\) ATPase promotes an unusual series of changes in bringing about Na\(^{+}\)/K\(^{+}\) transport, the salient features of which, presented in Figure 7, describe a full cycle illustrating, in sum, the outflow of 3Na\(^{+}\) and the inflow of 2K\(^{+}\).

**Figure 7. The mechanism of transport of ions by Na\(^{+}\)-K\(^{+}\) ATPase.**

The E\(_{1}\) conformation has high affinity for sodium ions. The resulting Na\(^{+}\) uptake triggers phosphorylation. The phosphorylated E\(_{1}\) conformation is unstable and everts to E\(_{2}\) conformation which having little affinity for Na\(^{+}\), releases it outside. Conformation E\(_{2}\) having great affinity for K\(^{+}\), picks up this ion. The uptake of K\(^{+}\) triggers dephosphorylation and in this state conformation E\(_{2}\) is unstable and everts to E\(_{1}\). E\(_{1}\) having little affinity for K\(^{+}\) releases it inside, thus completing this marvellous cycle!

In sum, we have here a story of two enzyme ensembles, that perform critical life operations by molecular architecture based machines, whose copying by humans, one can only dream of at this juncture!

**Suggested Reading**

Molecular Origami*
Modular Construction of Platonic Solids as Models for Reversible Assemblies

Platonic solids, representing the highest order of structural and molecular symmetry have been crafted from single modular elements that carry information relating to lengths and angles.

The assembly of even the most complicated structure is achieved by Nature using a modular protocol wherein each of the modules holds latent information. Thus, minerals – related to materials, and DNA, polysaccharides and proteins – related to cellular life, are assembled from simple monomers. The information content in the modules would be related to the complexity of structures that can evolve from it and by corollary, those which have the highest symmetry can be constructed from modules having minimum levels of information. In this paper, we demonstrate this, using protocols of origami with the construction of platonic solids.

Origami, the elegant art dating back to 500 AD provides intuitive protocols for the crafting of practically every type of three-dimensional object from two dimensional paper.

Important principles of mathematics are latent in these operations. The unraveling of these would bring origami to the realm of sciences, where it will surely find profound applications [1, 2]. We have illustrated this with the construction of platonic solids, based on mathematical principles [3].

Plato (427-347 BC), philosopher, mathematician and statesman, with commendable insight, limited to five – the number of convex polyhedrons whose faces are congruent, regular polygons forming equal dihedral angles at each edge. If ‘m’ number of regular ‘n’ sided polygons meet at each vertex, they must satisfy the equation, $1/m + 1/n = \frac{1}{2} + 1/E$, where $E$ represents the total number of edges of the polyhedron. The five fundamental solids that fulfil this requirement, called platonic solids, are tetrahedron, cube, octahedron, dodecahedron and eicosahedron (Chart 1).

Platonic solids have played a key role in the development of many facets of human endeavor, ranging from art, architecture, to cosmology to physical and life sciences. Therefore, the assembly of these from a single modular unit in a reversible way would be the obvious choice to illustrate how surfaces can be crafted from units carrying needed information. The modules that assemble to platonic solids need carry only one information, namely, the controller angle!

**The Design Principle**

All the designs can be made from thick square sheets of the size 20 cm × 20 cm (readily available A4 size photocopy paper, from which squares of the size 21 cm × 21 cm can be made is most suitable, and all the structures illustrated here are made from this type of paper).

Taking a corner of the A4 sheet to the opposite side, creasing across the diagonal and removing of the protruding strip can make the squares. The procedure involves preparing a number of identical modules by folding paper in a specified manner. Each unit will have a pair of projections or inserts and a complementary pair of receptors. Two units will be joined using the insert of one with the receptor of the other. The angles subtended at the junction will be controlled through simple trigonometric concepts, resulting in good approximations to 60º, 90º and 109º needed for constructing the platonic solids. Interestingly the whole process requires neither scissors nor glue! However, it is useful to have a scale to mark the crease while folding and clips to temporarily hold connections till the model is completely built.

Each module provides, in addition, an edge, corresponding to the eventual nature of the polyhedron. Therefore the number of edges in the platonic solid define how many modules need to be assembled (Chart 1). Tetrahedron, octahedron and eicosahedron belong to a sub family in the sense that they represent the congruence of respectively, 3, 4 and 5 equilateral triangles.

**Chart 1.**

<table>
<thead>
<tr>
<th>Platonic solid</th>
<th>m</th>
<th>n</th>
<th>E</th>
<th>Angle controller [º]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tetrahedron</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>2. Octahedron</td>
<td>4</td>
<td>3</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>3. Eicosahedron</td>
<td>5</td>
<td>3</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>4. Cube</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>90</td>
</tr>
<tr>
<td>5. Dodecahedron</td>
<td>3</td>
<td>5</td>
<td>30</td>
<td>109</td>
</tr>
</tbody>
</table>
Solids with Triangular Faces

Tetrahedron, octahedron and eicosahedron can all be constructed from an equilateral triangle, constructed from three modules. This is illustrated in Chart 2 and Chart 3. The triangle so constructed will have, at each corner, an insert and a receptor. These could then be used to add on triangular faces, till the polygon is complete, as shown in Chart 4.

Construction of Module for Tetrahedron, Octahedron and Eicosahedron (Chart 3)

Fold the square from A4 sheet of paper (see above) to make equal halves. Fold again in the same manner. Open the sheet and repeat the process in a perpendicular direction. This would result in the $4 \times 4$ grid AEDF (1) (Chart 2). Place a scale firmly along BC and tear off strip BCFE, resulting now in the $4 \times 3$-grid ABCD (2). Fold along the horizontal lines, EF, GH, IJ, as shown in 3, to secure strip DCI J (4) that is 4 layers thick. Now, fold the edges, DI, and CJ to, respectively, OP and QR, to make the mid crease lines KL and MN.
If each grid is assumed to be of size ‘a×a’, then in (4), the strips DKIL and CMNJ will be ‘a/2 × a’ and the core ‘2a×a’. Holding a scale firmly, crease the diagonal DL and MJ (5) and tuck segments DIL and MCJ so that they are not visible (6). The controller angle $\theta$ [KLM=LMN] would be close to the required 60°, as derived in Chart 2. To complete the module, holding LM firmly with a scale, bring LDKM forward (7). Figure 7 is a typical module. It has two inserts [LKD and MNJ], one in front and the other in the back, and two complementary receptors [DML and JLM]. In this module LM would be the edge (E)/side of the polyhedron. As stated previously, tetrahedron would need 6 modules, octahedron 12 and eicosahedron 30. By arranging the folding, three or four at a time, the numbers needed can be made easily.

The assembly of three of the modules to form the equilateral triangle is shown in Chart 3. Join module I and module II, by securely tucking the insert of module II behind the edge of I to give composite I+II, with an angle of ~60° with a projecting insert (until well familiar, it is advised to secure each joint with a paper chip, which can be removed after the model is constructed). Tuck in the left insert of ‘I+II’ to receptor in III and reciprocally, the insert of III to the receptor of ‘I+II’ to secure the key triangular motif [TM], as shown in Chart 3. In reality, TM will have a small triangular aperture in center. Each of the three corners has an insert (shown)
and a receptor (latent), for further assembly. The step-wise assembly from TM to tetrahedron, octahedron and eicosahedron is shown in Chart 4.

**Tetrahedron:** Make an I+II composite and insert it to the TM, adding another triangle. With a single module connect the corners to make the tetrahedron. Of the three, because of crowding, assembling tetrahedron could be vexing, but with patience this can be done.

**Octahedron:** Insert the I+II composite to two sides of TM and connect the tips with a single module to give the pyramid base. Attach an I+II composite to any baseline of the pyramid and connect the tip to the opposite base line to give the octahedron.

**Eicosahedron:** Construct two pentagonal pyramids, from two TM. Proceed as in the case of the octahedron to attach two I+II composites to the side of TM. Add another I+II composite to any of the new sides. Complete the pyramid by connecting the tips with a single module. The procedure can be clearly seen from Chart 4. Connect, in sequence, the corner of one of the pyramids to the base of the other, to create the eicosahedron.

It must be pointed out that the assembly protocol suggested here is one of the many and may not even be the best in the hands of a builder, who will usually develop alternate methodologies more suited to the individual perception.

**Cube:** The module for cube is a marginal variation of that outlines for platonic solids with triangular faces (Chart 1). The modification relates to the change of the controller angle from 60° to 90°!

Follow precisely procedure in Chart 2 till Figure 5, which is again shown as Figure 1 in Chart 5.
Holding firmly with a scale, crease diagonals DL, ML and MJ (2). Visually it can be seen that the controller angle DLM=JML is the required 90°. This can also be derived mathematically as shown in Chart 5. To complete the module, hold LM firmly with a scale, bring the flap MDIL forward. Module 3 has inserts LID and MCJ and as receptors LMD, JLM.

As before, the assembly of 12 units of 3 to the cube starts with building a basic square module [SM]. This is clearly shown in Chart 6. As could be expected, each corner of the SM will have an insert (seen) and a receptor (latent). The union of two SM with four modules, as shown in Chart 7 will result in the formation of a cube.
**Dodecahedron:** For any 3-D object conceivable, dodecahedron presents the highest symmetry. It also is the easiest platonic solid to construct and therefore the ideal start for modular assembly exercises!

The module is also the easiest to make. Start from the $4 \times 4$ grid (1) in *Chart 2*, which is shown as *Figure 1* in *Chart 8*. Without any cut, fold it to 2, to give the four layered front strip IJHG (3). Holding firmly with a scale, crease the diagonals, IK, KN and NH (3).

Since IKM and LNH are right-angled triangles with two equal sides, $\theta = 45^\circ$ or $\tan q_1 = 1$, $\theta = 45^\circ$. We have already derived the value of $63.5^\circ$ for $\theta_2$. Therefore the controller angle $\angle IKN=HNK=45^\circ + 63.5^\circ = 108.5^\circ$, which is close to the $109^\circ$ required! The module is completed by bringing forward the flap NKGI by holding firmly on KN with a scale. The module 4 has two inserts [KIG, NHJ] and two receptors [INK, HKN].

The assembly of five modules of (4) to the pentagon motif [PM] is illustrated in *Chart 9*. As with TM and SM, PM will have an insert (seen) and a receptor (latent) at each corner.

Of the many ways possible, for the assembly of the 30 modules of (4) (*Chart 8*) to dodecahedron, a simple way is to start from a single unit of PM and gradually add pentagons, with (4), in an anti-clockwise manner to reach the closed motif, which is called peristylane or cup! (*Chart 10*). The union of the five apices of peristylane to another unit of PM will generate the beautiful dodecahedron.
In carbon science, dodecahedron represents 20 perfectly, tetrahedrally disposed carbon atoms. Indeed the corresponding hydrocarbon dodecahedrane \([C_{20}H_{20}]\) has been made.

The module (4) (Chart 8) used here, can therefore be equally appropriate for construction of saturated carbon compounds, thus providing vast possibilities for modular construction. The basic principles of modular assembly outlined here have potential for further exploration along a myriad of avenues.

**Chart 8.**

**Chart 9.**

**Acknowledgement**

I am grateful to Professor J Chandrasekhar, Department of Organic Chemistry, Indian Institute of Science, Bangalore for valuable suggestions relating to the mathematical aspects.
Suggested Reading


The Modular Construction of DNA Double Helix*

In the annals of science, rarely if ever, has any molecule captured the imagination of mankind as DNA. Within five decades of the discovery, DNA structure has been able to disseminate knowledge of key aspects related to life. From grade levels to research studies, DNA is described, examined and analyzed from diverse vantages that extend from the simple double helix to the correlation of this structure with hundreds of properties that ensue from this unique arrangement. The overt structure of the DNA double helix is very deceptive. Although constructed from fewer modular blocks compared to proteins and enzymes, this simplification has been more than compensated by the exceptional versatility of the DNA double helix. Thus, varied functions such as replication, transcription, recognition and intercalation – each describing a different pathway – are possible because of its magical flexibility. DNA is a maverick and a good host; its usual right handed helix profile can change all the way to the left handed double one, the entire spectrum with expenditure of minimum energy. Its major groove can play host to countless guests leading to recognition and the resulting biological functions; its minor groove can receive antibiotics initiating a cascade that protects our lives from microbial invasion; its horizontal gap is a beacon for suitable guests to snugly fit in and thereby initiate many critical operations.

Our continued interest in the modular assembly to structures, made it logical to design one for the DNA double helix. The outcome, although appears very simple, took a long time. The design presented here can be assembled even by students at the grade levels. Yet, it encompasses the key structural aspects of DNA duplex, such as the pitch, major groove, minor groove and the helicity and, in addition is so versatile that it presents the DNA single strand complexed with complementary bases, the tethering of which can either give rise to the normal right-handed double helix, B-DNA or the left-handed double helix, Z- DNA.

Construction of the Module

Materials:

Card sheet of ~1mm thickness; scale; cutter/scissors; Fevicol.

Procedure:

A. The module

1. Cut out rectangle of size, 20 cm × 2 cm; holding firmly by the scale, make vertical lines at intervals, 2 cm, 4 cm, 6 cm, 14 cm, 16 cm and 18 cm – to produce segments, a, b, c, d and c’, b’, a’. Crease the lines, using the scale, by folding inwards and outwards (1, Figure 1).

2. Holding the d segment vertically, fold back c, fold to the front b and a. This procedure would place segment a, overlapping with d. Glue securely a with portion of d (2, Figure 1). Repeat the same procedure with, c’, b’, a’ (3, Figure 1).

3. Fold flaps b, c and c’, b’ to the middle (4, Figure 1). Crease firmly by moving the edge segment forwards and backwards. Now each flap will have four 1 cm wide strips. Gently open the two flaps on either side of d (5, Figure 1). Bring the b, c and c’, b’ edges to the two edges of d to form the module (6, Figure 1). The two sleeves (b, c and c’, b’) that sandwich segment d and placed orthogonal, could represent the sugar phosphate backbone of DNA and segment d, a hydrogen bonded pair of code bases. It is clear that tethering of the sleeves; equivalent to the operation of enzyme DNA polymerase, will generate the double helix.

Figure 1.
4. 15-20 modules are needed to assemble a DNA that would clearly show all the features (the pitch, the turn, major and minor grooves). In the beginning it is better if they are made individually. The required 15-20 rectangles can be cut out from sheets of size, $20 \times 30$, $20 \times 40$ respectively. In principle, the segment could be inscribed in the sheet, prior to their separation, to give not the rectangles, but the modules themselves. Because of alignment problems, unless great care is taken, the modules do not come uniform in this approach.

B. Tethering

1. Make the two tethering strands by cutting out rectangles from paper board of the same thickness. Their width should be $> 2$ cm this is because the inner side of sleeves made from 2 cm segments would be slightly less than this, $\sim 1.8$ cm). The length of the rectangle can be derived from the formula, $2n+5$ cm, where $n$ represents the number of modules to be tethered. Thus for a 20 module duplex, the strand should be of dimensions, $45$ cm $\times$ $1.8$ cm. Make one side of the strand pointed by cutting out triangles from the sides (7, Figure 2).

2. Each module, although symmetric, would have two sides, the plane one and the pasted one. For aesthetic reasons only, string the modules on one of the two strands, all facing the pasted side (8, Figure 2). Structure 8 models the two important functions of DNA, namely, replication and transcription. In the former case, 8 would represent a DNA single strand-generated by splitting of the mother duplex – where complementary DNA nucleotides (A, T, G, C; A = adenine, T = thymine, G = guanine , C = Cytosine) are lined up for tethering to generate the daughter DNA duplex. In the case of replication, 8 would represent a DNA single strand where complementary RNA nucleotides (A, U, G, C; A = adenine, U = uracil, G = guanine, C = Cytosine) are lined up for tethering to generate a single stranded m-RNA that can translate the message in the duplex to functional systems like enzymes, proteins and hormones.

3. Structure 8 is devoid of asymmetry needed for DNA. This key feature is to be introduced in the tethering with the second strand, to generate either a right-handed double helix or a left-handed double helix.
4. **The right-handed double helix (9):** Using the second strand, tether the modules such that each succeeding module is *above* the preceding one. Thus if the modules are A, B, C, D..., tether B *above* A, C *above* B, D *above* C etc. This will automatically produce a right-handed double helix, B-DNA (9, *Figure 2*). Stretch the strand till the right pitch is secured (~10-11 bases per full 360° turn of any one strand). Note the major groove, the minor groove and sites for intercalation.

5. **The left-handed double helix (10):** Tether the modules by stringing each succeeding module *below* the preceding one. Thus if the modules are A, B, C, D... tether B *below* A, C *below* B, D *below* C, etc. This will automatically produce a left-handed double helix, B-DNA (10, *Figure 2*). The operation is exactly the mirror image of the earlier one! Stretch the strand till the right pitch is secured (~ 10-11 bases per full 360° turn of any one strand).

### C. DNA Double helix from strips

**Material:** Stout envelope of ~1 mm thickness and size 12 cm × ~30 cm (11, *Figure 3*).

1. Holding firmly by the scale, fold 2 cm from the edges along a,b and a’, b’ (12, *Figure 3*). Gently open the seam of the envelope along c, d. Pull back along a, a’ and b, b’ (13, *Figure 3*), apply a layer of glue and fold back securely to the original position 12. Make 2 cm strips from 13 to give motif 3 (*Figure 1*). Proceed from here, precisely as shown in *Figure 1*.

### Suggested Reading

We have taken the modular construction of surfaces to the complexity of an eicosahedron, which describes a surface crafted from congruence of five equilateral triangles resulting in the inscription of a pentagon motif. Taking any pairs of opposite poles, each pole will have a pentagon, with the equatorial girdle harboring ten equilateral triangles. The surface of eicosahedron, a platonic solid with twenty equilateral triangles, can be viewed as a layering of interdigitating regular pentagons.

Compare this in complexity with a geodesic dome, a surface as close to sphere as you can get. Here one perceives the congruence of twelve regular pentagons, but each constituted by 10 triangles, which are irregular \(a \neq b \neq c\), with the neighboring module aligned in a mirror image configuration!

The word geodesy has esoteric origins! This branch of mathematics developed as a result of determining the properties of a spherical object like Earth, in terms of integration of largest number of plane surfaces. The two dimensional projection of the three dimensional Earth is done using such data. From mathematics, geodesic surfaces and the study of their properties have advanced to navigation, aerospace, electronic networks, molecular clusters and even to covered areas, with no support, termed now as geodesic domes.

We will construct a geodesic dome, from five postcards! (Figure 1)

A postcard, that costs 50 paise, is approximately 13.5 × 9 cm in size. This has to be trimmed precisely to size 13.5 × 9, where the ratio is 3:2. Each postcard will provide 4 modules

harboring six right angled triangles with unequal sides, arranged contiguously in a mirror image fashion with the non-hypotenuse sides in the precise ratio of 3:2. The procedure is illustrated in Figure 2.

Use a black marker pen and the front side of the postcard (1). Draw the two diagonals, A→E′, A′→E to create 4 triangles with mid-point X. Now divide the card into 16 rectangles by equally dividing along both the axes. Note that each rectangle will be of the size, 3.4 cm × 2.25 cm and their ratio would be ~3:2 (2). Draw diagonals, G→C′, C′→G′, G′→C and C→G to complete the first motif (3). Cut out the four triangles, AaG, GbA′, E′dG′ and G′CE (4). Using a sharp scissors, neatly cut out the 12 triangles numbered 1-12 (5). Notice that each of these is duplex of two triangles which are disposed in a mirror image fashion and whose non-hypotenuse sides are in the ratio 3:2.

The remaining two angles of the triangle element can be easily computed as shown in (6). These triangles, a total of 120 needed for the geodesic dome, come from 60 duplexes, each card giving rise to 12.
Arrange 3 duplexes in a contiguous mirror image pattern (7). Best results are obtained when the duplexes are joined from the inside using strips from ‘3M Scotch magic tape’. The real skill comes in the joining of these duplexes to modules, modules to pentagons and pentagons to the dome. Tape each duplex to the neighbor from inside, with perfect alignment. Check each operation to ensure that the pasting has lead to a perfect mirror image overlap, by folding along the seam. The joining to the third duplex will, as shown in 7, leave a gap of $180 - (5 \times 33.5) = 12.5\degree$. This is the elegant part of the design, since when the last pair of edges are pasted the center would be lifted up, thus providing the necessary curvature. A planar projection of the module would look like 8 (Figure 2).

The basic pentagon unit of the geodesic dome (Figure 3, 10) would result from joining of five modules as shown in Figure 3, 9. Note that of the 30 triangles in the 5 modules, ten are used for making the pentagon and 20 to provide attachment for other modules, as shown by arrows in 10. In both 9 and 10 the vertices of the module are marked by dark circles, which, as could be seen, align to form a pentagon.

The remaining 15 modules are to be pasted individually. The procedure for adding a second pentagon is shown in 11 (Figure 3). Two of the modules are perfectly aligned with the right side arrows of 10, to generate bonds, 1→2 and 8→7 of the daughter. The three modules needed here are placed in a staggered arrangement. The vertices of the daughter pentagon are indicated by open circles and the 10 triangles that are involved are marked 1→10 (Figure 3). From 11, it is clear that the vertices of the 20 modules develop to that of the pentagons. Each module has 3 corners, 1 vertex and three open lines, which would be half the length of a pentagon arm. Based on these principles, modules can be added as shown in 12→15 (Figure 4). Model 15 gives a good idea of the modular assembly and the principles involved. If all goes well, you will have, from five post cards, the dome, Figure 5.
Suggested Reading

Origami, Modular Packing and the Soma Puzzle*

Can one fit a square peg into a round hole? Never! Can you create high symmetry by assembling modules that lack them? Yes!

Consider this. Take any module – molecule or material – having a particular symmetry property, destroy this by assembling the same module in irregular ways and then put them together to create a macroscopic system that enjoys the precise symmetry of the original module! This is the crux of the ‘Soma puzzle’, discovered in the early part of the last century by the mathematician, Piet Hein. The potential applications of the principles here are enormous. The irregular composites can be used, in storage of information through endless networks, in materials to generate packing designs, in the molecular and structural arena ranging from, combinatorial science, supra-molecular chemistry, packing mechanisms and molecular biology.

Fortunately, to an extent, the feeling for three dimensions (3D) is a born instinct. A baby, three months old, when laid on a table with black checker design, above a floor having precisely the same design, will instinctively keep away from the edge! Pineapples are irregular objects and the way they are packed by unlettered vendors takes your breath away! Having said all this, the finer nuances of 3D have to be acquired and the history of science attests to what the mastering of this can lead to. From Einstein in physics, to Pauling and Woodward in chemistry, Archimedes, Euler, Kepler, Hawkings in mathematics, Michaelangelo, Leonardo daVinci, Picasso, Monet, Escher and Klee in arts, Ramachandran, Watson and Crick in molecular biology, they indeed form a brilliant galaxy!

In this article we will take a small step towards enjoying the exciting area of 3D, by amalgamating origami with mathematical principles; we will do this by transforming two dimensional sheets of paper into irregular objects having a basic cube module and then combining them to form a cube! We will illustrate that the irregular assemblies can be used to create endless 3D objects. The genesis of the Soma puzzle is steeped in high science. The Danish writer, poet and mathematician Piet Hein conceived the Soma cube during a lecture on quantum physics by Werner Heisenberg. Whilst Heisenberg was waxing eloquent on the slicing of 3D space into geometric entities, shuffling them and mixing them up, Hein’s supple imagination thought of using a regular cube to illustrate this principle.

Let us start constructing irregular shapes from a regular cube (a basic cube module), with one of the objectives being to create a cube from these irregular shapes (Figure 1).

Figure 1.

These can be constructed by a planned addition of single modules to the first irregular shape 1, along the X, Y, Z coordinates (Figure 2). Whilst the paths here are crooked, the final mathematics is neat, according to the equation, \( 27 \times a^3 = (3a)^3 \), where \( a \) is the edge length of the single module.

The core irregular shape 1 arises by a three-module combination (Figure 2), which has a cleft, or corner or bent. Six, and only six, unique options are open for the addition of another unit, such that the original irregularity is increased and not destroyed! These are presented in Figure 2.

To rationalize this, the planar composite 1, is placed at the origin of a 3D coordinate system. The construction of irregular objects by addition of a single module to 1 is shown in Figure 2. This procedure leads to 2-7, each having four modules. Note that 5 and 6 are mirror images and 7 uniquely asymmetric. None of the six composites is similar to the other and all lack the symmetry properties of the cube module, though they may possess other forms of symmetry.
Composites 1-7 are the Soma pieces and infinite forms can be created from these, much as that from a tetrahedral carbon. The real challenge is to arrange the composites to reach a predetermined objective, like in retro analysis protocol. This will involve a mental slicing of the end object, much as Piet Hein did with the cube! Indeed, more than 230 essentially different solutions, not counting rotations and reflections, are available for assembling 1-7 into a cube (Figure 1). With a good 3D sense, this can be done in minutes; if not so endowed, several hours! Look at the aesthetically pleasing cross motif in Figure 3. Even with a good 3D sense this may take some time. The real fun with Soma pieces is in this kind of exercise, which can really sharpen the 3D senses, a skill worth acquiring. One can also create abstract forms (Figure 4). This kind of creative activity can be introduced in classrooms. The handicap is the difficulty in making the seven Soma pieces without much effort. It is this problem that is remedied here, by an origami approach.
Construction of Soma Pieces

First let us make the six cube modules to be added to 1 (Figure 2).

Start with a thick marble board or thick hand made sheets and draw on it a rectangle of size 4 inches × 9 inches (Figure 5). Cut this into three 3″ × 4″ rectangles. Each of these can give two ‘T’ shaped modules that can be folded into a perfect 1″× 1″ × 1″ cube (Figures 1 and 5). Crease all the lines in the ‘T’ module and make the hollow cube by bringing edges ff’ to gg’ together and taping them. Folding and sealing the flaps (abcg and a’b’c’g’) will generate the cube module.
Construct 1 is the core for building the Soma pieces 2-7. We need seven pieces of this and the procedure to build 1 is shown in Figure 6.
Let us start with a 4" × 4" grid and cut it into the ‘T’ shirt motif and two constructs which are 3" × 1". The big piece can be folded into a cube duplex, and the cube precursor (the two 3" × 1" constructs) is transformed into the cube. Glue the single cube over the duplex as shown to generate 1. Repeat the operation six more times. We will then have seven of Construct 1.

To construct Soma pieces 2-7, join the single cube to 1 following precisely the pathways shown in Figure 2. In all we will have seven Soma pieces.

We urge you to make these models, experiment with various designs and let us know of any exciting findings. In case you are not able to make the cross, let us know; we have the solution!

If you become a Soma enthusiast you can go to the next step of making a 4 × 4 × 4 composite with 64 cubes. I have made it from 16 pieces and after two days remade the cube. Once disassembled, I have not been able to make it again. So, the complexity of the Soma problem can be enhanced, the limit being your intuition and patience. If you are a mathematician, I would like you to derive a general theorem about the Soma cubes and let me know.
Suggested Reading


Editorial*

While words of learned length, and thund’ring sound
Amazed the gazing rustics rang’d around,
And still they gaz’d and still the wonder grew,
That one small head could carry all he knew.

— Oliver Goldsmith (1728–1774), ‘Deserted Village’

I considered it as a great honor to accept the kind invitation from Professor K L Sebastian, to edit a special issue on Professor R B Woodward, for Resonance.

The presentation is entirely original and educational and addressed to students, teachers and scholars. The contents can form an excellent course in ‘The Art in Organic Synthesis’.

Never before has the synthesis of Vitamin B12 been presented that allows one to compare two independent approaches to this formidable target. The simulation of Nature is often cited as the inspiration for organic synthesis, and here one can compare the two independent routes cited above to the way Nature builds Vitamin B12 from simple starting materials. I am grateful to Dr. Wayne Craig for putting together such a composite profile. In addition to Vitamin B12, we have illustrated the total synthesis of Strychnine, Chlorophyll and Cephalosporin C. We have added, as prologue, ‘The spirit of adventure and the art of creation’ and as epilogue, ‘Woodward seminars’. The prologue is preceded by a brief analysis of the personal profile of R B Woodward, where we have created a virtual image of his that hopefully would provide the total profile of this genius as well as the latent traits that are always associated with such obsession.

Only a handful are gifted with, at a very young age, the path laid out for them in life. Indeed Woodward’s obsession with organic chemistry sprouted very early. His initiative, at the age of eleven, to secure few original publications in German journals via consular channels in Boston defies imagination. By the time he entered high school, he had already managed to perform most of the experiments in Gattermann’s book on experimental organic chemistry.

Two factors dominated Professor Woodward’s profile: exceptional brilliance and unyielding determination. The former fuelled the latter and drove him to seek seemly impossible objectives.

Robert Burns Woodward (1917–1979)*

A Personal Profile

Gie me ae spark o’Natures fire, That’s a’ the learning I desire.

– Robert Burns
(1759–1796)

Robert Burns Woodward was born in Boston on April 10, 1917, Massachusetts, to Margaret (née Burns, an immigrant from Scotland) and Arthur Chester Woodward, Roxbury, Massachusetts. When Robert was one year old, his father died in the flu pandemic of 1918.

Although his mother remarried, she was soon abandoned by her second husband and left to bring up her son in straitened circumstances. Woodward received his primary and secondary education in the public schools of Quincy, Massachusetts, where he was allowed a triple promotion, enabling him to enrol in MIT (Massachusetts Institute of Technology) at age of 16! In the remarkably short span of four years Woodward completed both his BS (1936) and PhD (1937) in chemistry with the sympathetic support of Professor James Flack Norris, who remarked in June 1937 that “we saw we had a person who possessed a very unusual mind and we wanted it to function at its best. If the red tape necessary for less brilliant minds had to be cut, we let it go. We did for Woodward what we have done for no other person like him in our department. We think he will make a name for himself in the scientific world” (Boston Globe, 8 June 1937).

From a very early age, Woodward was attracted to and engaged in private study of chemistry while he attended the public primary and secondary schools of Quincy, Massachusetts. By the time he entered high school, he had already managed to perform most of the experiments in Ludwig Gattermann’s then widely used textbook of experimental organic chemistry. In 1928, Woodward contacted the Consul-General of the German Consulate in Boston, and through him, managed to obtain copies of a few original papers published in German journals. Later, in his Cope lecture, he recalled how he had been fascinated when, among these papers, he chanced upon Diels and Alder’s original communication about the Diels–Alder reaction. Throughout his career, Woodward was to repeatedly and powerfully use and investigate this reaction, both in theoretical and experimental ways. Woodward’s doctoral work involved investigations

related to the synthesis of the female sex hormone estrone. MIT required that graduate students have research advisors. Woodward’s advisor was Avery A Ashdown, although it is not clear whether he actually took any of his advice. After a short postdoctoral stint at the University of Illinois, he took a Junior Fellowship at Harvard University from 1937 to 1938, and remained at Harvard in various capacities for the rest of his life. In the 1960s, Woodward was named Donner Professor of Science, a title that freed him from teaching formal courses so that he could devote his entire time to research.

What kind of a person was Bob, and how do we remember him? He was a genius and a very sensitive individual with a prodigious memory. He also had a drive to solve difficult problems and liked teaching in the broadest sense of the word. His lectures were models of clarity, originality, and insight. He enjoyed starting at the upper left-hand corner of a very large blackboard and finishing at the lower right-hand corner with precise formulation of his ideas and thoughts and a total package that was characteristically Woodwardian. He eschewed the use of slides and drew structures by using multicolored chalk. Typically, to begin a lecture, Woodward would arrive and lay out two large white handkerchiefs on the countertop. Upon one would be four or five colors of chalk (new pieces), neatly sorted by color, in a long row. Upon the other handkerchief would be placed an equally impressive row of cigarettes. The previous cigarette would be used to light the next one. His Thursday seminars at Harvard often lasted well into the night.

He had a fixation with blue, and many of his suits, his car, and even his parking space were coloured in blue. In addition, in his later years he had a well-loved blue Mercedes sedan that occupied this parking space during the days and nights when he was doing science in Converse Memorial Laboratory. He detested exercise, could get along with only a few hours of sleep every night, was a heavy smoker, and enjoyed Scotch whisky and martinis.

As Woodward’s post-doctoral student I have imbibed his personal work habits. On an average he used to put in 14–15 hours a day (Saturday half day); when I joined he told me that he expected me to work for 100 hours a week! Towards the end it came to much more than that. His only regular round was between 10:30–11:00 pm perhaps ensuring our presence.

His intensity as a scientist is well known (vide supra), but he was just as intense in the non-scientific areas of his life. When he wanted to be, he was quite a social person. I remember some of the parties at his Belmont, Massachusetts, home, where puzzles and games were played at his behest and with his participation. He loved such challenges, and as an example, I should tell you that he loved doing The New York Times crossword puzzle every day, but of course, only in ink. It wasn’t necessary for him to erase. He loved and appreciated good food and also
good drink. As we know from some of his scientific activities, symmetry played a large part in his thinking and, in fact, it played a part in his personal life. He had a very symmetrical license plate, and he tried to have symmetrical relations with his children, although that was not always successful. I can testify that he also liked adventure in areas other than science. I remember well when I bought a new twin engine fishing boat in 1960, and we tried it out one day by going from Cuttyhunk to Doxie’s homeport of Bridgehampton on Long Island. The day was very foggy, and we did not have any instruments aboard except a compass and a depth meter. Did Bob want to try running the boat? “Of course,” he said. He loved it, and actually very much enjoyed piloting the boat for several hours without incident (an account by Professor Albert Eschenmoscher, ETH).

In 1938 he married Irja Pullman; they had two daughters: Siiri Anna (b. 1939) and Jean Kirsten (b. 1944). The second marriage with Eudoxia Muller in 1946 had very good times as well as many rough spots. As a result of this marriage he fathered two additional children: a daughter who Bob and Doxie named Crystal and a son named Eric. This marriage broke apart in 1966.

I have learned much more from Professor Woodward’s personal life than his chemistry. His deep obsession with chemistry made every other aspect of his life a tragedy. His total negligence of his own health (heavy smoking and drinking) and even more typically his family suffered greatly. In his heady days even his children had to wait for days to talk to them with the result that except his son Eric, none others fared well. The last time I was in Harvard, RBW said, “Sorry Subram, I cannot drive you to the airport. I am waiting for a call from Eric!” I felt sad! How the tables have turned! When his second marriage broke up in 1966, he left his 5-Belmont residence and moved to a Hotel where he passed away! Friends took turns to take care of him!

Central to all this was Ms. Dolores Dyers (Dodie), RBW’s nearly lifelong secretary. Every day I have seen RBW coming with one red rose to give it to her! Dodie played a central role in RBW’s accomplishments which has never been acknowledged! When Dodie passed away in the early seventies by cancer, RBW wrote to every one of his co-workers about this great loss! Colleagues tell me that in the ensuing days RB was so distraught that they feared for him.

Apart from his excessive fondness for the spirit, his smoking habit by any yardsticks was inadmissible. He used to smoke 3 packs a day with his own blue match folders. When the surgeon general’s report in the early sixties stated that cigarette smoking is directly linked to heart, RB tried to give up smoking! Too late! Those days he was impossible and we kept clear of him. Fortunately he soon returned to his smoking.
His fighting spirit is illustrated in the following story narrated by Barton*. By pure chance, the two great men met early on Monday morning on an Oxford train station platform in 1951. Robinson* politely asked Woodward what kind of research he was doing these days; Woodward replied that he thought that Robinson* would be interested in his recent total synthesis of cholesterol. Robinson, incensed and shouting, “Why do you always steal my research topics?”, hit Woodward with his umbrella. This story must be true, because Woodward told me about it several days later.

He was also fond of literature, art and music. We arrived at the night club and Armstrong was already playing. I introduced Bob to my friend saying, “This is Bob Woodward.” My friend turned around impatiently, shook his hand, and returned his attention to the music. I said, “Look, Bill, Bob Woodward is to organic chemistry what Louis is to the trumpet!” At that my friend turned around slowly, looked Bob in the eye, and said, “Man, you must be one hell of a chemist!” Bob said he thought that was the most sincere compliment he ever got**.

He had a fountain of stories to tell, some perhaps invented. One such is that, when he went to one of his postdoctoral lab at night, he found the man strangling himself making terrible noises; on enquiry it was found that he was merely imitating a play on the radio which was on.

When he was awarded the Nobel Prize, he took his entire Basal group including me, to Stockholm. Unusual observations aroused his curiosity. During the lunch for Nobel laureates at the palace, he found the waiters were wearing chest full of medals. On enquiry he found that many royals visit the palace and they give these medals which are cheaper than cash!

He was very fond of my late wife Darshan. He used to ask her particularly how she liked his lectures. On one occasion, his trousers got torn and he asked Darshan to loan her sari so that he could wear it like a Toga!

In his last years he became much more social, not in a global sense, but in his relationships. When he was in Cambridge we had dinner at least once a week. Even though he loved having a home-cooked meal practically every week with my wife, Gail (Ms E Blout**), and me, we varied the routine by occasionally going to local restaurants. The night before he died we had a wonderful dinner together at the Stockyard and left him in a very good mood when we separated at about 11:00 pm. During the next hours he suffered a fatal heart attack, and I never saw him again. Although in this period he had many symptoms of a cardiac condition, he ignored them as if they weren’t important, and maybe such symptoms were not important to him**.

* Barton and Robinson are both Nobel Laureates in Organic Chemistry.
The Spirit of Adventure and the Art of Creation*

Camphor to Vitamin B\textsubscript{12}

What is described in the pages that follow is the recounting of an exciting epoch in creative chemistry, namely, the synthesis of the complex molecule cyanocobalamin or vitamin B\textsubscript{12}. It is the saga of the total laboratory synthesis of a molecule that we humans cannot do without and yet do not have the built-in biochemical machinery within ourselves to make it. We depend on the microorganisms that have colonized our intestines to biosynthesize it for us, in a symbiotic manner.

With Woodward too, the challenges that he met increased in grandeur, from the total synthesis of quinine in 1944, to strychnine in 1954, to cephalosporin C and chlorophyll in the 1960s and finally win over vitamin B\textsubscript{12} in 1976.

With Woodward too, the efforts and the strengths (technical and theoretical) that he had to commandeer varied from challenge to challenge, and climaxed with vitamin B\textsubscript{12}, when he and his associates had to put together 181 atoms in space in over a dozen circles with nine centers of chiral asymmetry.

In any endeavor of this dimension, and the challenges and efforts of this scale, strategy, techniques and the creativity of approach are noteworthy. It is this aspect of creativity that is addressed in large measure in the following pages. Any act of creativity is a fusion of matrices of thought. These matrices run independent of one another, with no connectivity or commonality. It is when the twain meet that creativity is manifested. Arthur Koestler, in his book *The Act of Creation*, has discussed several instances where such impacting of two different matrices of thought has led to novelty and creativity. One can describe Woodward’s art in organic synthesis in the same words – his naming the challenge, his courage and efforts to meet it and his creative ways of winning it.

The synthesis of vitamin B\textsubscript{12} will remain as the parting masterpiece offering by Robert Burns Woodward to the world that he left in 1979.

From his early days, two aspects of carbon science, namely, the principle of aromaticity and the logical construction of molecules captivated Woodward. These two fortuitously found convergence in the synthesis of vitamin B\textsubscript{12}, and this alone should make the adventure unique.

More explanation is needed to understand how Woodward, in his own lifetime, became a cult personality. He deliberately created an aura around him, setting himself as an example of a highly motivated and dedicated person who considered his time most precious and was loath to part with it. His liking for blue, manifested in his tie and suit, his meticulous attention to appearance, his prodigious smoking with matches that were custom made, his proclivity to imbibe vast quantities of spirit, his addiction to give lengthy lectures which were so meticulously prepared and so beautifully delivered and his famous Woodward Seminars that gave him a splendid opportunity to cut people to their dimensions, all contributed to this. He built for himself a reputation of total knowledge of what was happening and happened in the domains of organic chemistry and even distantly related subjects. His voracious reading habits became a legend. The stories got passed on and with each transfer more color was added! He enjoyed these immensely. Who can forget the scene, where Woodward was carried by four of his group in a sedan chair, on the occasion of his birthday, a year before he passed away. Sitting pretty in full regalia and puffing away, he remarked, “This harkens back to days of yore – days of monarchy – in my opinion better days!”

During the synthesis of strychnine, at one very difficult stage, he made the comment to his group, “Either we make strychnine or we take strychnine!” Indeed it is such conviction that made his colleagues do reactions under esoteric, exotic, unusual, wild and dangerous conditions, to accomplish the desired targets. The extent of such involvement can be assessed from the fact that during the later stages of vitamin B₁₂ synthesis, apart from the rigors that had to be imposed in terms of exclusion of air and moisture, the analysis had to be performed in tanks that had admixed in it hydrogen cyanide! In most cases his convictions actually paid off. This could be illustrated with his obsession to transform chlorin to chlorophyll as happens in Nature and his obstinacy in crafting cephalosporin-C from the simple amino acid cysteine and his design for the prostanoid nucleus from glucose. This is best reflected in his plan for vitamin B₁₂, where he was able to craft all the four rings of the vitamin from camphor! He created the two left-hand rings of the vitamin from the left-handed camphor and the two right-hand rings from the right-handed camphor!

Infrequently, his analysis of the situation became awry but even here he emerged as a notable winner gaining great advantages. His pondering on how strychnine was made in Nature laid out a plan for the chemical synthesis, which is one of the most amazing feats in synthetic organic chemistry. Years later, it was shown that his biosynthetic plan was not correct, but by that time he had accomplished the feat of strychnine synthesis based on such erroneous principles! In the case of vitamin B₁₂ the isoxazole route had as the linchpin the cyclisation of a triene system generating two chiral centers whose disposition was absolutely critical for the total
synthetic plan. In the event, the reaction preferred an exactly opposite path. Still Woodward took great advantage of this failure to generate the now famous Woodward–Hoffmann rules, which arguably enjoys a greater impact.

The great irony in the vitamin B$_{12}$ synthesis is that Nature had the last laugh and showed that there is much to be learned about its very subtle nuances. The point I am trying to make is that the entire synthetic plan to vitamin B$_{12}$ rested on the differentiation of one of the carboxyl groups of the corrin system from the remaining six, which was thought to be essential for the attachment of the complete nucleotide. Years later, it was found that in even the undifferentiated hepta acid system, the preference was for the correct carboxyl group to interact with the nucleotide over six others, and therefore there was no need for a strategy based on such differentiation! In retrospect, one could argue that because in Nature a particular carboxyl group is differentiated, it must enjoy a preference. A sample set of experiments would have shown this and saved a lot of efforts, but then such hindsight is quite prevalent in our efforts at simulation of Nature. As mentioned earlier RBW’s biosynthetic route to strychnine was wrong, so also his triene cyclisation that lead to Woodward–Hoffmann Rules!

From 1962 when synthesis of vitamin B$_{12}$ was initiated, to 1976 when the totally synthetic vitamin B$_{12}$ was made, an odyssey spanning 15 long years and involving more than 100 collaborators and amounting to over 200 post-doctoral years at Cambridge and a similar contingent across the seas at Zurich under the banner of Eschenmoser, encompasses a mural that seems to bring out all the subtle, elegant and ingenious nuances in the art of building molecular structures. One can asseverate that never in the history of human endeavours was there such a prodigious amount of energy injected to achieve a single objective, namely, the aggrandizement of vitamin B$_{12}$, a formidably complex natural product, which perhaps could be ranked amongst the very first in terms of evolution protocols. In the annals of carbon science, the synthesis of vitamin B$_{12}$ would always stand as a unique monument to the glory of the organic chemist, as a genius in understanding the myriads of ways by which carbon seeks and discards partners and use this to specific advantage in the construction of molecular edifices of extreme complexity.

The subset of elements that followed the train of the synthetic flow and over such a long period, provided knowledge of immense value, in the realm of synthesis, reaction mechanisms, strategies, pitfalls, pointers and a complete and fascinating story of lasting value! Indeed, in the realm of the synthesis of vitamin B$_{12}$, one could see synthesis, reaction mechanisms, reagents, discovery and new principles, the latter exemplified with the enunciation of the Woodward–Hoffmann rules, which perhaps constitute the most significant theoretical advance pertaining to formation of covalent bonds and their disruption. This directly arose from work on vitamin B$_{12}$.
1. **Prolog**

Unlike other epics in this turf, the full story of the vitamin $B_{12}$ synthesis has neither been told nor the details published. It is this aspect I wanted to rectify above all, to put on record, even after 40 years, the complete story of the vitamin $B_{12}$ synthesis.

I strongly feel, and was encouraged by many, that this should be done to preserve in our annals such a precious achievement. During my examination of many articles related to this topic, in spite of the fact that four decades have elapsed and in spite of the fact that science tends to become old fashioned as a function of time, I found that here was an example of accomplishment that would always stand the test of time and would serve as a beacon that illustrates the art of organic synthesis.

From the synthesis of quinine in the forties to the culmination of the construction of vitamin $B_{12}$ in the late seventies, run a stream of unparalleled accomplishments by Woodward. In this journey, one could also perceive that the challenges that were taken and met were of increasing complexity. This upward gradient, in a sense, towards the end, made Woodward a prisoner of circumstances. Thus, after the completion of chlorophyll synthesis he had little choice but to embark on an attack on vitamin $B_{12}$.

2. **The Plan**

Described simply, vitamin $B_{12}$ is an assembly of four rings, which though look similar to the porphyrins, are far more complex, in the sense that the rings are saturated and harbor a string of chiral centers. In the plan that won the quest, each of the four rings either arises from camphor or is correlated to camphor. Thus camphor, whose absolute configuration has been rigorously established, not only provided all the four rings but also supplied chemical proof for the absolute configuration of vitamin $B_{12}$, whose three-dimensional disposition was accepted, as revealed by X-ray crystallography.
The plan presented in Figure 1 shows the quintessence of the adventure. The left rotating camphor was correlated to ring A and restructured to ring D and from the right rotating camphor were created rings B and C of vitamin B_{12}. The top half of the figure shows where the atoms of camphor end up in the rings of Figure 1, in which all the highlighted carbon centers arise from camphor.

The union of the left-hand side (LHS/western-half) and the right-hand side (RHS/ eastern-half) (Figure 2) encapsulates the core of the plan. To make reading and correlation easier the corrin numbering system is provided. LHS having six contiguous asymmetric centers reflects a brilliant effort by Nature, and Woodward deemed it as a most covetable object to create, a notion from which he never wavered, in spite of incredible obstacles.
3. TCK, the Mascot for the Team!

Tricyclic ketone (TCK) (1) enjoys a pre-eminent position in this story by virtue of its presence from the debut to curtains. TCK possesses all the elements needed to mold the ring A of vitamin B$_{12}$ and has the information to direct the correct union to ring D as well as the generation of, in a specific manner, all the carbon asymmetric centers.

Scheme 1.
The boron trifluoride mediated condensation of m-anisidine with acetoin afforded 2,3-dimethyl-6-methoxy indole (2) (Scheme 1), which was transformed to the indoline 3 by reaction with propargyl magnesium bromide. The reaction of 3 with mercuric oxide–boron trifluoride–methanol smoothly afforded TCK (1).

Two inputs are needed to take TCK to the mainstream, namely, resolution and determination of the absolute configuration. Woodward took advantage of the amphoteric NH unit in TCK, to bring about an exceptionally easy resolution, as shown in Scheme 2. The reaction of 1 with (−) α-phenethyl isocyanate afforded the diastereomeric mixtures from which one crystallized and the other not at all! Therefore their separation was exceptionally facile. On thermolysis these reverted to chiral TCK. It turned out that TCK obtained from the crystalline diastereomer had the required absolute configuration presented as 1.

Woodward took great delight in stating that starting with a racemic material has great advantages since the undesired mirror image is a perfect system to carry out model experiments.

The delightful correlation of 1 with left rotating camphor is shown in Schemes 3 and 4.
4. Correlation of 1 with (–) Camphor to 6

(–) Camphor was subjected to fuming sulfuric acid to afford camphor-10-sulfonic acid 7, by a series of rearrangements as shown in Scheme 4. Treatment with PBr₃ and NaOAc followed by oxidation leads to the carboxylic acid 8. The (–) camphor $\rightarrow 8 \rightarrow 9$ change represents an elegant carbonyl switch and mirror image formation mediated by the carboxyl group (Scheme 4).
Compound 9 was subjected to Curtius rearrangement and the resulting isocyanate on addition of methanol gave urethane 10. Treatment with potassium tertiary butoxide followed by quenching with water gave 6, identical in all respects to that derived from 1 (Scheme 3). The $10 \rightarrow 6$ change presents a unique sequence. The strong base brings about a cyclization to a fragile 1,3-diketo system that readily relaxes with hydroxide to give 6.

5. The Making of the D-ring from Camphor

The reaction of (−) camphor with amyl nitrite-potassium-t-butoxide afforded the isonitroso compound, which in the presence of sulfuric acid underwent the Beckman rearrangement (fragmentation mode) to give the carboxy amide. This, on Hoffmann degradation readily afforded the amusing lactam 13, the overall change amounting to the replacement of a methylene of camphor with the NH equivalent! The nitroso derivative of 13, under carefully defined conditions underwent a clean N-nitroso rearrangement leading to the desired chiral 14, the overall process involving fragmentation, specific methyl group migration and loss of nitrogen (Scheme 5).

![Scheme 5](image_url)

Being now familiar with the vitamin B$_{12}$ structure (Figure 1), it can be concluded that the single chiral center in 14, that carries the methyl group, is destined to be the C-17 of the vitamin B$_{12}$. This center is unique; it is a spatially unalterable center where the downward disposition of the
propionic acid side chain is to serve as the link to the cobalt center through a nucleotide. In terms of the plan, this would be the sixth center of LHS. TCK harbors centers 2 and 3 and the aromatic ring is programmed to generate the first one by a Birch reduction sequence. Therefore the union of TCK with 15 should lead to 33 (Scheme 9) that can generate centers 4 and 5 in a specific manner to give a single product. A sequence as shown in Scheme 5 readily took 14 to the acrylate 15 having the required qualities.

6. **Camphor → False Ozonide → Ring C**

Camphorquinone arising from the selenium dioxide oxidation of (+) camphor when subjected to careful treatment with boron trifluoride in dry acetic anhydride afforded 16 (Scheme 6). Although the acyl cation that initiates the rearrangement can complex with either of the two carbonyl units, the course of the reaction seems to be dictated by the stability of cation that can arise by this complexing, as shown in Scheme 6. Compound 16 was readily transformed to the key amide 17 via the acid chloride.

![Scheme 6](image-url)
The relation between 17 and ring C of vitamin B$_{12}$ is clear, viewed from vantage of the gem dimethyl marker. Thus, the bonding of the amide nitrogen with a carbonyl generated proximal to the gem dimethyl unit could lead to ring C. Although this was achieved eventually, the path involved the condensation with the opposite carbonyl to form the glutarimide 20 (Scheme 6).

Treatment of 17 with ozone results in ozonide 19, which is stable enough to be chromatographically purified! In truth, this ozonide bears no resemblance to that expected from 17, namely, 18 (Scheme 6) and therefore it is appropriately labelled a false ozonide, an imposter! Compound 17, endowed with proximal and distal combatants, is the one really programmed to perform unusual acrobatics. The real fellow fragments to an anhydride and a keto-oxide (Scheme 6). The distal amide nitrogen steps in to remove the acetate to form a glutarimide whose nucleophilic carbonyl readily accepts the waiting keto-oxide to form the false ozonide 19. Zinc reduction to 20 followed by treatment with methanolic hydrochloric acid leads to the α-methoxy pyrrolidone 21, which thermally eliminates methanol to give unit 22 to be incorporated as the ring C of vitamin B$_{12}$.

7. Two Approaches to Ring B of Vitamin B$_{12}$

Although quantities of ring B precursor, 27 were made by a short sequence initiated with a cyclo-addition, along the path shown in Scheme 7, the one from (+) camphor not only fulfilled aesthetic expectations but also was pivotal in determining the correct absolute configuration to be used.

The cyclo-addition of butadiene with E-3-methyl-4-oxo pent-2-enoic acid in presence of stannic chloride gave the cyclo adduct 23, which was resolved with (–) α-phenethyl amine. The absolute configuration needed, namely 23, was determined by correlation with that of (+) camphor (vide infra) as well as with fragment derived from ozonolysis of heptamethyl cobyrinate, the methanolysis product of vitamin B$_{12}$.

In this reaction ring C fragment is also obtained. The π bond of 23 was cleaved to 24 with chromium trioxide. Under the acidic conditions of the reaction, compound 24 underwent cyclization to the bicyclic system 25, whose acetic acid side chain was transformed to that of propionic acid by Arndt–Eistert homologation protocol. Ammonolysis afforded lactam 26. At first sight it may look strange that, in the bicyclic system 25 the more-hindered carbonyl is preferentially lactamized, a process that involves attack from the α-side. The reality is that both the lactams are formed. The resulting compound having two nitrogen functions attached to the same carbon is unstable and equilibrates with open conformers that could recyclize either through the oxygen or the nitrogen. In this dynamic flux, the imino lactone corresponding
to the less hindered site prevails, which on hydrolysis gives 26. We know all this because Woodward took great pains, typical of him, to understand this apparent aberration. Treatment with phosphorous pentasulfide specifically yielded the thiolactam 27, the construct that would be ring B of vitamin B₁₂ (Scheme 7).

Schemes 7 and 8.

To reach the same objective (+) camphor was transferred to 9 by procedures outlined in Scheme 4 and the carboxyl function was re-structured to 28, as shown in Scheme 8. The transformation of 28 to the camphor quinone 29 followed by sequence, metamorphosis to cyclohexene 30 by real ozonide and false ozonide protocol (Scheme 6) afforded 31, which in methanolic HCl was transformed to 32 and then 33. Deprotection followed by Cr(VI) oxidation under carefully controlled conditions afforded 26, identical in all respects to that secured from the Diels–Alder approach.
8. **The Crafting of LHS, a Unique Molecular Constellation (Figure 2)**

In the general plan for vitamin B<sub>12</sub>, outlined in Section 2, the coveted synthetic objective was the left-hand side of vitamin B<sub>12</sub>, LHS, possessing six contiguous asymmetric centers, where all the carbons, excepting those involved in the bridging to the right side carry chiral centers.

The cyclopentene acrylic ester 15 derived from (–) camphor (Scheme 5) was saponified and converted to the acid chloride 34 with oxalyl chloride. The reaction of TCK (1) and 34 afforded the composite 35 (Scheme 9). Compound 35 has the required 2, 3 and 6 chiral centers, with the first masked as the aromatic ring. The intervening chiral centers 4 and 5 were created in one move in a specific manner by Michael addition of the conjugate base of the TCK segment to the π - bond of the acrylic system to afford, in excellent yields 36, which now harbors five of the required six centers in their proper absolute configuration. The convex nature of the TCK, coupled with the presence of endo-oriented methyl groups, which augment the convex profile, further ensure the addition from the top side to the trans-oriented receiving unit. These ensure the stereochemical disposition as shown in 36.

The stage is now set to unmask the chiral center at the first position. The obvious choice is the Birch reduction, which should be preceded by proper protection of the susceptible functions like the carbonyl group and the lactam unit. Whilst the former could be accomplished by ketalization, the latter took considerable efforts and the solution found was unique. The reaction of the ketal with triethyloxonium fluoroborate afforded the lactam ether, which on treatment with methoxide gave the unusual ortho system 37 (Scheme 9). This being possessed of three lone pair harboring ligands converging on a single carbon center, readily ejected methanol on heating to give the imino ether 38. The bond in 38 harboring two electron donating groups at single termini, is highly electron rich and is totally impervious to the conditions of the Birch reduction. In the event, treatment of 38 with lithium in ammonia in presence of butyl alcohol with dry THF as the solvent followed by treatment with acid gave enone 39.
Scheme 9.
Obviously, the initial Birch reduction product underwent a series of prototropic rearrangements leading to the more stable 39. This molecule harbors all the six chiral centers of LHS. Whilst the positions of the prevailing five are certain, that for the nascent one is uncertain. It turned out from subsequent experimentation that at this point the configuration is the undesired one, having α-orientation for the hydrogen (Scheme 9).

The stage is now set to bring in the second nitrogen needed for the corrin structure. As could be seen from Figure 1, the two nitrogens on the LHS of vitamin B_{12} are 1, 4 positioned, linked by two chiral centers. Such a positioning could be realized from a Beckman rearrangement of the cyclopentanone oxime. provided the oxime hydroxyl is placed anti to the remaining part of the molecule. Considering the steric constraints this is to be expected. In the event, the reaction of 39 with hydroxylamine hydrochloride–sodium acetate afforded the dioxime, which could be readily transformed to the desired mono-oxime 40, by the removal of the more exposed oxime with sodium nitrite acetic acid.

The treatment of 40 with ozone in methanol at –80°C followed with periodic acid and esterification with diazomethane afforded in good yields compound 41. In this series of reactions, both the double bonds present in 40 were cleaved without affecting the obviously very sterically hindered oxime function. The cleavage of the cyclohexenone system generated the five-membered lactam, destined to be the A ring of the B_{12} on the one hand and α-diketo system on the other. The latter suffered loss of carbon atom on periodic acid treatment to the required propionic acid chain, which was protected by esterification.

The enamine of the less-hindered carbonyl smoothly underwent addition to the desired enone which by the reaction of methane sulfonyl chloride-pyridine to afford 42. The reaction of 42, under conditions described earlier, namely, treatment with ozone followed by periodic acid and esterification with diazomethane afforded compound 43 where the methyl group carrying the chiral center originally designed from (–) camphor harbors the ligands for further transformation. Having the required chiral centers and ligands at hand in structure 43, endeavors were taken up to place the oximino nitrogen at the correct position enabling the formation of ring D. This turned out to be an extremely difficult process, since under most conditions, the mesylate was unaffected. The fact that the ultimate conditions that won the rearrangement involved heating of 43 in methanol at 170°C for 2 hours in presence of the strong acid, polystyrene sulfonic acid, highlights the recalcitrant profile of this compound. Under such drastic conditions little control could be expected on the events that follow. However, in one of the few fortunate occurrences in this story, it led to the delightful 47, (Scheme 9) which has the elements of the A–D composite with all chiral centres in the correct disposition excepting at the carbon 3, whose configuration
needed to be established. Compound 47 was fondly called as α-cornorsterone, which name harbors diverse nuances, the most significant being that it is the cornerstone for further progress to produce the corrin system from something that looks like a steroid.

The one-step transformation of 43 → 47 highlights a cascade of events that has taken place dictated by, naturally, the strong conditions of the reaction. The analysis presented in Scheme 9 provides a rational explanation for the change, although permutation of the sequence is perfectly plausible. In its simplest form this change could be understood as initiated by the Beckman rearrangement wherein methanol plays a key role to produce the enol lactam ether 44. Compound 44 then undergoes an acid induced Claisen condensation to afford the 1,3 diketone system 45 which is exceptionally well aligned for the formation of the critical bond uniting the nitrogen and the carbonyl function generating, at last, the D ring of the vitamin B12. This process is made very facile by the highly nucleophilic imino ether function and by events shown in Scheme 9 leading to the enone 46.

These highly interesting series of dramatic events are provided with a fitting finale in the liberation of the acetic acid side chain, the ligand at the 18 position of corrin, by methanolysis. Whilst liberating the acetic acid side chain from the grip of lactam relating to ring D was facile, that pertaining to similar ligand in ring A proved to be an extraordinary adventure which is undoubtedly one of the points that finds illustration as to how seemingly impossible objectives could be obtained, by carrying out several parallel reactions coupled with an analysis of each of such events in detail. The success here not only led to the desired construct but also enabled the identification of the stereochemical disposition at chiral center 1, apart from magnificent insights into physical organic chemistry.

The methanolysis of the six-membered lactam in 47 proved extremely difficult under acidic and basic conditions. Several pathways were explored with uniform failures. At this point Woodward remembered that along with 47 there was obtained, as he puts it, a minute quantity of another crystalline compound, whose chemical and spectroscopic properties left no doubt that it was 48 isomeric to 47 (Scheme 9). In sharp contrast to 47 this isomeric compound very readily underwent methanolysis of the lactam giving rise to the desired product. Analysis of this event clearly pointed out that whereas the lactam grouping in 47 is hindered, that in the isomeric 48 was easily accessible to the rupture of the lactam carbonyl. A comparison of 47 with isomeric 48 would easily show that the β-oriented propionic ester grouping at C-3 in the former offers significant steric hindrance to the methanolysis of the lactam which has to also take place from β-side. In view of the enormous overcrowding at the α-location, the shifting of the propionic acid side chain from [β→α] (Scheme 9) removes a major obstacle and makes
the opening of the lactam ring easy. Having determined that the isomer which is now called β-corrnorsterone (48) as the appropriate intermediate for further progress, the problem was to have this compound in ‘substantial amounts’, on the face of the finding that in the Beckman rearrangement cascade, the near exclusive product was the α-corrnorsterone 47!

Studies showed that, under equilibrium conditions, the concentrations of 47 and 48 were nearly equal. In sharp contrast, in the case of the corresponding acid salts, arising from treatment with strong base, the equilibrium was heavily shifted in favour of the desired 48. Thus, treatment of α-isomer 47 with strong base, equilibration, acidification and esterification led to production of the desired cornorsterone, 48, in over 90% yields.

This marvellous illustration provides a rationale for the great success of Woodward, always arising from a conviction, detailed experimentation and an incise analysis.

The reaction of 48 in methanol containing hydrogen chloride with phenyl mercaptan afforded smoothly in excellent yields the thiophenyl compound 49 (Scheme 9). Compound 49 is written in a corrin profile as 50.

Treatment of 49≡50 with ozone followed by liquid ammonia readily afforded 51 which has all the six stereo centres in the right configuration and where the crucial propionic acid side chain is differentiated from the others in the form of an amide. A noteworthy point is that the ene-aldehyde survived the ozone treatment. The aldehyde grouping was re-structured for union with the BC fragment by transformation to the corresponding bromomethyl compound 54, by reduction to the alcohol 52, transformation to the mesylate 53 and neucleophilic displacement with lithum bromide.

In this process the amide function was transformed into the nitrile, so that in the completion of the synthesis it had to be converted to a carboxylic acid, differentiated from the others.

What we have seen here in the transformation of TCK (1) to LHS (54) is a story of significance in the art of organic synthesis and those who traverse it would derive great satisfaction and encouragement arising from the feeling that those edifices crafted by Nature can be constructed provided basic facets underlying them are understood. It would not be out of place to mention here that extremely complex natural products that abound must have evolved over a large time span. When viewed from this vantage the synthesis of the LHS of vitamin B₁₂ in a matter of a decade deserves great appreciation.
9. The Union of Rings B and C

This was achieved by a novel and general strategy with sulfur as the initial linker followed by its extrusion uniting the two fragments. The role of sulfur here has been colorfully described by Woodward as the agent which brings in enforced propinquity of the partners, a sure medicine for leading to greater intimacy. The strategy here is best illustrated with the union of the B and C rings, which proceeded without major complications. The reaction of 27 with 22 with benzoyl peroxide in methylenechloride containing catalytic amounts of hydrogen chloride led to the sulfur bridged system 56 (Scheme 10). The overall process taking place here can be envisaged as oxidation of the thiolactam grouping in 27 to an electrophilic disulfide, which, in presence of acid, readily accepts the nucleophilic termini of 22 giving rise to the intermediate 55 which by an expected prototropic shift leads to 56.
On treatment of 56 with triethyl phosphite in xylene, the sulfur is extruded to give the desired bridged system 58. This change can be understood as shown in Scheme 10, as taking place via an episulfide intermediate 57. The B-C composite was then prepared to accept the A-D segment by transformation to the thiolactam 59, which could be best achieved by initial transformation to a lactam ether with trimethyl oxonium fluoroborate in presence of isopropyl methyl mercury followed by treatment with hydrogen sulfide. The facility with which the B-C ring construct was achieved was not an unqualified success. It was found that the propionic acid side chain at the 8 position readily underwent epimerizatin to give mixtures. In these complicated structures the mixture behaved as a single entity, crystallized beautifully and required careful spectroscopic analysis for their differentiation and HPLC for separation. From this point on, the constructs were generally a mixture of epimers, which at an appropriate stage could be easily separated to pure components.

Whilst such easy epimerization arising from proximity to a carbon nitrogen double bond was an unwelcome intrusion, it also provided a solution to a most vexing problem relating to the union of the left-hand side with the right-hand side bridging rings D and C.

10. **The Construction of the Southern Bridge**

The union of LHS (54) and RHS (59) was the next logical step to establish the southern bridge.

11. The reaction of 54 and 59, representing the left/west and the right/east segments, with potassium tertiary butoxide in tertiary butyl alcohol afforded the sulfur-linked composite 60 (Scheme 11). Under stringent conditions compound 60 (thioether I) can be prepared in quantitative yields. However the reaction of this with trialkylphosphite, which under mild conditions led to successful B-C bridging (Scheme 10) failed. Most such efforts led to the isomer 61 (thioether II), arising from a prototropic shift from the chiral 13 position to the nitrogen. This compound was quite stable and could be prepared easily by treatment of 60 with traces of trifluoroacetic acid. The failure of bridging arises from the fact that under these conditions, 60 isomerizes to 61, which cannot participate in the sulfur extrusion protocol.
In addition to all this confusion, the isomerization epimerized the chiral center 8, a most unkindest shift! Woodward vents his exasperation thus: “The situation at this point may be summarized by depicting thioether I as a substance precariously balanced on a precipice, of which all of our efforts pushed it into the valley represented by the dormant thioether II...”. The light at the end of the tunnel came from the observation that during purification of thioether I, in addition to thioether II another isomer, thioether III was obtained. The latter had the southern part intact and arose from an equally dirty trick now performed in ring B, which destroyed the chirality in position 8.

When the recalcitrant 61 was treated with 4.5 equivalents of tris 5-cyanoethyl phosphine and 5.3 equivalents of trifluoroacetic acid in sulfolane nitromethane at 60°C for 24 hr, the
bridged system 64 was obtained in 85% yields. The overall change could be understood in terms of shift of hydrogen from ring C to the chiral center at 13 to give 62 and the extrusion of sulfur from the resulting episulfide 63 (Scheme 11). The lactam unit present in 64 is the magnet to bring about the last bond on the northern side that will create the corrin system. Towards this objective, compound 64 was treated with phosphorous pentasulfide in presence of catalytic amounts of picoline. The thiolactam (A) thiolactone (B) intermediates so produced was specifically converted into the ene-thioether 65 by treatment with trimethyl oxonium fluoborate (Scheme 12).

**Scheme 12.**

12. **Enter Cobalt, Creation of the Northern Bridge and the Corrin Framework**

Dimethyl amine smoothly opens the thiolactone 65 giving rise to a stable dimethyl amide 66 with its all-important exo-cyclic methylene group (Scheme 12). The reaction of 66 with cobalt chloride in tetrahydrofuran followed by aerated aqueous potassium cyanide afforded the cobalt system 67.

The reaction of 67 (Scheme 12) with diazabicyclononane in dimethyl acetamide at 60°C for a few hours affected a smooth cyclization leading to the establishment of the cobalt corrin complex 68.
13. Selective Methylation of Corrin 68

A problem that was well foreseen was the need to introduce methyl groups at two of the three bridges present in the corrin system 68. An obvious plan to achieve this selectivity would be to take advantage of the fact that in compound 68 (Scheme 12), whilst the 10 position is flanked in the south by a gem dimethyl grouping and in the north by the propionic acid chain, the others, namely the 5 and 15 locations, are relatively more accessible. The northern bastion was further secured by transforming position 8, to that one fully substituted by crafting a ring in a simple and ingenious manner. Thus, the reaction of 68 with iodine in acetic acid afforded lactone 69 (Scheme 13) where the 10 location is completely boxed in from both sides.

The reaction of 69 with chloromethylbenzyl ether in sulfolane at 75–80°C for few hours followed by treatment with thiophenol afforded the bis thiophenyl methyl compound 70 (Scheme 13). The reaction takes place via initial substitution at both the locations by the benzyloxy methyl group, which undergoes acid-induced fragmentation to the corresponding halide and benzyl alcohol. Introduction of thiophenol at the appropriate stage gives rise to compound 70.

Treatment of 70 with Raney nickel and esterification with diazomethane afforded cobyrinic acid abcdeg hexa methyl ester f-nitrile 71 (Scheme 13) as a mixture of epimers.

As stated previously, compound 71 is a mixture of epimers related to position 13. Treatment of this with concentrated sulfuric acid for one hour brings about a smooth transformation to the f-nitrile to the f-amide without affecting any other functionalities. At this point the f-amide 72 (Scheme 14) and the isomer called the neo-amide could be separated cleanly by preparative HPLC. Ironically, it turns out that at equilibrium the desired f-amide 72 was present only at 25% levels. (The f-amide 72 so obtained was identical to that secured from vitamin B₁₂ via vigorous methanolysis to give the heptamethyl ester followed by ammonolysis under mild conditions).

Separation of these by HPLC gave a compound, which was identical in all respects to 72 obtained by total synthesis. The problem now was to transform the f-amide 72 to the f-acid by hydrolysis without affecting the susceptible six ester units present. In the arsenal available to the organic chemist, there appears to be only one method to achieve preferential amide hydrolysis, which is the treatment with nitrous compounds. Unfortunately, in many variations
of this approach, rather than the desired transformation of the \( f \)-amide to the acid, the 10 position of the corrin system was nitrosated.

Around the same time in Cambridge, which was not used to taking, as Woodward puts it, any nonsense about a reaction being not possible, it was eventually found that the treatment of 72 with nitrogentetroxide in carbon tetrachloride in presence of sodium acetate for one hour at 0°C, afforded the desired acid 73 in very good yields.

The glorious culmination of all the efforts over a period of 15 years was reached by the transformation of 73 with liquid ammonia–ethylene glycol–NH\(_4\) (trace) to cobyric acid (74, Scheme 14).

The compound so obtained was found to be identical in all respects most particularly in HPLC with the cobyric acid derived from natural sources. With the footnote that cobyric acid was transformed to vitamin B\(_{12}\), the synthesis is now complete.

15. Totally Synthetic Vitamin B\(_{12}\)

Woodward’s determination to create crystals of totally synthetic vitamin B\(_{12}\), where each one of the 181 atoms was placed at its precise location, a feat accomplished at the expense of colossal human efforts, is indeed very laudable.

The connection starts with ribazole (5,6-dimethyl-1-\( \alpha \)-D-ribofuranosyl-1H-benzimidazole (77) (Scheme 15), whose synthesis from \( \alpha \)-D-Ribose (75), accomplished in the fifties of the last century, is very much worth recounting to show that organic synthesis was well progressed even those days!

The primary hydroxyl in \( \alpha \)-D-ribose 75 was specifically protected as the trityl derivative, the nitrogen function introduced at the mesomeric position by reaction with 2-nitro 4,5-dimethyl aniline in refluxing dry benzene containing acetic acid, to afford the composite 76, which on catalytic hydrogenation, formylation, acid-promoted cyclization and deprotection afforded ribazole 77 (Scheme 15).
Scheme 15.

Treatment of 77 with dibenzylchlorophosphosphate followed by treatment with acid and separation afforded the 3' ribazole phosphate 78. Compound 78 was transformed to the cyclic phosphate 79 by treatment with DCC in formamide-tertiary butyl alcohol. Opening of 79 with N-benzyloxy carbonyl amino 2-R-hydroxy propane in dioxan containing hydrogen chloride afforded mixtures, which were de-protected by hydrogenation and separated to afford the desired composite 80. Cobyric acid 74 was activated by treatment with ethylchloroformate to the anhydride 81 which on condensation with 80 with potassium t-butoxide in t-butanol-acetic
acid, followed by chromatographic separation afforded vitamin B$_{12}$ (82) identical in all respects to the natural compound. The souvenir that was gifted to all associated with this adventure consisted of pictures taken from a polarizing microscope of crystals of both the natural and synthetic vitamin B$_{12}$, placed side by side. They were identical!

**Suggested Reading**


The Total Synthesis of Strychnine*

The enormous reach of R B Woodward in the design and synthesis of carbon constellations is further exemplified with the total synthesis of strychnine (p.105), which even when viewed from the vantage of ensuing significant developments in organic synthesis is an amazing feat! This is followed by the total synthesis of chlorophyll (p.109), where RB pledged the entire efforts on an untested porphyrin to purpurin change, an essential transformation to achieve the total synthesis. The third additional example is the total synthesis of cephalosporin C (p.113), The Nobel Lecture delivered by RB, above all, reflects the fact that in all these creations, he identified an anchor from which he never waivered – in this case the simple molecule cysteine.

Strychnine! No other molecule has captured the popular imagination as strychnine, perhaps because thousands of writers of fiction have used it to dispatch the recipient and then several have made thrillers using ingenious deduction to catch the perpetrator! Known since the 16th century from the forests including the Coramandal Coast of India, it was isolated in a pure form in 1818 and the structure established in 1947! Unlike the 181 atoms scattered in space as in vitamin B\textsubscript{12}, strychnine, having six asymmetric centres and 7 rings is packed with a mere 24 skeleton atoms!

2-Veratryl indole (1) readily prepared by Fischer indole synthesis from acetoveratrone was transformed to tryptamine 3, whose Schiff’s base with CHOCOOEt underwent smooth cyclization with TsCl/Py to generate the spiro ring-V, 4 which was transformed to 5. Ozonolysis followed by treatment with MeOH/HCl generated the critical pyridone 6 (ring-III) (Scheme 1). Initial efforts to effect a Dieckman condensation of the two ester groups were thwarted by the highly electrophilic Ts group present, forming in preference, the Sciff’s base. The Ts group was removed (HI, red P) and replaced by Ac (Ac\textsubscript{2}O, Py), esterified (CH\textsubscript{2}N\textsubscript{2}). The resulting 7 underwent smooth Dieckman condensation to give 8, generating ring-IV.

The enol ester group in 8 was transformed to acrylate 9 and then subjected to reduction. This process creates another chiral centre where the major product turned out to be unwanted $\beta$-ester which was readily epimerised to the more stable $\alpha$-acid, 10. The structure of compound 10 was conformed from a sample secured from natural strychnine. For this purpose 10 was readily resolved using quinidine and esterified to the methyl ester corresponding to 10 which was identical to that obtained from the natural sources. This enabled further transformations with the more readily obtained material from the natural sources. The linking of the $\alpha$-carboxyl group in 10 to the nitrogen that would generate ring-VI necessitated the inversion of this centre; this was achieved in an unusual manner by treatment of 10 with Ac$_2$O and pyridine to form the enol acetate 11 (Scheme 2).

The formation of 11 could be rationalized by the initially formed anhydride, that undergoes nucleophilic acyl transfer, decarboxylation and acylation of the thus generated enolate! Vigorous acid hydrolysis of 11 afforded 12 (Scheme 3). The protanation of the enolate takes place from the $\beta$-side. Thus 12 is not disposed for linking with the trans-NH. Woodward did not consider this as an impediment because of the ready epimerisation of this centre. Indeed this turned out to be true! Treatment of 12 with SeO$_2$-EtOH gave 13 with the generation of ring-VI. The 3D representation of 13 clearly shows that the epimerization has indeed taken place!
The pathway to strychnine now involves addition of two carbon atoms and creation of chiral centres at 8, 13 and 12 positions (12) (Scheme 3). At this stage compound 13 is highly concave and the carbon at 8 rests at the bottom of it. To deliver an H to this carbon is the kind of challenge that Nature often posed and Woodward overcame this using an Al-courier! Compound 13 was treated with sodium acetylide in THF and the acetylinic moiety was reduced to provide 14. Compound 14 when reacted with LAH in refluxing ether effected the reduction of the amide present in ring-VI and delivered the hydrogen to the most inaccessible carbon-8 to form 15. Compound 15 is related to isostrychnine 16 where the allyl alcohol is isomerised to provide a hydroxy methyl isomer. This transformation proved exceptionally difficult. Eventually, treatment of 15 with HBr/AcOH at 120°C, and the resulting mixture of halo compounds on
hydrolysis in boiling aq. $\text{H}_2\text{SO}_4$ generated the desired 16, isostrychnine! The action of ethanolic KOH led to the closure of the 7-memberd oxide ring-VII, which also generated the chiral centre at 12 and 13 in a correct order.

Even in the light of significant developments in organic synthesis during the intervening six decades, Woodward’s synthesis of strychnine defies the imagination of chemists! Here again Woodward had to overcome the problems raised by Nature in placing one of the Hs inside the bowl with 4 outside!

Suggested Reading

The Total Synthesis of Chlorophyll*

Fresh from his dramatic conquest of the blood pigment, Fischer hurdled his legions in the attack on chlorophyll, and during a period of approximately 15 years, built a monumental corpus of fact. As this chemical record, almost unique in the scope and depth, was constructed, the molecule was transformed and rent asunder in innumerable directions, and the fascination and intricacy of the chemistry of chlorophyll and its congeners was fully revealed. These massive contributions were crowned by the proposal, in 1940 of a structure which was complete except for stereochemical detail.

— R B Woodward

Ping-pong is played by the proton on the Chlorophyll table!

— S Ranganathan

The four simple building blocks, two of which were known and others easily made must now be united in a specific manner. The control of the nature of the ring nitrogen presented a formidable challenge in this endeavour.

Ring II + III

Ring II is notable because the \( \alpha \)-carbonyl needed, is protected with malanonitrile \((1)\). This condensed readily with \(2\) to specifically provide \(3\), which was functionalized with \(\beta\)-carbomethoxy propionyl chloride to provide \(4\). AqNaOH removed the protecting group to generate the aldehyde which on esterification afforded the methylester \(5\) which was transformed to the thio aldehyde \(6\) \((Scheme\ 1)\) via the Schiff’s base from EtNH\(_2\).

Ring I + IV

4-methyl pyrrole 3-carboxaldehyde (7) was transformed to 8 coupled with aldehyde 9 and the resulting product reduced to give the key intermediate 10 (Scheme 2) which on treatment with 6 (A), gave the sensitive Schiff’s base 11 which was introduced into CH₂Cl₂, evaporated and immediately introduced into MeOH.HCl to give the stable 12. It may be noted that in the formation of 12 both the bridges connecting all the four rings were simultaneously formed.

Scheme 1.
Compound 12 was oxidized with I₂ and the product isolated to give 13. This crystalline porphyrin can be isolated in gram quantities! The next task would be the proper placement of the only chiral centres at 7 and 8. Treatment of 13 with AcOH in air on steam bath led to the porphyrin 14, which when held at 110° C in AcOH afforded the purpurine 15. This is the first example of porphyrin→purpurin change. Indeed Woodward anticipated this because such a change not only makes 7 and 8 tetrahedral, but also relieves the strain around the lower bridge! As the next step, the CH₂CH₂NHAc of 15 was transformed to the -CH=CH₂ group by a sequence of hydrolysis, methylation and Hoffmann elimination to 16. When 16 was exposed to strong visible light in the presence of air, it was transformed to 17. It is most appropriate that the key reaction in this synthesis is the one brought about by oxygen! Treatment of 17 with MeOH/KOH, the methoxy group was cleaved and replaced. The hydrolysed acrylic acid interacted with proximate CHO, eventually leading to 18 (Scheme 3). The maverick nature of the lactolether in 18 has been beneficially taken advantage by Woodward in reaching 19! Dieckman cyclization of 19 afforded methyl pheaphorbide α (20; R = Me). The ester at the chiral centre was replaced by phytol and the magnesium introduced to yield 21, chlorophyll-α₂.
Suggested Reading

The Nobel Prize in Chemistry for 1965 has been awarded for contributions to the art of chemical synthesis. It gives me much pleasure to record here my gratification with the citation, which properly signalizes an exciting and significant aspect of synthetic activity. But the aspect is one which is more readily – and I dare say more effectively– exemplified and epitomized than it is articulated and summarized. Having here this morning the responsibility of delivering a lecture on a topic related to the work– for which the Prize was awarded, I have chosen to present an account of an entirely new and hitherto unreported investigation [namely, the total synthesis of Cephalosporin C] which, I hope, will illuminate many facets of the spirit of contemporary work in chemical synthesis.


The total synthesis of Cephalosporin C is yet another example where Woodward identifies an anchor from which he never wavered, in spite of enormous problems. The anchor here was L (+) cysteine (1). The choice of 1 was indeed ingenious! Not only does 1 contain half of the carbon framework but one of the chiral centres too.

Compound 1 was transformed to the key intermediate 2 by normal procedure. Not only did these protocols protect all the active centres of 1, they also enhanced the activity of the -CH₂-group, on which the whole synthetic strategy was pledged. Innumerable rational procedures to introduce a functional group failed. Success was finally achieved by an entirely novel path with MeOOC-N=N-COOMe leading to 3, which can be rationalized by initial acceptance by sulfur eventually leading to an S-N shift (Scheme 1).

Organic Chemistry Masterclasses

Scheme 1.

The transformation of 3 to 4 involving the specific replacement of with $\beta\text{-NHNHE}$ with $\beta$-OH reflects the deep understanding of reaction mechanisms (Scheme 2).

The transformation of 4 to the $\alpha$-amino group, well placed to form the desired $\beta$-lactam was accomplished without much impediments (Scheme 3).

However, the desired peptide bond leading to the $\beta$-lactam 6 (Structure 1), proved very difficult. Woodward felt that there was a need to enhance the activity of the -C=O unit and this he achieved in an ingenious manner using ($Bu_3$) Al in toluene!
The next challenge was to attach the remaining framework of cephalosporin C, taking advantage of the NH grouping present in the fragile 6. A strongly electrophilic partner had to be created and the chosen target was the olefin 7 endowed with three electrophilic substituents. Here again Woodward chose to start with simple partners, $d$-tartaric acid and 1,1,3,3-tetramethoxypropane (Scheme 4).

Scheme 4 belies the fact that compound 7 and some of the precursors are nasty customers, highly lacrimatory and need handling with great care! The desired union of 6 and 7 was smoothly accomplished on heating with $n$-octane leading to 8 (Scheme 5).
The time had come now to fire the ‘magic bullet’ (TFA) to generate the entire cephalosporin C skeleton! That memorable night (8 pm in Basel, Switzerland) 8 was treated with TFA. The cascade of reactions that followed and constantly monitored by RB from Boston, involved removal of the BOC group; the freed nitrogen lone pair swung in to free the S from its shackles which in turn attacked the proximate-CHO, leading to loss of water on one hand and hydrolysis of Schiff’s base on the other to yield 9! (Scheme 6).

It may be noted that $6+7$ addition generates a new chiral centre as a mixture of epimers. However this centre becomes a tertiary one in the final product and hence of no major consequence.

A sequence of amidation of 9 with $\mathbf{A}$ followed by chromatography gave 10, a heavily protected cephalosporin C! (Scheme 7).

Diborane reduction of 10 (-CHO ! CH$_2$OH), acetylation, equilibration to $\alpha\beta$ ($\beta\gamma\leftrightarrow\alpha\beta:: 3 : 1$) (Py, RT) and TCE deprotection (Zn, aq. AcOH) afforded cephalosporin C identical in all respects to the natural antibiotic (Scheme 8).
Scheme 8.

Suggested Reading

Woodward Seminars*

A prologue to ....

“A Stool has been sitting outside one of our labs. It has gone missing for the last three days, if it is returned without delay we will turn it as a temporary loan. Otherwise it will be treated as a theft.”

– R B Woodward

P.S. The stool was never found again.

In the Boston area ‘Woodward Seminars’ were quite famous. They always took place on Thursdays, started around 8.00 pm and were open ended!

Most of us had our baptism from these seminars! It would start with ‘an entertainment’ where a sacrificial scientist (postdocs, academists, visitors, ...) would make a presentation of his work. This would be followed by a lengthy analysis by all and RB enjoyed making most of the comments.

Then, major developments in organic chemistry, of the interim period, would be beautifully analyzed by him.

The final part would be the ‘show’, where RB handpicked unusual transformations. These were drawn and the audience was invited to solve them. Most of us made false starts and gave up midway! Then RB would regale us with a detailed analysis.

I have chosen 14 examples of the type of problems that would have fascinated RB:

1.

[![Chemical Structure](image)]


2. 

![Chemical reaction diagram](image)


3. 

![Chemical reaction diagram](image)


4. 

![Chemical reaction diagram](image)


5. 

![Chemical reaction diagram](image)

Organic Chemistry Masterclasses


