

## Impossible Dreams

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You will understand the title at one level by knowing that I have been a fan of the Boston Red Sox for about seventy years. This loyalty was partially rewarded about seventeen years ago when by chance I had the pleasure of spending an hour with my boyhood hero, Ted Williams. At about the time that I started to follow the Red Sox games by radio, I acquired the notion that I would like someday to know in detail how to build from scratch radios, planes, skyscrapers, bridges, and all the other objects of modern life. I sometimes wonder, in retrospect, whether this impossible dream somehow had an influence on the course of my life.

I had no idea that I would choose chemistry as a profession when I entered MIT as a 16-year-old freshman in June of 1945. In fact, until my senior year in high school, the only science that I had ever taken in school was mathematics. I enjoyed math more than any other subject, although I liked all of my studies. My preference for math led to my being handed a two-page application form for MIT which I completed in less than an hour and returned to my high school advisor, Mr. O'Brien. A few weeks later, I learned that I had been admitted into MIT. Mr. O'Brien's advice was that I should consider majoring in electrical or chemical engineering at MIT because the chances of finding good employment in math were low. I eventually found my way into chemistry in my sophomore year at MIT because it was more interesting to me than the engineering options. My hope was that I might find work as a scientist with a large corporation after graduation from college. I never dreamed that in the short space of about five years I would have a Ph.D. degree in chemistry and a faculty position at the University of Illinois. My undergraduate years flew by—partly because MIT was then still on an accelerated wartime academic schedule. I usually took three extra courses each semester since that was permitted then. As a result, I was able to take all of the available MIT chemistry courses, the other requirements, and a few engineering courses as well. At the invitation of Professor John C. Sheehan I stayed on for graduate research at MIT as a member of his pioneering project on the chemical synthesis of penicillins. Early on in my third year of graduate work, I received word that Roger Adams, then Head of the

Department of Chemistry and Chemical Engineering at the University of Illinois, was visiting Cambridge and wanted to see me. I well remember that very cordial meeting on the campus at Harvard where Adams served as an Overseer. A week later I was offered an Instructorship at Illinois provided that I could report for work within six weeks, at the start of 1951. It was astounding that somehow I had been chosen from so many other young chemists for what was clearly one of the premier academic positions that year. Professor Sheehan readily agreed that I could accept the offer despite such short notice. For years it remained a mystery to me that I could be so lucky. Just a few years ago I learned from Nelson Leonard, a faculty colleague of Adams, that it was a group of my former fellow MIT students, then at Illinois as graduate and postdoctoral fellows, who recommended that I be considered for the Illinois opening and that Nelson had relayed their suggestion to Roger Adams. I remained at the University of Illinois until mid-1959 when I assumed my present faculty position at Harvard. It has been a privilege to work for this period of over fifty years at these two great institutions with wonderful students and faculty colleagues.

At Illinois, I was especially close to Roger Adams, C. S. Marvel, Nelson Leonard, John C. Bailar, I. C. Gunsalus, David Y. Curtin, and Douglas E. Applequist—all great chemists for whom I have enormous respect. I am grateful to John Bailar for a very stimulating collaboration that produced the first conformational analysis of metal chelates and led to what are now known as the  $\delta$  and  $\lambda$  stereochemical descriptors. A collaboration with "Gunny" Gunsalus on the microbial hydroxylation of camphor led to his pioneering and historic biochemical program over the next four decades on cam P-450, the first and now the best understood member of the P-450 class of biochemical oxidants. There were a number of other research discoveries at Illinois that brought great pleasure to me. I shall mention just a few: the recognition that stereocontrol in a reaction could arise from a preference for a three-dimensional transition state involving the maximum overlap of the perturbed molecular orbitals (which I called stereoelectronic control); the determination of the structures of the natural products

friedelin and limonin; the first functionalization of unactivated methyl groups, such as those in steroids; syntheses of natural products, including the pentacyclic triterpenes  $\alpha$ - and  $\beta$ -amyrin, and the steroid alkaloid conessine; and development of general methods for prediction of the stereochemistry and absolute configuration of  $\alpha$ -haloketones.

During my tenure at Illinois, I became fascinated by the deeper thought processes involved in planning pathways for the chemical synthesis of complex molecules such as natural products, a topic that had intrigued me even as an undergraduate at MIT. Because my research group at Illinois was small and spread out over many research areas, including reaction mechanisms and stereochemistry, new synthetic methodology, and structure determination, it was not feasible to undertake complex synthetic projects. Nonetheless, I spent considerable time thinking about the design of syntheses at an abstract level. A flood of novel and unusual natural product structures that came along during the 1950s provided much food for thought, especially because many of these structures lacked features which might suggest either starting materials or building blocks for synthesis. Thus began a thirty-year involvement with the logic of chemical synthesis.

At Harvard, I continued my research along a broad scientific front and conducted my own experiments in a small laboratory that was connected to my office, as at Illinois. I thoroughly enjoyed teaching both undergraduate and graduate students. My initial ideas on logical procedures for analyzing synthetic problems led to an entirely new and systematic way of thinking about synthetic planning that had a dramatic impact on both my research and teaching in synthesis. By the mid-1960s, several quite novel syntheses of challenging molecular targets were designed in this way and demonstrated experimentally. In addition, I was able to teach students in just 3–4 months how to design complicated syntheses on their own. Another exciting advance was the development of the first graphical input and output of organic structures to and from a computer and the evolution of a computer program that effectively generated possible syntheses by retrosynthetic analysis. That computational research proved the validity of the logic that I had developed and made available the computerized organic formula graphics that are omnipresent today. On May 4, 1964, I suggested to my colleague R. B. Woodward a simple explanation involving the symmetry of the perturbed (HOMO) molecular orbitals for the stereoselective cyclobutene  $\rightarrow$  1,3-butadiene and 1,3,5-hexatriene  $\rightarrow$  cyclohexadiene conversions that provided the basis for the further development of these ideas into what became known as the Woodward–Hoffmann rules. During the 1960s, my group also developed many new synthetic reagents and reactions that are now standard tools of the synthetic chemist. In addition, this period saw our experimental demonstration of 2,3-oxidosqualene as a key intermediate in the remarkable biosynthesis of cholesterol. Eventually we were able to clone the gene for the cyclizing enzyme (yeast and human), purify the protein, and characterize the fine mechanistic details of this remarkable reaction that generates the steroid ring system in a single step.

Between the mid 1960s and 1990 my group carried out research on the superfamily of natural compounds that I named the “eicosanoids” which includes prostaglandins and leukotrienes. This effort led to the first general synthesis of the natural prostaglandins from a common intermediate and many further refinements. We surmised the correct structures of the immune mediators now known as the leukotrienes A, B, and C and synthesized these unambiguously even before they were isolated and characterized. It has been noted in the medical literature that there is no field of medicine that has not been impacted by fundamental research on these eicosanoids. This work was summarized in my Japan Prize lecture of 1989.

For almost five decades, a constant theme of our research has been the development of new tools for synthetic chemistry including enantioselective methodology. We have also been continuously engaged in the multistep synthesis of complicated target molecules and have accomplished a large number of such total syntheses. A good fraction of this work and the essentials of retrosynthetic thinking are summarized in my 1989 book, *“The Logic of Chemical Synthesis”*. Because it is so challenging to do, total synthesis is often compared metaphorically with climbing mountains. However, I prefer to think of our syntheses using a musical metaphor, as our sonatas and string quartets, because I see in them a clear and lasting beauty.

Over the years, I have had the pleasure of working one-on-one with almost seven hundred young chemists. I am very proud of them not only because of their outstanding contributions to my research program but because of their impressive achievements in subsequent years, from Nobel Prizes to Presidencies to Professorships. I am absolutely convinced that the synergy between research and education is one of the great aspects of modern science and one of the best investments a society can make in its future. Unfortunately, this happy relationship is still not widely appreciated. For about fifty years I have been an advisor to Pfizer, Inc. This part of my career has also been gratifying. In the early days, Pfizer was just establishing itself in the pharmaceutical business and the research effort was tiny. Today, Pfizer is a global leader in the field with a research budget of \$7 billion and a market capitalization approaching \$300 billion.

From my long involvement with biologically active substances such as the eicosanoids and from much study on my own and years of advising pharmaceutical researchers, I have received a great medical education. I would like to share some of my current thoughts with you on the linkages between chemistry, progress in medicine, health care, and the future of humankind on this planet. I believe that chemistry, including chemical synthesis, will be a key driver of progress in medicine and human health during the rest of the 21st century. Not long ago, I gave a short talk at the dedication of a major new Pfizer research complex in which I speculated that a hundred years from that day there might well be a celebration at the same site of that facility's centennial. I expressed my opinion that the celebration might be especially appropriate because the discoveries made by health care companies and academia had resulted in the

cure or control of the vast majority of metabolic, organ, circulatory, malignant, and infectious diseases. Although a massive effort by academic, industrial, and medical scientists will be required, such an accomplishment seems to me to be very possible. Enlightened, wise, and fair investment in fundamental research by government and the private sector will play a crucial role. Government support of high-quality, fundamental research therefore needs to continue with emphasis on quality and minimization of political issues.

I believe even more strongly that the 21st century will see the general availability of up-to-date, good-quality *basic* health care and education in all countries of the earth because this will be seen by the more advanced countries not only as achievable but also as a prerequisite to world stability and the well being of peoples everywhere. I hope that it is not an impossible dream because the economic and social benefits will be great, especially as medicine advances. I believe that scientists, medical professionals, economists, the media, those skilled in governance, and especially the young and altruistic should start to champion this cause and make clear plans for how it might be accomplished. I should stress the young because it will be a very complex and lengthy undertaking. To them and to those starting careers in chemistry, I would offer the following advice: Never underestimate what you can accomplish if you prepare yourself well, continue to learn, work hard and optimistically, and value your integrity.

I am often asked about my vision for the future of chemistry, especially synthetic chemistry. As just stated, I believe that chemical synthesis will make enormous contributions to human progress in the next century especially when coupled to biology and medicine. However, those developments will not be fully realized without great and continuing advances in the central disciplines of chemistry. There is so much that remains to be discovered, in my opinion, that today's chemistry will seem archaic to a 22nd century chemist. I envy the young people in chemistry who will experience the excitement and pleasure of making the many discoveries of the next century of chemical research. Yet, at the same time, I worry about whether the younger generations of this country and the world will aspire to high creativity and persevere to achieve their impossible dreams.

If I may, I would like to close on a personal note by thanking my family, especially my wife, Claire, and children David, Bethany, John, and Susan for the companionship, love, and support that have guided me along the path to the present.

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