Chemistry of Natural Products: A Unified Approach

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N R Krishnaswamy
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The study of natural products chemistry is a subject of considerable aesthetic interest and also has special relevance for our country. A few decades ago, the subject was practised with great vigour in many university laboratories having many internationally renowned researchers in this field. Over the years, there has been a noticeable slackening, primarily due to the lack of modern analytical instrumentation. The current excitement involving neem, turmeric and a host of other herbal products in agriculture and healthcare has heightened the awareness about natural products. It is very important that students are adequately trained in the study of the chemistry of natural products from a modern perspective and at the same time are exposed to the challenges in the area.

The title, preface, contents and chapter headings of this book hold out great promise of working to fill an important educational and reference need for undergraduate and postgraduate students besides the teachers. It is a pleasure to read through this book which is written in a simple and elegant style. It is divided into seven chapters with a subject index.

Chapter 1 is a discussion on the structure of a diverse group of carefully chosen natural products by using chemical degradation and spectroscopic studies. The molecules chosen are strychnine, nepitrin and pedalin, colchicine, longifoline, β-amyrin, wedelolactone, protoaphin-fb, tylophorine, heliangine and delphisine. These molecules are chosen as representatives of different biosynthetic pathways to indicate how structures can be elucidated by conducting ingeniously designed experiments both chemical and spectroscopic, and also by logically interpreting the data thus generated. The presentation is very clear and sound and adequate references are provided for further reading.

Chapter 2 deals with a discussion on the stereochemistry of some important natural products, with reference to the intrinsic principles involved in their conformations. The examples chosen are morphine, quinine and related alkaloids, emetine, enhydrin and other germacranolides, rotenoids, some sesquiterpene lactones, abietic acid, catechins, and sphingosine. In this chapter, the usefulness and limitations of the chemical method for defining the stereochemistry of the above natural products is discussed. Although this method has serious limitations, the author feels that a lot of new chemistry can be generated despite the superiority of the physical methods, NMR, CD and X-ray diffraction data. The discussion is very clear and informative.

Chapter 3 focuses on the reactions and rearrangements of some of the natural products. Examples are chosen from alkaloid, terpenoid and flavonoids to illustrate the background information. Thus acid catalysed rearrangements in morphine and thebaine, photochemical rearrangements in monoterpenes, the Wesley–Moser rearrangement in the flavonoids, some reactions of reserpine and papavarene, and transanular reactions of medium size rings and epoxide ring opening reactions have been discussed with emphasis on mechanistic considerations.The student will find it extremely easy to follow these transformations.

Chapter 4 deals with the synthesis of natural products which has been discussed in-depth, not only the successful syntheses but also the failures (e.g. quassinoids) with respect to the molecular behaviour. The examples chosen are from diverse groups of compounds such as polyoxygenated flavonoids, anthracyclenones, quassinoids, some insect pheromones, a perfumery product, khusimone and the marine natural products, didemnenones.

Chapter 5 provides a good overview of the general biosynthetic pathways to the secondary metabolites covering the polyketide and terpenoid biosynthesis. The biosynthesis of benzyl isoquinoline alkaloids and their conversion into morphine group has been discussed in detail. Besides the biosynthesis of flavonoids and polyphenolic compounds, the conversion of mevalonic acid into monoterpenes and further to lanosterol has been presented in a manner which can be easily understood.

Chapter 6 is a brief but excellent coverage on the biological significance of the secondary metabolites, well illustrated by examples. The examples chosen are semiochemicals, insect pheromones, the plant-insect reactions, plant-vertebrate interactions, plant-plant interactions and defensive secretions of insects. This topic is very important in view of the ecological considerations, which will lead us into green chemistry.

Unlike the traditional books on natural products, this book is unique in that it has a chapter containing the analysis of number of problems on natural products. Both the students as well as teachers will benefit from this exercise as it provides degradation studies and spectral data. I am happy that the author has included this chapter as a case study.

The organization of the various chapters may remind regular Resonance readers of the series of articles written by N R Krishnaswamy in the inaugural volume. The possibility of studying all the varied aspects of organic chemistry through examples chosen exclusively from natural products was explored in the *Resonance* articles. Readers whose appetite was whetted by that series would find a rich fare, with numerous case studies and extended discussions.

This book is certainly a very good text as well as a reference book. There is something for every one and the book can be recommended as an excellent material in natural product chemistry for undergraduate students. I find some of the chapters are a source of inspiration for those in search of natural product study. The structures are neatly drawn and devoid of any errors. The book is relatively inexpensive and I feel that students should be in a position to buy this without hurting their purse. I must congratulate the author, Krishnaswamy, a dedicated teacher himself, for such a wonderful book.

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Hilbert

R Sridharan

Hilbert
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by Constance Reid
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Many are the ways in which the glory of classicism can be contemplated upon. One could stand for instance before the masterpiece fresco of Raphael called 'The School of Athens' in the Stanza della Segnatura in the Vatican and admire the austere gathering of philosophers in a beautiful ambience. My feeling is that a reading of the biography of Hilbert by Constance Reid produces a very similar feeling for the glorious bygone days of mathematics in Germany. Though termed a biography of Hilbert, this book is indeed the story of the remarkable pair Hilbert and Minkowski whose lives (till Minkowski's unfortunate early death) influenced and enriched each other intellectually. While Hilbert occupies the centre stage, one gets to know not only about Minkowski but also something about all the mathematicians of that time who enter and exit the stage, giving a fair account of themselves. Here then is a brief account of this remarkable book written with great empathy and feeling for the mathematics and mathematicians of a vanished epoch.

Königsberg which could boast itself as the birth place of the great philosopher Immanuel Kant also has the distinction of being essentially the birth place of David Hilbert, who was born in 1862 in Wehlau as the son of a county judge and a mother who was rather an original, interested in astronomy and with a fascination for prime numbers. Hilbert's experiences at the gymnasium were not happy, but the one subject where he was comfortable was mathematics, which he learnt effortlessly. In his last year of study, Hilbert went to another gymnasium where his mathematical talents were appreciated by the teachers.

Though termed a biography of Hilbert, this book is indeed the story of the remarkable pair Hilbert and Minkowski whose lives influenced and enriched each other intellectually.

Hermann Minkowski (whose family had settled in Könisberg, having run away from Russia where the Jews were persecuted by the Czarist regime) with whom Hilbert was to have a life long friendship and who was mathematically very precocious, was two years younger to Hilbert. He went to a different gymnasium in Königsberg, finished his studies there and went away to the local university earlier.

Hilbert enrolled in the autumn of 1880 at the University in Königsberg. He went to Heidelberg for the second semester where he had lectures from Fuchs and to Berlin in the next semester where there was an impressive collection of great scientists like Weierstrass, Kummer, Kronecker and Helmholtz. Hilbert however returned to Königsberg, a town which he loved (In his old age , Hilbert insisted once that Königsberg was the most beautiful town in Germany!).

In the spring of the year 1882 when Hilbert was at the Königsberg University, Minkowski returned to Königsberg from Berlin. Though hardly seventeen, Minkowski had already obtained deep results on the representation of a number as a sum of five squares (using the theory of integral quadratic forms), which, though he had no time to translate into French, he decided to submit to the French Academy for the Grand Prix. (He was indeed awarded the prize which he shared with the British mathematician Henry Smith). Hilbert in his dedicatory preface to the collected works of Minkowski mentions, with admiration, this work which showed Minkowski's deep knowledge of the subject at such a young age. Hilbert became a close friend of Minkowski (despite the fact that Minkowski was a very shy person), a warm friendship which lasted till the death of Minkowski. (H Weyl in his obituary notice of Hilbert refers to this friendship and says that Hilbert played the sweet flute of the Pied Piper seducing so many rats into the deep river of mathematics!) It was also the time when their views on mathematics took a definite shape. For instance, they utterly abhorred the tenet of the French philosopher Du Bois-Reymond (whose ideas were very fashionable at that time) that some problems were certainly unsolvable, even in principle, by science.The catch phrase was "*Ignoramus et ignorabimus*" (We are ignorant and shall remain ignorant). In fact, the credo of Hilbert was the very opposite: "*We must know and we shall know*." He held this view and fought for it all his life.

Lindemann who was then at the University, brought Hurwitz from Göttingen. Hilbert and Minkowski found in Hurwitz an excellent teacher and a mentor and they learnt mathematics just by talking to him. Hilbert wrote his doctoral thesis on the theory of invariants. It was a very nice and original piece of work.

Hilbert spent the year 1885 with the legendary Klein, who indeed was very much impressed by Hilbert. At Klein's suggestion Hilbert went to Paris in 1886, where he and Study were offered extraordinary friendship and hospitality by Hermite. Hilbert then became a docent at Königsberg and he began to lecture on invariant theory. In the meantime, Minkowski who was at Bonn began taking an active interest in mathematical physics. In the beginning of 1888, Hilbert went to Erlangen to meet the famous Gordan, who twenty years before, had proved through heavy computations, the existence of a finite basis for binary forms. Hilbert decided to tackle the general problem of proving the existence of a finite basis for *all* forms, and in September 1888 he solved this in a totally unexpected manner, by giving an existential proof. Gordan at first neither understood nor liked this, and said with a loud voice "It is theology, it is not mathematics", though he eventually conceded the proof of Hilbert. This proof really opened up a new branch of mathematics–modern algebraic geometry. The famous Nullstellensatz and the so called 'Basis theorem' are some of the offshoots of this proof.

Hilbert married Käthe Jerosch in 1892 (their families had known each other and been friends). Käthe had a strong character, was upright and was a perfect companion for Hilbert for the rest of their life together. Around the same time, Hurwitz left for Zurich and Hilbert occupied Hurwitz's chair in Königsberg. Minkowski meanwhile was offered a chair at Bonn. He was then writing a book on geometry of numbers and he visited Hilbert frequently. Hilbert produced at this time a greatly simplified proof of the transcendentality of the numbers π and e.

The German Mathematical Society which met at Munich in 1893 (Hilbert presented here his new results on the decomposition of primes in number fields) decided that he and Minkowski should prepare a joint report on the current state of number theory. It so turned out that Minkowski got a position in Königsberg and it was agreed that Minkowski would deal with rational number theory while Hilbert would treat algebraic number theory. The friends however were not destined to be together in Königsberg for long. Klein managed to invite Hilbert for a position in Göttingen. Hilbert arrived at Göttingen, whose scientific tradition goes back to the great Gauss in 1795, exactly a hundred years after Gauss. The project of the report continued to grow through correspondence. Hilbert was ahead of Minkowski and he finished his part by 1896. Minkowski readily agreed to Hilbert's proposal that the report be published as such, with Minkowski's part to be included as it stood. The '*Zahlbericht*' was published in 1897 and was regarded as an inspired work of art. It contains remarkable ideas which have permeated mathematics in the years to come. For instance, it led to the study of 'Class field theory', which with its variants, is to this day, one of the most fascinating areas of mathematical research.

It was characteristic of Hilbert not to stay in one area of research for long. He did something beautiful and fruitful and then moved on to a different field, leaving the original field for others to develop. Hilbert's next goal was to axiomatize geometry. His idea was to set up a foundation of geometry by giving a complete set of independent axioms and deduce all the familiar theorems of euclidean geometry from these. As soon as his lectures in Göttingen entitled in English 'The Foundations of Geometry' appeared in print, they attracted the attention of the mathematical community. Poincare called it a classic! Hilbert showed that the question of consistency of euclidean geometry depends on the consistency of arithmetic, so that geometry was at least as consistent as arithmetic. The next achievement of Hilbert was to show how by placing some conditions on the boundary, the solution of Riemann for the so called Dirichlet principle can be resuscitated. This removed the serious objections raised by Weierstrass to the original proof of Riemann.

In the beginning of the twentieth century, Hilbert was invited to deliver one of the major addresses at the second international congress of mathematicians, which was to be held in Paris. After much discussion with Minkowski, Hilbert decided to articulate in this lecture his clear views on mathematics. In a bold address, he asserted his belief in the vitality, organic unity and the internal harmony of mathematics and added "As long as a branch of science affords an abundance of problems it is full of life... . One without a definite problem before he searches for methods, will probably search in vain...". He ended his address by proposing a list of twenty-three concrete problems for the future. As we enter the next century now, we can clearly see in retrospect that these problems have indeed played a crucial role in the development of mathematics during the last hundred years.

In 1902, Hilbert managed to create a position of Professorship in Göttingen for Minkowski which enabled him to resume their mathematical partnership once again. It was at this time that Hilbert produced a simple and original derivation of Fredholm theory of integral equations. Minkowski on the other hand was once again busy with his beloved theory of numbers. During this period both Hermann Weyl and Max Born became students at Göttingen, which had now come to be recognised as the Mecca of German mathematics. It also had privatdozents like Otto Blumenthal – who was to be distinguished for the rest of his life as "Hilbert's oldest student" and Zermelo, who worked in set theory.

Hilbert suffered a breakdown in 1908, and when he came back to mathematics, he produced at the end of the year a remarkable solution of the so called Waring's problem, which had remained open since 1770 and in which Hilbert got interested through the work of Hurwitz. Minkowski, who was also at a point of great creativity (he was working on relativity at that time) died in January 1909 subsequent to a violent attack of appendicitis. This was a personal tragedy to Hilbert who lost his best and closest friend. He dedicated his paper on Waring's problem to the memory of Minkowski.

During the first world war when the fever of patriotism in Germany ran high, Hilbert remained singularly unaffected. He was at that time primarily interested in the fundamental problems of physics and their mathematical formulation. Emmy Noether, (daughter of the mathematician Max Noether), who was a student of Gordan, arrived in Göttingen. There was heavy opposition from the entire philosophical faculty, which included philosophers, historians, natural scientists and mathe-maticians when she was to be appointed a privatdozent. Hilbert was furious and he made the famous statement, "I do not see that the sex of the candidate is an argument against her admission as a privatdozent. After all the Senate is not a bath house". When he could not obtain her a habilitation, Hilbert solved this problem in his own way, by announcing lectures in his name, but letting her give them.

When the war was going on, Brouwer raised a foundation crisis in mathematics, by challenging the logical principle of the excluded middle. Although Hermann Weyl, Hilbert's gifted pupil was supporting Brouwer, Hilbert was violently opposed to Brouwer's theory. If one had to accept Brouwer's point of view, much of mathematics including existence proofs, a great part of analysis and Cantor's theory of infinite sets would have to be given up. He refused to accept such a mutilation of mathematics. As was characteristic with him, he wanted to launch a frontal attack on the problem and proposed to formalise mathematics into a system where mathematical theorems and proofs would be expressed in the language of symbolic logic as sentences which have a logical structure but no content. The consistency of the system would then be established through finitary methods.

Hilbert turned sixty on January 23rd 1922. There was a birthday banquet which was attended even by the seventy-three year old Klein, who was now confined to a wheelchair. A new order had begun at Göttingen with Courant occupying the chair of Klein. Klein and Hilbert also wanted Hermann Weyl who was in Zurich back in Göttingen – Hermann Weyl, who was still in his thirties, was then at the height of his creative powers and wrote mathematics as a piece of poetry. However, Hermann Weyl refused the offer saying that he would not like to exchange the tranquillity of Zurich for the uncertainties of post-war Germany. The great Emmy Noether was at last being made a privatdozent in 1919 and she came under the spell of Hilbert's axiomatic method (in spite of the fact that she was very much influenced by Gordan during her doctoral work).

Hilbert's main contribution to physics (even though he kept himself thoroughly informed of all the recent developments in relativity and quantum mechanics) was to be in the mathematical methods which he created in his work on integral equations. In 1924, when Courant published the first volume of his 'Methods in Mathematical Physics', he included the name of Hilbert as his co-author. This act was indeed very justified by the fact that the material was from Hilbert's papers and lectures. In fact Hilbert's spirit radiates from the entire book.

In 1925 Klein died and Hilbert himself fell ill. It was recognised that he was suffering from pernicious anaemia, which was generally considered as a fatal disease. However with the help of G R Minot, who was at Harvard, who treated pernicious anaemia, through the administration of raw liver, Hilbert's condition almost by a miracle began to improve and he got well.

Hilbert turned sixty eight, the mandatory age of retirement for a professor. Hilbert delivered his farewell address on invariants. A street was named after him. Many honours were showered on him. The one that pleased him most was the conferring of an honorary citizenship by the town council of Königsberg. The topic he chose to speak on for this occasion was 'The understanding of nature and logic'. He began his address by remarking "The understanding of nature is our noble task". He mentioned the principle of *a priori* enunciated by Kant and insisted that new foundations of mathematics should be laid based on a priori insights. In short, he was referring to his programme of formalising mathematics. He said that mathematics is the only bridge between thought and experiment and the intellectual understanding of nature rests on mathematics. He said that, however, applications of mathematics should never be made a measure of its value. Hilbert ended his speech by repeating his credo "Wir müssen wissen. Wir werden wissen" ("We must know, we shall know"). It was indeed a triumphant call for success especially for his programme of formalisation of mathematics. It is indeed ironic that Gödel was just then in the process of writing a paper which was to deal a death blow to the programme of formalisation initiated by Hilbert.

"Account ye no man happy till he die" is a prophetic statement of Euripides. Indeed the last few years of Hilbert were far from happy. Hilbert's personal life had became unhappy much earlier when his only son became a source of disappointment and anguish. Though Hilbert and his colleagues tried to circumvent the objections of Gödel and to build once again a strong foundation for mathematics, time was running out for Hilbert. The Nazis brought evil to Germany and scientists like Hilbert were childlike and were incapable of accepting the existence of such an organized reign of terror. When Hilbert heard that many of his Jewish friends were put on "forced leave" as the current euphemism had it, he told Courant angrily "It is illegal for such a thing to happen. Why don't you sue the Government?"

The Berlin academy decided to celebrate Hilbert's eightieth birthday with a special citation of the influence that his work had on the progress of mathematics. On the very day the award was to be voted by the academy, Hilbert fell on the street in Göttingen and died a little more than one year later. The news of his death did not even reach the rest of the world immediately because of the war that was on. The tribute which Caratheodory had written (he could not attend the funeral due to his illness) was read at the funeral. It contained the true and touching lines "You have made us all think only that which you would have us think." Yes, Hilbert was no more, but the torch he had lit continues to guide us, the mathematicians .

Perhaps the best way to pay tribute to Hilbert is to quote the truly objective evaluation of his work that Blumenthal included in his biographical article on him:

"For the analysis of a great mathematical talent one has to differentiate between the ability to create new concepts and the gift for sensing the depth of connections and simplifying the fundamentals. Hilbert's greatness consists in his overpowering, deep penetrating insight. All his works contain examples from far flung fields, the inner relatedness of which, and the connection with the problem at hand, only he had been able to discern; from all these, the synthesis – and his work of art – was ultimately created. As far as the creation of new things is concerned, I would place Minkowski higher and from the classical great ones, for instance, Gauss, Galois, Riemann. But in his sense for discovering the synthesis only a very few of the great have equalled Hilbert''.

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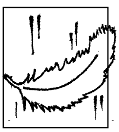

The British physicist Tyndall was quick to appreciate the terrific punch that carbon dioxide, in particular, can pack by being both powerful and rare. He realized that plants are constantly breathing carbon dioxide in and out, and that the gas fluctuates naturally for a hundred other reasons as well. If the amount of carbon dioxide in the air ever dropped even a little bit too much, the change could chill the planet. Tyndall even suggested that this might be the explanation for ice ages.

Oddly enough Tyndall never made much of the other side of the coin – in retrospect so obvious. He was not dull. He was a polymath who made important discoveries in chemistry, physics, bacteriology, and the theory of the origin of life. He even explained why the sky is blue. He was also a great mountaineer and a brave controversialist and he would not have flinched from the implications of the dark side of the greenhouse effect.

It is as fatal as it is cowardly to blink facts because they are not to our taste," wrote Tyndall in "*Science and Man*".

Perhaps he would have come to it in time. But in his early fifties his health began to fail and he retired to a villa on the heath to write his autobiography. His young wife Louise looked after him, giving him a big dose of magnesia every morning for his indigestion and a small dose of chloral every night for his insomnia. One wintry morning in 1893 she got the two bottles mixed up and gave him a giant dose of chloral. He swallowed it and said it tasted sweet.

"John, I have given you chloral!"
"Yes, my poor darling," he said, "you have killed your John." He was dead before sundown.

Three years after Tyndall's death a Swedish chemist, Svante Arrhenius, finally turned the coin. Arrhenius, who won one of the first Nobel prizes in chemistry, put together a few simple facts: Every year people were burning a lot of coal, oil, and firewood, each year more than the year before. Burning these fuels injects millions of tons of carbon dioxide into the atmosphere. Carbon dioxide is a greenhouse gas.

From: *Next Hundred Years*, J Weiner, 1990.